[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BOSTON UNIVERSITY]

REACTIONS OF MORPHOLINEMETHANOL WITH COMPOUNDS CONTAINING ACTIVE HYDROGEN ATOMS

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It has been shown by Henry (1) that the substituted aminomethanol formed by the interaction of a secondary amine and formaldehyde will react with nitroethane to replace both of the alpha hydrogen atoms of nitroethane with dialkylaminomethyl groups (I).

(I) $R_2NH \xrightarrow{HCHO} R_2NCH_2OH \xrightarrow{C_2H_5NO_2} (R_2NCH_2)_2C(CH_3)NO_2$

Henry (1) and also Duden, Bock, and Reid (2) obtained similar results with substituted aminomethanols and nitromethane. More recently, Cerf de Mauny (3) studied the reaction of secondary amines and formaldehyde with certain nitroparaffins. He postulated the rule that the number of hydroxymethylamine groups that would react with a nitroparaffin is one less than the number of hydrogen atoms linked to the carbon atom to which the nitro group is attached. According to this rule, nitroethane should react with only one molecule of hydroxymethylamine. Our results show that two molecules of morpholinemethanol react with one molecule of nitroethane, thus confirming the observations of Henry (1). It should be noted that Cerf de Mauny postulated his rule on the basis of experiments with nitromethane, 1-nitropropane, and 1-nitrooctane. Apparently, nitroethane must be considered an exception to Cerf de Mauny's rule.

We have isolated the morpholinonitroalkanes obtained by the reaction of morpholinemethanol with (a) nitromethane, (b) nitroethane, and (c) 1-nitropropane.[1] In view of the fact that our results with nitroethane were contrary to those predicted by Cerf de Mauny's rule, this reaction was carried out using one equivalent of nitroethane with one equivalent of morpholinemethanol as well as by using one equivalent of nitroethane with two equivalents of morpholinemethanol. The same product was formed in each experiment. In the reaction with 1-nitropropane, even though the proportion of morpholinemethanol was increased, only one morpholinomethyl group could be introduced.

The morpholinonitroalkanes were reduced readily in a Parr hydrogenation apparatus of the low-pressure type, using a Raney nickel catalyst activated by the method of Covert and Adkins (4). Several attempts were made to reduce these nitro compounds with tin and hydrochloric acid, but only the 1-morpholino-2-nitrobutane was reduced by this method.

Although 1,3-dimorpholino-2-aminopropane and 1,3-dimorpholino-2-amino-2-methylpropane formed solid ureas readily with phenyl isocyanate, a thick gum was the product of the interaction of 1-morpholino-2-aminobutane and

[1] We are grateful to the Commercial Solvents Corporation for giving us these nitroparaffins.

phenyl isocyanate. α-Naphthyl isocyanate also yielded a gum with this amine. Attempts to make the acetyl and the *p*-bromobenzenesulfonyl derivatives were also unsuccessful. A benzoyl derivative was obtained as a soft waxy solid. The hydrochloride was found to be gelatinous and sticky. A satisfactory solid derivative was finally obtained as a salt formed by the reaction with 3,5-dinitrobenzoic acid (5). It is interesting to note that the two amines which contained two morpholine rings formed solid ureas with phenyl isocyanate, while the amine with only one morpholine ring formed a gum. This observation confirms that made by Harradence and Lions (6) that the presence of the morpholine ring in a molecule improves the crystallizing ability of the molecule.

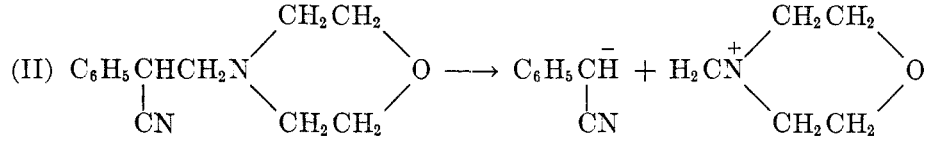
According to the principle of vinylogy (7) it would be reasonable to expect that *o*- and *p*-nitrotoluenes would resemble nitromethane in the reaction with morpholinemethanol. Both compounds were tried, but there was no evidence of any reaction. When 2,4-dinitrotoluene was used, an explosive decomposition occurred during an attempted distillation of the reaction mixture under reduced pressure.

Henry (8) observed that dialkylaminomethanols reacted readily with secondary aliphatic and heterocyclic amines. We have found that morpholinemethanol reacts similarly with diethylamine, dibutylamine, dicyclohexylamine, piperidine, and morpholine. Methylaniline yielded a mixture from which no pure compound, other than dimorpholinomethane, was isolated. Three primary amines, *n*-butylamine, aniline, and *o*-toluidine, were allowed to react with morpholinemethanol. The products obtained were those expected by the reaction of one equivalent of morpholinemethanol with one equivalent of primary amine. Several unsuccessful attempts were made to cause a reaction between dimethylaniline and morpholinemethanol.

It was found impossible to form picrates of these methylene diamines, because the diamines were readily hydrolyzed in the 95% alcohol used as a solvent for picric acid. In this solvent, dimorpholinomethane yielded a precipitate of morpholine picrate on standing overnight. When an anhydrous benzene solution of picric acid was used in a glass-stoppered bottle, the precipitate of morpholine picrate came down slowly over a period of several days, along with some gummy material. Replacement of one of the methylene hydrogen atoms with a phenyl group did not prevent hydrolysis during attempted picrate formation. This was shown by the fact that when phenyldimorpholinomethane was treated with alcoholic picric acid solution, morpholine picrate was the product obtained.

Since the cyanide group is known to have an activating effect on hydrogen atoms linked to an adjacent carbon atom, morpholinemethanol was allowed to react with methyl, ethyl, propyl, and benzyl cyanides. The only one of these to react was benzyl cyanide which formed α-morpholinomethyl-α-toluonitrile. This compound did not form a picrate with alcoholic picric acid solution, as hydrolysis occurred and morpholine picrate was obtained. This was unexpected because β-phenethylmorpholine (9) formed a stable picrate. The ready hydrolysis of α-morpholinomethyl-α-toluonitrile may be due to two factors, (a) the electron-attracting character of the cyanide group and (b) the tendency of

the amine nitrogen to assume an onium structure. The molecule is believed to separate according to equation II.



The positive iminium ion (10) would then combine with the hydroxyl ion from the water to form morpholinemethanol which would decompose readily in the presence of picric acid to form morpholine picrate.

In view of the fact that both a phenyl group and a cyanide group are necessary in order to have a reactive methylene group and also in view of the fact that simple aliphatic ketones, *e.g.*, acetone, react with morpholinemethanol (6), we were interested in determining whether phenylacetone would react with one or with two moles of morpholinemethanol. It was found that two molecules of morpholinemethanol reacted with one molecule of phenylacetone.

EXPERIMENTAL

Morpholinonitroalkanes. These compounds were made by the method of Cerf de Mauny (3) using 17 cc. of 37% formalin and 17 cc. of morpholine. After cooling to 0°, 0.1 mole of the nitro paraffin (0.2 mole was used in the experiment with 1-nitropropane) was added. The mixture was shaken and allowed to stand. In the experiment with nitromethane, the entire mass solidified in thirty minutes; with nitroethane, a solid separated on standing overnight; with 1-nitropropane, the mixture was allowed to stand for two days, when two layers had separated. The solids were recrystallized from absolute ethyl alcohol. In the experiment with 1-nitropropane, the lower, non-aqueous layer was fractionally distilled under reduced pressure. The results are given in Table I.

Morpholinoaminoalkanes. Each morpholinonitroalkane was dissolved in 175 cc. of 95% alcohol and eight grams of activated (4) Raney nickel was added. The reduction was continued until the pressure remained constant, and was complete within an hour. The mixture was filtered, the alcohol removed by distillation, and the residue distilled under reduced pressure. The results are given in Table II, together with the melting points and analyses of solid derivatives of the three amines.

Reduction of 1-morpholino-2-nitrobutane with tin and hydrochloric acid. Twenty-eight grams of 1-morpholino-2-nitrobutane was mixed with 30 g. of mossy tin, and 70 cc. of concentrated hydrochloric acid was added slowly. The mixture was heated on the steam-bath for two hours, diluted with 600 cc. of water and saturated with hydrogen sulfide. The tin sulfide was removed by filtration and the filtrate was concentrated on the steam-bath to approximately 100 cc. The solution was made alkaline and extracted with four 60-cc. portions of ether. The ether extracts were dried over solid sodium hydroxide pellets. After filtration, the ether was removed by distillation and the residue was distilled under reduced pressure. Fourteen grams of colorless oil distilled at 102–104° at 15 mm. Yield 60%.

Morpholinemethanol (11). To 18 cc. of 37% formaldehyde solution was added 17.4 g. (0.2 mole) of morpholine. The mixture was cooled in an ice-bath. Five grams of potassium carbonate was added, the mixture was shaken and allowed to stand for thirty minutes. The upper layer, consisting of an aqueous solution of morpholinemethanol, was separated and titrated with hydrochloric acid, using methyl orange as an indicator. The results indicated that a 95% yield of morpholinemethanol was obtained. Since the morpholinemethanol was made in this way for all subsequent experiments, only the upper layer

being used, all yields were based upon the amount of morpholinemethanol present in this upper layer.

Reaction of morpholinemethanol with primary and secondary amines. To the ice-cold solution of morpholinemethanol obtained from 17.4 g. (0.2 mole) of morpholine was added 0.2 mole of the secondary amine. After thorough mixing, 5 g. of anhydrous potassium carbonate was added and the mixture was allowed to stand at room temperature for twenty-four hours. The two layers were separated and the upper, non-aqueous layer was distilled fractionally under reduced pressure. The results, including analyses, are given in Table III.

TABLE I

MORPHOLINONITROALKANES

COMPOUND	YIELD, %	M.P., °C.	NITROGEN, %	
			Calc'd	Found
1,3-Dimorpholino-2-nitropropane	81	119–120	16.22	16.24, 16.10
1,3-Dimorpholino-2-nitro-2-methylpropane	70	124–125	15.38	15.00, 14.95
1-Morpholino-2-nitrobutane[a]	68	134–136[b]	14.89	14.68, 14.69

[a] *Anal.* Calc'd for $C_8H_{16}N_2O_3$: Neut. equiv., 188. Found: 195, 201. M.p. of picrate, 120–122°. *Anal.* Calc'd for $C_{14}H_{19}N_5O_{10}$: N, 16.79. Found: N, 16.53, 16.59.

[b] B.p. at 15 mm.

TABLE II

MORPHOLINOAMINOALKANES

COMPOUND	WT. OF NITRO COMPOUND USED, G.	YIELD, %	B.P. °C	PRESSURE, MM.	NITROGEN, %	
					Calc'd	Found
1,3-Dimorpholino-2-aminopropane[a]	14	80	67–68[b]		18.34	17.90, 17.88
1,3-Dimorpholino-2-amino-2-methylpropane[c]	15	56	148–150	1	17.28	17.01, 17.11
1-Morpholino-2-aminobutane[d,e]	18.8	51	102–104	14	17.72	16.91, 16.89

[a] M.p. of phenylurea, recrystallized from 95% alcohol, 233–234°. *Anal.* Calc'd for $C_{18}H_{28}N_4O_3$: N, 1609. Found: N, 15.61, 15.70. [b] M.p. [c] M.p. of phenylurea, recrystallized from 95% alcohol, 177–178°. *Anal.* Calc'd for $C_{19}H_{30}N_4O_3$: N, 15.47. Found: N, 15.21, 15.17. [d] Calc'd for $C_8H_{18}N_2O$: mol. wt., 158. Found: Mol. wt. in benzene, 160.9, 161.4. [e] M.p. of substituted ammonium 3,5-dinitrobenzoate, recrystallized from absolute ethyl alcohol, 162–163°. *Anal.* Calc'd for $C_{15}H_{22}N_4O_7$: N, 15.14. Found: N, 14.80, 14.81.

In the experiment with *n*-butylamine, a 59% yield of dimorpholinomethane was obtained. The only other experiment which yielded an appreciable quantity of dimorpholinomethane as a by-product was the experiment with diethylamine, where the yield of dimorpholinomethane was 22%.

Hydrolysis of morpholinomethylaniline. This compound was hydrolyzed with 20% sodium hydroxide solution in the presence of benzenesulfonyl chloride, and the well-known Hinsberg method (12) of separating primary amines from secondary amines was followed. The benzenesulfonyl derivative of morpholine, m.p. 118–120°, and benzene-sulfonanilide, m.p. 110–112°, were obtained.

α-Morpholinomethyl-α-toluonitrile. This compound was made by the procedure used for the reaction of morpholinemethanol with secondary amines. The product distilled at 103–105° at 7 mm. and the yield was 51%.

Anal. Calc'd for $C_{13}H_{16}N_2O$: Neut. equiv., 216; N, 12.96.
Found: Neut. equiv., 214; N, 12.75, 12.77.

Reaction between morpholinemethanol and phenylacetone. This reaction was carried out according to the usual procedure, except that 5 g. of morpholine, 5 cc. of 37% formaldehyde solution, 3 g. of potassium carbonate, and 6.7 g. (0.05 mole) of phenylacetone were used. Five grams of a colorless oil distilled at 109–111° at 11 mm.; yield 60%.

Anal. Calc'd for $C_{19}H_{28}N_2O_3$: Neut. equiv., 166; N, 8.43.
Found: Neut. equiv., 175; N, 8.00, 7.96.

An attempt to make a picrate of this compound resulted in the formation of morpholine picrate. The hydrolysis of this compound indicated that it would be impossible to determine definitely to which of the carbon atoms the two morpholinomethyl groups were linked. It is highly probable that they are both linked to the carbon atom to which the phenyl group is attached and that the compound is 1-phenyl-1,1-di(morpholinomethyl)acetone.

TABLE III

MORPHOLINOMETHYLAMINES

MORPHOLINOMETHYL	°C B.P.	PRESSURE, MM.	YIELD, %	NEUT. EQUIV.		NITROGEN, %	
				Calc'd	Found	Calc'd	Found
Butylamine	58–62	13	20	86	86.7		
Aniline[a]	108–112	10	52			14.58	14.37, 14.40
o-Toluidine	107–109	10	39			13.59	13.40, 13.42
Diethylamine	86–89	13	64	86	84.1	16.28	16.50, 16.52
Dibutylamine	134–136	14	58	114	112.0	12.28	11.92, 12.11
Dicyclohexylamine	112–116	8	64	140	138.6	10.00	10.12, 9.61
Piperidine	111–113	12	66	92	91.6	15.22	15.32, 15.29
Morpholine[b]	122–124	12	63	93	94.0	15.05	15.13, 15.15

[a] Calc'd for $C_{11}H_{16}N_2O$: mol. wt., 192. Found: mol. wt. in benzene 194.

[b] Harradence and Lions, *J. Proc. Roy. Soc. N.S. Wales*, **73**, 22–28 (1939).

Phenyldimorpholinomethane. To 21.2 g. (0.2 mole) of benzaldehyde was added, with cooling, 17.4 g. (0.2 mole) of morpholine. The clear solution gradually became turbid, and in about an hour a white solid appeared. The mixture was allowed to stand overnight and filtered. The filtrate consisted of 10 cc. of unreacted benzaldehyde. The dry, crude product weighed 20.4 g., representing a yield of 77%. Recrystallization from 95% alcohol gave white crystals, m.p. 101–101.5°.

Anal. Calc'd for $C_{15}H_{22}N_2O_2$: N, 10.69. Found: N, 10.58, 10.64.

SUMMARY

Morpholinemethanol has been found to react with nitromethane, nitroethane, 1-nitropropane, *n*-butylamine, aniline, *o*-toluidine, diethylamine, dibutylamine, dicyclohexylamine, piperidine, morpholine, benzyl cyanide, and phenylacetone.

The morpholinonitroalkanes have been reduced to the corresponding morpholinoalkyl amines.

The methylenediamines, phenyldimorpholinomethane, α-morpholinomethyl-α-toluonitrile, and 1-phenyl-1,1-di(morpholinomethyl)acetone were found to hydrolyze so readily that picrates could not be formed.

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[CONTRIBUTION FROM PURDUE UNIVERSITY]

THE UTILIZATION OF ALIPHATIC NITRO COMPOUNDS. V. REDUCTION OF NITRO ALCOHOLS AND NITRO GLYCOLS TO THE CORRESPONDING AMINES[1]

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In a previous paper it has been shown that (a) the nitro paraffins were first prepared by Victor Meyer in 1872, (b) these compounds were subsequently studied by a number of investigators, (c) vapor-phase nitration was developed by Hass and co-workers, (d) reduction of nitro paraffins gives good yields of amines, and (e) controlled reduction of the nitro parafins gives as high as 40% yields of oximes. In the present paper the production of amino alcohols and amino glycols is considered.

The nitro paraffins will condense with aldehydes in the presence of a small amount of base and form nitro alcohols or nitro glycols. Triethanolamine has a large number of uses, particularly in the form of fatty acid salts as emulsifying and wetting agents, and other amino alcohols should have commercial importance.

Demuth and Meyer were the first to reduce nitro alcohols (1). With sodium amalgam as the reducing agent they obtained impure products. Henry (3) and Tordoir used tin and hydrochloric acid but reported low yields (11). Mousset (7) and Montmollin and Ackermann, used aluminum amalgam and obtained yields of approximately 50% (6); *cf.* Stiénon (10). Kondo and Muragama (5) reduced phenylnitroethanol in the presence of palladium hydrosol and a little active carbon. Their yields were about 80%.

The nitro glycols were first reduced by Piloty and Ruff (8), who used hydrogen iodide in the presence of yellow phosphorus (yield, about 60%). They also used tin and hydrochloric acid. Schmidt and Wilkendorf (9) have reduced 2-nitro-1,3-propanediol in the presence of palladinized barium sulfate. They reported a 93% yield.

EXPERIMENTAL

Experiments by the present authors and others have shown that neither the nitro alcohols nor glycols are very stable in the presence of acids and bases. When ferrous sulfate was tried as the reducing agent, only a 25% yield of 2-amino-1-butanol was obtained. This type of reduction was abandoned, consequently, in favor of catalytic hydrogenation.

Only the actual hydrogenation experiments will be discussed here as the identification and determination of the properties of most of the products are reported in the work of Hass and Vanderbilt (2).

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[1] Abstracted from a portion of a thesis submitted to the faculty of Purdue University by Kenneth Johnson in partial fulfillment of the requirements for the degree of doctor of philosophy, June, 1937. This research project was sponsored by Commercial Solvents Corporation.

The first four papers of this series appears in *J. Am. Chem. Soc.*, **61,** (I) 3194, (II) 3195 (1939); (III) **64,** 1063, (IV) 1735 (1942).

The apparatus used has already been described in the discussion of hydrogenation of the nitro paraffins (4). The procedure and technique involved was also the same. In all cases the catalyst used was Raney nickel.

TABLE I

HYDROGENATION OF NITRO ALCOHOLS IN ETHANOL AT ROOM TEMPERATURE[a]

NO.	NITRO ALCOHOL	CATALYST, G.	PRESS., LBS.	TIME, HRS.	CONVERSION TO BASE, %
1.	2-Nitro-1-butanol (½ mole)	1.5	1300	2	95.
2.	2-Nitro-1-butanol (½ mole)	7.5	600	8	74.5
3.	2-Nitro-1-butanol (¾ mole)	7.5	1800	3	91.
4.	2-Nitro-1-butanol (¾ mole)	7.5	1800	10	91.
5.	5-Nitro-4-octanol (¼ mole)	7.5	1750	4	93.
6.	2-Methyl-2-Nitro-1-butanol (¼ mole)	7.5	1700	4	86.
7.	3-Nitro-2-pentanol (¼ mole)	7.5	1600	3	92.

[a] Run No. 1 was carried out at 100°.

TABLE II

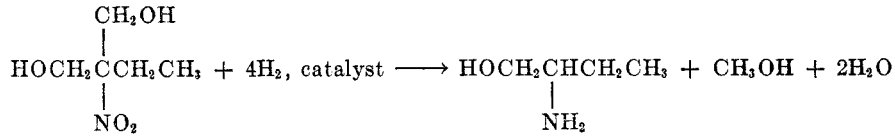
HYDROGENATION OF NITRO GLYCOLS IN ETHANOL AT ROOM TEMPERATURE[a]

NO.	NITRO COMPOUND	CATALYST, G.	PRESS., LB.	TIME, HRS.	CONVERSION TO BASE, %
1.	2-Ethyl-2-nitro-1,3-propanediol (½ mole)	3	1200	1	70
2.	2-Propyl-2-nitro-1,3-propanediol (½ mole)	3	1200	1	88.5
3.	2-Ethyl-2-nitro-1,3-propanediol (½ mole)	3	2000	15	92.8
4.	2-Methyl-2-nitro-1,3-propanediol (¼ mole)	1.5	2000	4	89.2
5.	2-Propyl-2-nitro-1,3-propanediol (¼ mole)	2.5	1800	1	90
6.	2-Ethyl-2-nitro-1,3-propanediol (¼ mole)	2.5	1700	3.5	91.2
7.	2-Isopropyl-2-nitro-1,3-propanediol (¼ mole)	2.5	1500	5	93.4
8.	2-Methyl-2-nitro-1,3-propanediol (1 mole)	7.5	1000	9	80
9.	2-Ethyl-2-nitro-1,3-propanediol (1 mole)	7.5	700	20	85.2
10.	2-Propyl-2-nitro-1,3-propanediol (½ mole)	7.5	700	12	86.5
11.	2-Ethyl-2-nitro-1,3-propanediol (½ mole)	7.5	700	10	99
12.	2-Ethyl-2-nitro-1,3-propanediol (½ mole)	7.5	700	10	99
13.	2-Ethyl-2-nitro-1,3-propanediol (½ mole)	7.5	700	10	99
14.	2-Isopropyl-2-nitro-1,3-propanediol (½ mole)	7.5	2000	2	96
15.	2-Isopropyl-2-nitro-1,3-propanediol (½ mole)	7.5	2000	1.75	91
16.	2-Isopropyl-2-nitro-1,3-propanediol (½ mole)	7.5	2000	2	96
17.	2-Isopropyl-2-nitro-1,3-propanediol (¾ mole)	7.5	1800	5	88
18.	2-Methyl-2-nitro-1,3-propanediol (¼ mole)	7.5	1700	4	89.2
19.	2-Propyl-2-nitro-1,3-propanediol (¼ mole)	7.5	1700	4	89.8
20.	2-Isopropyl-2-nitro-1,3-propanediol (¼ mole)	7.5	1700	4	93
21.	2-Ethyl-2-nitro-1,3-propanediol (¼ mole)	7.5	1700	4	91.5
22.	2-Ethyl-2-nitro-1,3-propanediol (¼ mole)	7.5	1700	5	86

[a] The hydrogenations at room temperature were ones in which no external heat was applied. The reaction is exothermic and at average conditions the heat evolved was enough to raise the temperature of the bomb to 40 or 50°. Runs No. 1 and No. 2 were carried out at 100°, whereas No. 3 was at 30°.

The conversions to base, as indicated in the tables, were practically complete in all cases, but there were occasionally some ammonia and lower amines and amino alcohols

formed. In the hydrogenation of 2-ethyl-2-nitro-1,3-propanediol it was found that 2-amino-1-butanol is a by-product. This suggests hydrogenolysis as expressed by the equation:



As already stated, the nitro glycols are not stable in the presence of alkali and it is possible that the amines formed during the hydrogenation are basic enough to cause the decomposition of unreacted nitro glycol.

In order to determine yields, a number of runs were made of which the following is an example (*cf.* Table I and Table II).

2-Amino-2-methyl-1-propanol. 2-Nitropropane was condensed with formaldehyde, and the resulting mixture concentrated at reduced pressure until the water solution was approximately 70% in 2-methyl-2-nitro-1-propanol. This was diluted with methanol to a 30% nitrohydroxy compound concentration and then reduced in the bomb at 500 lbs. pressure and 30°. Raney-Ni equivalent to 5% of the nitrohydroxy compound was used. The reduction time was six to eight hours.

Bomb runs were concentrated by atmospheric distillation until all the methanol and part of the water was removed. The concentrates from several bomb runs were combined and distilled at 100–103° at 64–65 mm. pressure. The yield was 70.5% based on the 2-nitropropane charged into the nitrohydroxy compound. The balance of the nitrogen was accounted for as low-boiling amines (in the recovered methanol and water cuts of distillation) and as a high-boiling cut and residue.

SUMMARY

Several nitro alcohols and nitro glycols were reduced to the corresponding amino compound by catalytic hydrogenation with fair yields. Some decomposition caused the simultaneous formation of other bases.

The procedure listed was used in the preparation of: 2-methyl-2-amino-1,3-propanediol, 2-ethyl-2-amino-1,3-propanediol, 2-propyl-2-amino-1,3-propanediol, 2-isopropyl-2-amino-1,3-propanediol, 2-amino-2-methyl-1-propanol, 3-amino-2-pentanol, 3-amino-4-octanol, 2-amino-1-butanol, and 2-methyl-2-amino-1-butanol.

The nitro alcohols and glycols were found to be unstable under most reducing conditions, and catalytic hydrogenation was the only method that gave good yields.

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VI. PRODUCTION OF ALDEHYDES AND KETONES FROM NITRO PARAFFINS

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Primary and secondary nitro paraffins are acidic in nature and form sodium salts. When mineral acid is added to these sodium salts, the nitro paraffins are regenerated. The action is different, however, when the sodium salts are added to an *excess of the acid.* In the latter case aldehydes or ketones are formed with the evolution of nitrous oxide. The action may be summarized by the following equation but the mechanism of the reaction is not known:

$$2RCH{:}N(\rightarrow O)ONa + 2H_2SO_4 \rightarrow 2RCHO + N_2O + 2NaHSO_4 + H_2O, \text{ or}$$

$$2R_2C{:}N(\rightarrow O)ONa + 2H_2SO_4 \rightarrow 2R_2{:}CO + N_2O + 2NaHSO_4 + H_2O$$

Nef (2) prepared acetaldehyde from nitroethane by adding a 10% solution of the sodium salt to 20% sulfuric acid. The yield was 70%. Nef also prepared acetone by this method. Konowaloff (1) prepared ketones from the sodium salts of several nitro paraffins but his reactions were probably accompanied by simultaneous reduction, as in several cases he dropped the salt into a mixture of zinc and acetic acid, and in another, into an acid solution of stannous chloride.

EXPERIMENTAL

The general procedure is: one-sixth of a mole of nitro paraffin is dissolved in 150 ml. of a solution containing 8 g. of sodium hydroxide, and then added dropwise to an ice cold mixture of 25 ml. of concentrated sulfuric acid in 160 ml. of water. Efficient agitation is used during the addition. Gas is evolved as the solution is added. The mixture is rectified, and the aldehyde or ketone determined quantitatively by its reaction with hydroxylamine hydrochloride.

The procedure was modified in one series of experiments by using 7 g. of calcium hydroxide instead of the sodium hydroxide.

By these two procedures the aldehydes and ketones available from nitroethane, 2-nitropropane, 1-nitropropane, 1-nitrobutane, 2-nitrobutane, and 1-nitro-2-methylpropane were prepared. With the exception of isobutyraldehyde, all of these aldehydes and ketones were obtained in 80–85% yield. It might be noted that in several attempts to regenerate the nitro paraffin, from the sodium salt, the recovery of nitro paraffin was limited to about 85%.

The calcium salts gave as good yields as the sodium salts, but more time had to be given for the reaction between the calcium hydroxide and nitro paraffins in order to assure an appreciable concentration of the enolic or salt form. The calcium salts of the nitrobutanes are not very soluble in water.

The decomposition of the salts of the nitro alkanes is practically instantaneous. The nitrous oxide is evolved as soon as the salt solution comes in contact with the acid.

The data on experimental procedure and yields are summarized in Table I.

TABLE I

PREPARATION OF ALDEHYDES AND KETONES FROM CERTAIN NITRO PARAFFINS

NO.	NITRO PARAFFIN	SALT USED	PRODUCT	% YIELD
1.	Nitroethane	Calcium	Ethanal	77
2.	1-Nitropropane	Calcium	Propanal	79.5
3.	1-Nitropropane	Sodium	Propanal	80
4.	2-Nitropropane	Calcium	Propanone	83.5
5.	2-Nitropropane	Sodium	Propanone	83.7
6.	2-Nitropropane	Sodium	Propanone	73
7.	1-Nitrobutane	Calcium	Butanal	85
8.	1-Nitrobutane	Sodium	Butanal	85
9.	1-Nitrobutane	Sodium	Butanal	45.5
10.	2-Nitrobutane	Calcium	Butanone	85.5
11.	2-Nitrobutane	Sodium	Butanone	82
12.	1-Nitro-2-methylpropane	Calcium	2-Methylpropanal	36
13.	1-Nitro-2-methylpropane	Sodium	2-Methylpropanal	32.4

The salt was prepared, added to the sulfuric acid, and the mixture distilled into a solution of hydroxylamine hydrochloride. With No. 9 no excess acid was used. A representative mix for the salt solution is 103 g. of 1-nitrobutane, 45 g. of NaOH, and 500 ml. of water, which is added to 100 g. of H_2SO_4 in 500 ml. of water. All products were identified as the oxime.

SUMMARY

Aldehydes and ketones were prepared from primary and secondary nitro paraffins by the action of their sodium or calcium salts on sulfuric acid. The conversions were 80–85%.

The procedure listed was used in the preparation of acetone, acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, and ethyl methyl ketone. The reaction is generally applicable for the syntheses of aldehydes and ketones.

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[CONTRIBUTION FROM PURDUE UNIVERSITY]

VII. THE CONDENSATION OF ARYL DIAZONIUM SALTS AND/OR HYDROXIDES WITH SECONDARY NITRO ALKANES[1]

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HISTORICAL SURVEY

The fact that aromatic diazonium salts condense with nitro alkanes was first discovered in 1875 by Meyer and Ambühl (15). They allowed benzenediazonium sulfate to react with sodium nitroethane, obtaining an orange solid which they formulated as $C_6H_5N{:}NCH(NO_2)CH_3$ and found to possess acid properties. In attempting to prove the structure of this compound Meyer and Ambühl (16) reported a yellow transparent oil, $C_6H_5N{:}NC(NO_2)(CH_3)_2$, from the reaction of benzenediazonium nitrate on the potassium salt of 2-nitropropane. All attempts to isolate and purify this derivative were unsuccessful, hence there is no positive proof that this compound was obtained even in an impure form.

The same year (1875) Friese (10), working in Meyer's laboratory, reported the formation of nitroformazyl, $C_6H_5NHN{:}C(NO_2)N{:}NC_6H_5$, from benzenediazonium hydroxide and nitromethane. In the eighteen years that followed, Meyer and his students continued their study of the condensation of aromatic diazonium salts with 1-nitro alkanes (17), 3-nitropropene (1), and 1,3-dinitropropane (14). Duden in 1893 (9) reported a condensation with the potassium salt of dinitromethane.

Bamberger and his students, for a period of eight years starting in 1894, condensed 1-nitro alkanes with aromatic diazonium salts (2, 3, 4, 5, 6). Similar work was done by Hantzsch and Kissel on nitroethane (11, 12).

Ponzio and collaborators studied condensations of aromatic diazonium salts with aromatic dinitromethanes (19, 20, 26), with diphenylnitromethane (25), and with trinitromethane (28, 29). This group of workers did much to investigate the reactions and behavior of these compounds (21, 22, 23, 26, 27, 28, 29).

Later investigators have condensed aromatic diazonium salts with nitro alcohols (13), with trichloro-1-nitro-2-acetoxy alkanes (8), with methyl 2,4-dinitrophenylacetate (18), and with 1,5-dinitropentane (30).

THEORETICAL

In carrying out this reaction, the diazonium chloride is prepared in the usual manner in excess acid. It is then neutralized cold with a slight excess of base, and finally coupled with a salt of a secondary nitro alkane. The reaction

[1] Abstract of a thesis submitted by C. F. Feasley to the faculty of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy in chemistry. Present address, Socony-Vacuum Oil Co., Inc., Paulsboro, N. J.

between benzenediazonium chloride and the sodium salt of 2-nitropropane may be shown by:

$$C_6H_5N(:N)^+\ ^-Cl + (CH_3)_2C{:}N(\rightarrow O)ONa \xrightarrow{OH^-} C_6H_5N{:}NC(NO_2)(CH_3)_2 + NaCl.$$

Highly colored compounds result from these condensations. When the aryldiazonium chloride contains one or more auxochrome groups, the final compound is found to serve for dyeing silk, wool, or other animal fibers. When the coupling reaction is carried out in fibers of cotton or rayon, a fast color is obtained.

Not all of the compounds prepared by this condensation are stable and a number of them decompose even when cold. This behavior has been reported also by Ponzio and co-workers (22, 26) for the condensation product from any *para* substituted diazonium salt. They found that the *para* substituted derivatives, in dry organic solvents, gave first a benzoylarylnitrosohydrazine, $C_6H_5C(:O)$-$N(NO_2)N(NO)C_6H_4X$, and then, in moist ether, benzoylazophenyl compounds of the type $C_6H_5C(:O)N{:}NC_6H_4X$, which resulted from loss of three atoms of oxygen and two atoms of nitrogen (possibly as NO and NO_2).

It has been proved by Ponzio and others (7, 24, 25) that a nitro group in a few cases shifts from the aliphatic carbon atom to the *para* position of the benzene nucleus in the condensation.

In the normal coupling reaction, Ponzio (19) found that, starting with benzenediazonium acetate, sodium acetate, and the potassium salt of phenyldinitromethane, the expected salt was the first product formed. In dry benzene, chloroform, or carbon disulfide, this product was found to be transformed in the cold into the isomeric benzoylphenylnitronitrosohydrazine, $C_6H_5C(:O)N(NO_2)$-$N(NO)C_6H_5$, while in the presence of water, ethyl alcohol, diethyl ether, or acetone it was found to go over into another isomer, phenylazophenyldinitromethane, $C_6H_5C(NO_2)_2N{:}NC_6H_5$.

It is apparent from the work in this laboratory that the compounds prepared from 2-nitropropane, which are more symmetrical, are more stable than those prepared from 2-nitrobutane. The compounds synthesized from 2-nitrobutane, however, have additional interest in that optical isomers are theoretically possible. No attempt has been made to separate the expected optical isomers.

The advantages of these condensation products over those prepared from primary nitroalkanes are quite important. They are more easily prepared and purified, since only one main organic product is formed. In primary nitro alkane condensations, one or two equivalents of the diazonium salt may be allowed to react to give compounds of various types such as $ArN{:}NCH(NO_2)R$; $ArNHN{:}C(NO_2)R$; and $(ArN{:}N)_2C(NO_2)R$. With nitromethane the products would be even more complicated. The compounds prepared from secondary nitro alkanes, moreover, have a stabler chromophoric group than those prepared from primary nitro alkanes, as evidenced by a 1-nitro alkane condensation product equilibrium:

$$ArN{:}NCH(NO_2)\cdot R \rightleftarrows ArNHN{:}C(NO_2)R.$$

In addition to the destruction of the desired azo linkage by the shift of a hydrogen atom, the resulting aryl hydrazone formed is much more subject to degrada-

TABLE I

AZONITRO ALKANES

COMPOUNDS	NITROGEN		COLOR	M.P., °C.
	Calc'd	Found		
1. 2-(Phenylazo)-2-nitropropane	21.7	21.6 ± .1	Yellow-red oil	(b.p. 98/0.7 mm.)
2. 2-(2-Nitrophenylazo)-2-nitropropane	23.5	23.3 ± .1	Dark brown	56.9
3. 2-(3-Nitrophenylazo)-2-nitropropane	23.5	23.6 ± .3	Yellow	71.2–72.2
4. 2-(3-Nitrophenylazo)-2-nitrobutane	22.2	22.1 ± .1	Yellow	63.3–63.7
5. 2-(2-Methyl-5-nitrophenylazo)-2-nitropropane	22.2	22.3 ± .1	Red-yellow	70.1
6. 2-(2-Methyl-5-nitrophenylazo)-2-nitrobutane	21.0	21.1 ± .2	Yellow	48.9
7. 2-(4-Acetamidophenylazo)-2-nitropropane	22.4	22.3 ± .1	Yellow	125.3–125.8
8. 2-(4-Chlorophenylazo)-2-nitropropane	18.5	18.5 ± .2	Red-brown	67.8
9. 2-(4-Bromophenylazo)-2-nitropropane	15.4	15.4 ± .1	Brown-orange	90–91
10. 2-(2,5-Dichlorophenylazo)-2-nitropropane	16.1	16.2 ± .2	Yellow	57–58
11. 2-(2,5-Dichlorophenylazo)-2-nitrobutane	15.3	15.5 ± .2	Yellow	40–40.3
12. 2-(2,4,6-Tribromophenylazo)-2-nitropropane	9.8	9.9 ± .2	Yellow	58.1
13. 2-(2,4,6-Tribromophenylazo)-2-nitrobutane	9.5	9.6 ± .1	Yellow	57.4–58
14. 2-(4-Methylphenylazo)-2-nitropropane	20.3	20.4 ± .1	Red oil	20 ± 1
15. 2-(2-Carboxyphenylazo)-2-nitropropane	17.7	17.8 ± .1	Orange-yellow	93.2–93.6
16. 2-(4-Carboxyphenylazo)-2-nitropropane	17.7	17.8 ± .3	Yellow	167–169
17. 2-(4-Carboxyphenylazo)-2-nitrobutane	16.7	16.9 ± .2	Yellow	129–130
18. 2-[Phenyl-(1,4-phenylenedisazo)]-2-nitropropane	23.5	23.2 ± .2	Brown	107–108
19. 2-[Phenyl-(1,4-phenylenedisazo)]-2-nitrobutane	22.5	22.2 ± .2	Light brown	80.9–81.4
20. 4,4′-[Bis-2-(2-nitropropaneazo)]-biphenyl	21.9	21.5 ± .2	Brown	162–163.6
21. 2-(2-Naphthylazo)-2-nitropropane	17.3	17.1 ± .3	Purple-brown	67

tion under hydrolytic conditions. No such shift is possible in the condensation product from a secondary nitro paraffin.

EXPERIMENTAL

In preparing these azo compounds, the general method is: A solution of the aromatic amine (0.2 mole) in 60 ml. of concentrated hydrochloric acid (sp. gr. 1.19) and 125 ml. of water is diazotized by the dropwise addition of 15 g. of sodium nitrite in water. The diazotized solution is then neutralized by pouring it with stirring into a suspension of 300 g. of ice in 500 ml. of about 2 *N* sodium hydroxide (41.3 g. of sodium hydroxide in 500 ml. of water). Immediately after neutralization, a previously prepared solution of 0.2 mole of the secondary nitro alkane in 8.0 g. of sodium hydroxide and 250 ml. of water is poured in with stirring. The solution is stirred until the azo compound appears and then filtered cold. The compounds are purified by recrystallization (3 to 5 times) from 95% ethyl alcohol.

Not all of the compounds prepared by this condensation are stable and a number of them decompose when cold, usually with the evolution of gas and heat.

A wide variety of condensation products containing sulfonic acid groups were prepared. Nitrogen analyses showed these materials to be slightly contaminated with salts, and they are not included in the table of pure compounds.

A number of compounds were prepared by tetrazotizing an aromatic diamine and coupling with two equivalents of a salt of a secondary nitro alkane. The most readily prepared of these compounds was 4,4′-[bis-2-(2-nitropropaneazo)]biphenyl. The corresponding compound prepared from 2-nitrobutane was not stable to boiling ethanol used as a recrystallization medium. A reddish-brown condensation product prepared by tetrazotizing 2,4-diaminotoluene and coupling with the sodium salt of 2-nitropropane proved rather difficult to purify and did not give close enough nitrogen analyses to be included in the table of pure compounds.

To obtain good yields of these condensation products the actual coupling must take place in a basic medium, using a salt of the nitro alkane, the reaction mixture must be kept ice-cold, and the product isolated as quickly as possible. For alkali-soluble products sufficient time should be allowed for coupling before the products are precipitated cold by the addition of dilute acid.

Duplicate nitrogen determinations (Dumas) were made on samples carefully dried for several weeks in a desiccator over anhydrous magnesium perchlorate. These nitrogen determinations and the method of synthesis offer adequate proof for the azo-linkage in these compounds, since two known chemicals were being condensed.

SUMMARY

1. Twenty new compounds have been prepared by condensing aryl diazonium salts with nitro alkanes, and their properties recorded. These are found in Table I.

2. These compounds offer advantages over the already known primary nitro alkane condensation products in ease of purification and stability of the chromophoric azo linkage.

3. The condensation products formed with 2-nitropropane are more stable in general than those prepared from 2-nitrobutane. This may be attributed to the greater symmetry of the compounds prepared from 2-nitropropane.

4. To obtain good yields of the condensation product, the actual coupling must take place in a basic medium using a salt of the nitro compound; the reaction mixture should be kept ice-cold and the product isolated as soon as the reaction is complete.

5. For alkali-soluble products, sufficient time must be allowed for coupling before the products are precipitated in the cold by addition of dilute acid.

6. If the original aromatic amine contains acidic auxochromic groups the

condensation product is found to dye wool and silk directly. Success in dyeing has also been obtained by carrying out the coupling reaction in the fibers of the cloth.

7. This coupling reaction should make many new and interesting compounds available to serve as dyes or organic intermediates for further synthesis.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

MESITYL OXIDE AND DIACETONE ALCOHOL IN THE BUCHERER SYNTHESIS OF HYDANTOINS

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In connection with a study of the identification of carbonyl compounds through conversion into hydantoins (1), we had occasion to investigate the behavior of mesityl oxide and diacetone alcohol, respectively, with potassium cyanide and ammonium carbonate in diluted alcohol at about 60°, these being the conditions developed by Bucherer (2) for the synthesis of hydantoins. During the earlier portion of this investigation we read the report by Marsh and Lazzell (3) of their synthesis of 5-methyl-(2-methylpropenyl)hydantoin and 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin by the Bucherer method. Since the data recorded for these hydantoins differed from those which we had noted (4) for the compounds, we have repeated our study and succeeded only in confirming our previous findings. A partial explanation of the apparent discrepancy between the data of Marsh and Lazzell and our own may be had from a consideration of the behavior of mesityl oxide and diacetone alcohol towards dilute alkali, ammonia, and cyanides.

Diacetone alcohol (II) is prepared (5) by a condensation of two molecules of acetone (I) in the presence of alkali; this reaction is reversible, the equilibrium depending on the *p*H and salt concentration of the medium. Koelichen (6) observed that for dilute aqueous solutions of diacetone alcohol the equilibrium was so far displaced toward acetone that the decomposition might be considered as proceeding to completion, and in dilute solutions of alkali hydroxides the rate of reactions is proportional to the concentration of hydroxyl ions. French (7) reported the effect of potassium ions in catalyzing the conversion of diacetone alcohol to acetone, and Miller and Kilpatrick (8) described the catalytic action of ammonia.

In addition, diacetone alcohol is in equilibrium also with mesityl oxide (III). Harries (9) found that in regenerating mesityl oxide from its bisulfite addition compound by means of aqueous sodium hydroxide, the expected yields of oxide were considerably reduced by conversion of oxide into acetone. The above relationships may be formulated as follows:

$$\underset{\text{I}}{2CH_3COCH_3} \rightleftarrows \underset{\text{II}}{(CH_3)_2COHCH_2COCH_3} \rightleftarrows \underset{\text{III}}{(CH_3)_2C{=}CHCOCH_3} + H_2O$$

Since it is an α,β-unsaturated ketone, mesityl oxide is able to add to itself the elements of hydrogen cyanide, not only at the carbonyl grouping to form the cyanhydrin but also at the ethylenic linkage. Lapworth (10) has discovered that ". . . hydrogen cyanide is more efficient as an additive reagent when its

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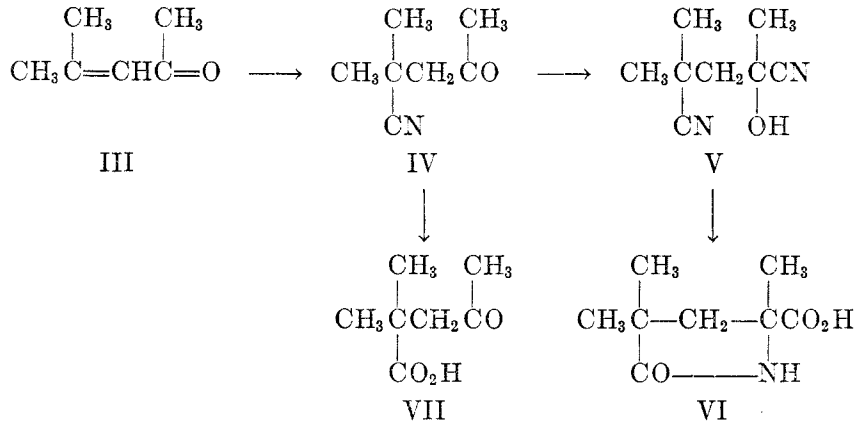
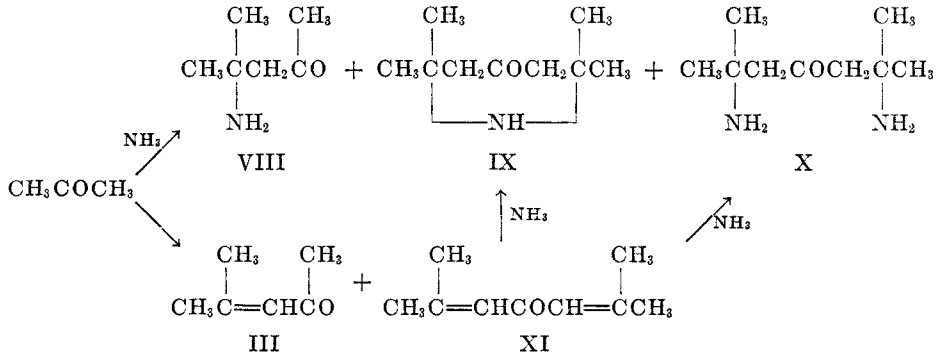
own salts are present." When mesityl oxide is mixed with an aqueous solution of potassium cyanide several products are formed depending on the concentration of reactants and the temperature. Mesitonitrile (IV) is first formed but reacts much more rapidly with potassium cyanide solution to form mesitonitrile cyanhydrin (V) than does mesityl oxide to form additional mesitonitrile. Mesitylic acid (VI) is produced to some extent by hydrolysis of mesitonitrile cyanhydrin in the alkaline potassium cyanide. The hydrolysis of mesitonitrile to mesitonic acid (VII) is possible, especially if the concentration of potassium cyanide is too low to convert the nitrile to cyanhydrin.

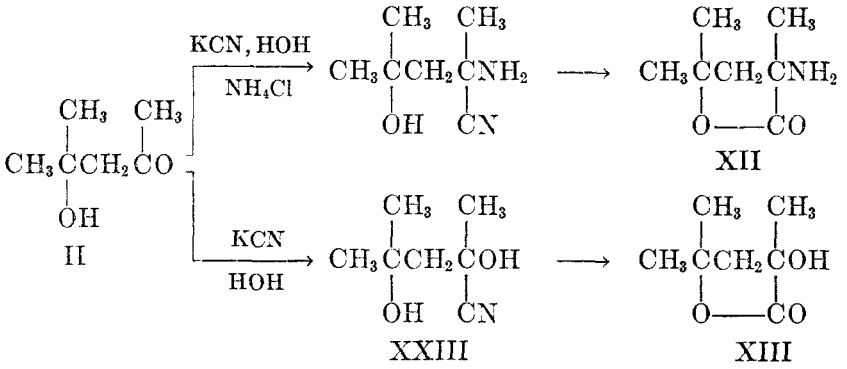


Since in the synthesis of hydantoins by the Bucherer procedure it is the common practice to acidify the reaction mixture and to remove the solvent partially before crystallization begins, acid hydrolysis of nitriles is possible, also.

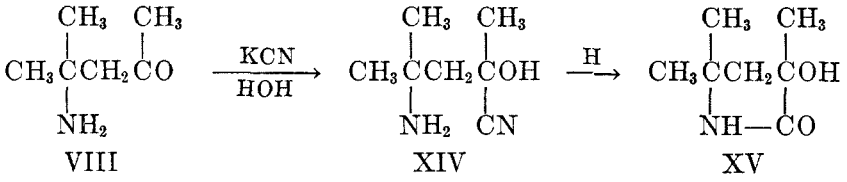
The presence of ammonia under the conditions of the Bucherer procedure affords the possibility of amine production. Indeed, diacetone amine (VIII) is prepared readily from mesityl oxide and aqueous ammonia (11) and also by the interaction of acetone and ammonium hydroxyide, the latter method also producing triacetoneamine (IX) and triacetonediamine (X) (12). Triacetoneamine may also be formed (13) by the interaction of acetone and diacetoneamine. In addition, phorone (XI), which may arise from condensation of three molecules of acetone, likewise reacts (14) with ammonia to yield a mixture of IX and X. The relationships of these amines are sketched below.



Cyanhydrin and amino nitrile formation are plausible intermediates in hydantoin synthesis but, should the final conversion of the nitriles to hydantoin derivatives be incomplete, subsequent acid hydrolysis should convert these to acids. In cases where a gamma hydroxyl or amino group is present in the nitrile, lactonization or lactamization would result. As a case in point, Kohn (15) reported the preparation of α-amino-α,γ-dimethyl-γ-valerolactone (XII) and α-hydroxy-α,γ-dimethyl-γ-valerolactone (XIII).



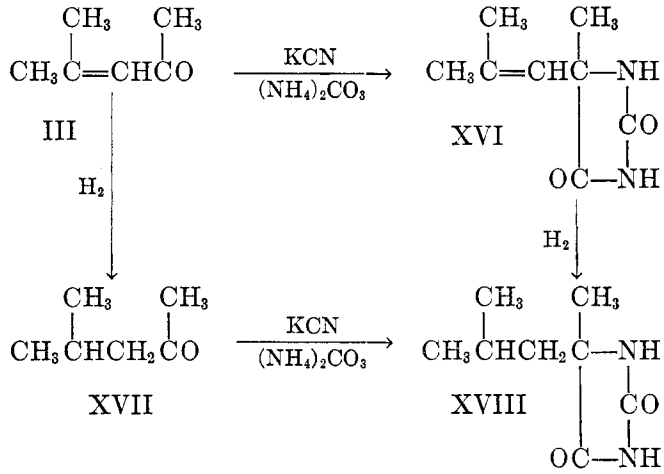
Should diacetoneamine (VIII) be present, a reaction analogous to that pictured above could occur, as described by Weil (16), to produce 3-hydroxy-3,5,5-trimethyl-2-pyrrolidone (XV) as indicated below.



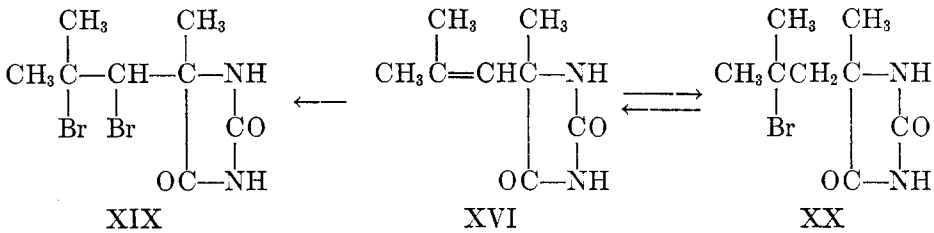
Since the various possibilities cited are to a greater or lesser degree plausible under the conditions of the Bucherer procedure (2), investigations of the behavior of mesityl oxide and diacetone alcohol, in their possible conversion into hydantoins, had the added purpose of determining whether the presence of any of these by-products could be detected.

From a mixture, resulting from interaction of mesityl oxide, potassium cyanide and ammonium carbonate in diluted alcohol warmed at 60°, a compound was readily isolated; data for analyses and molecular weight determination of this compound are in agreement with those for 5-methyl-5-(2-methylpropenyl)hydantoin (XVI). However, the melting point of this compound, namely, 194° (corr.), does not agree very well with that of 210° reported by Marsh and Lazzell (3) for a product claimed by them to be 5-methyl-5-(2-methylpropenyl)hydantoin and prepared by the same method. These authors record only the determination of molecular weight and percentage of nitrogen to substantiate their claim. Because of the difference of sixteen degrees in melting point temperatures, additional proof was obtained for the validity of the structure postulated for XVI.

Low-pressure catalytic hydrogenation of mesityl oxide yielded isobutyl methyl ketone (XVII). The latter was converted into 5-isobutyl-5-methylhydantoin (XVIII) by the Bucherer method (2). Next, the unsaturated hydantoin XVI, produced from mesityl oxide, was catalytically hydrogenated to yield a product identical with XVIII. The presence of the ethylenic linkage in XVI was also shown by addition of bromine and of hydrogen bromide to



yield 5-methyl-5-(1,2-dibromo-2-methylpropyl)hydantoin (XIX) and 5-methyl-5-(2-bromo-2-methylpropyl)hydantoin (XX), respectively. The structure of XX is predicated upon normal addition of hydrogen bromide to an ethylenic linkage.



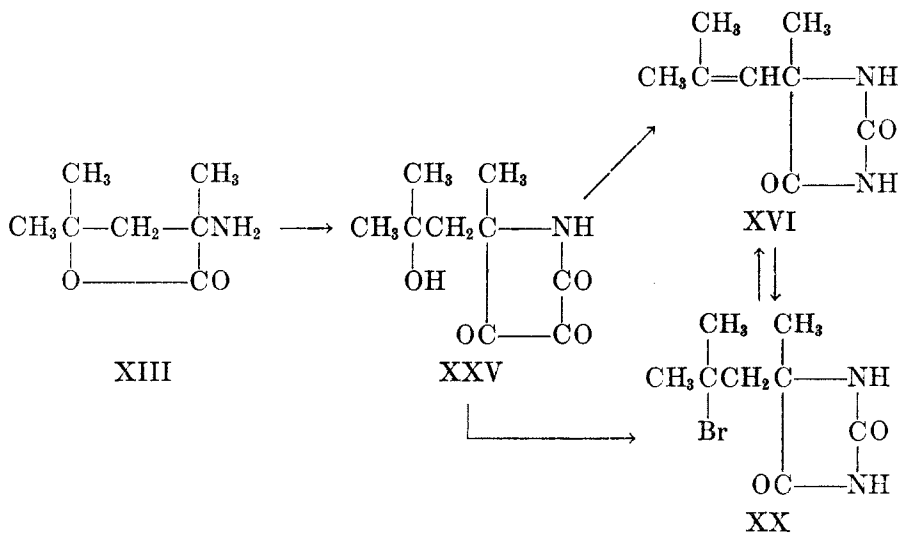
After separation of XVI from the reaction mixture, concentration of the mother liquor yielded a hygroscopic solid which could not be purified by recrystallization. However, when subjected to vacuum sublimation, a product was obtained which melted at 209–210° (corr.) and possessed the molecular formula $C_7H_{13}NO_2$. This compound has been identified as 3-hydroxy-3,5,5-trimethyl-2-pyrrolidone (XV) which Weil[3] had prepared from the cyanhydrin of diacetoneamine.

[3] Weil (16) reported m.p. 202°. It was found that Weil's method for preparing XV could be shortened and the yield improved by treating diacetoneamine hydrogen oxalate with aqueous potassium cyanide, followed by acid hydrolysis.

The utilization of diacetone alcohol in the Bucherer synthesis has been found to yield a mixture of products, the time of heating having considerable effect upon the nature as well as the amounts of the products formed. After thirty-six hours of reaction time, a 22% yield of 5,5-dimethylhydantoin (XXI) and 24.3% yield of α-hydroxy-α,γ-dimethyl-γ-valerolactone (XIII) were obtained. However, after fifty hours the reaction mixture yielded 6% of XXI, 21% of XIII, and 8.6% of a compound (XXII) melting at 210° (corr.) and having the composition, $C_8H_{14}N_2O_3$, anticipated for 5-methyl-5-(2-hydroxy-2-methylpropyl)-hydantoin. Since acetone can be converted into XXI under the conditions of the Bucherer synthesis, it is logical to assume that this hydantoin is formed from acetone which results from the decomposition of diacetone alcohol (II). Since XIII can be prepared by acid hydrolysis of diacetone alcohol cyanhydrin (XXIII), it is quite probable, under the Bucherer conditions, that any cyanhydrin formed from diacetone alcohol and not converted into a hydantoin is hydrolyzed, by subsequent acidification, yielding the hydroxy lactone (XIII).

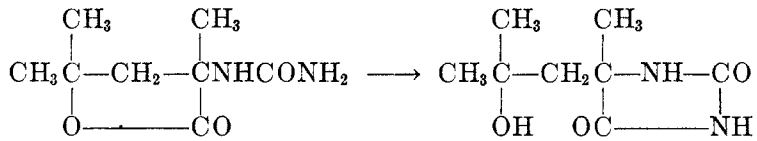
Although the molecular formula of compound XXII is in agreement with that for 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin described by Marsh and Lazzell (3), its melting point is 28° higher than that reported by these authors. Therefore, attempts were made to synthesize XXII by another method or to convert it into some other substance of established configuration. It was visualized that the bromine atom of 5-methyl-5-(2-bromo-2-methylpropyl)hydantoin (XX) might be replaced by a hydroxyl group; however, attempts to accomplish this with aqueous sodium hydroxide, moist silver oxide, or aqueous sodium acetate resulted only in formation of 5-methyl-5-(2-methylpropenyl)hydantoin (XVI). It was found also that XX in aqueous solution loses the elements of hydrogen bromide even at room temperature. Since XX thus can be converted readily into XVI, compound XXII was treated with thionyl chloride in the hope that its postulated hydroxyl group could be replaced by chlorine and the chloro compound by subsequent treatment with water yield XVI. It was noted, with some surprise, that boiling thionyl chloride caused no change and XXII was recovered unaltered. Since the hydantoin nucleus is rather stable to mineral acids, in an attempt at dehydration of XXII to produce XVI the former was warmed with 60% sulfuric acid. The product obtained was not XVI, but was an acidic material $C_8H_{13}NO_4$, in all probability α-carbamido-α,γ-dimethyl-γ-valerolactone (XXIV).

In order to synthesize 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin by another method, XIII was treated with potassium cyanate essentially according to the method used by Boyd (17) in preparing hydantoins from amino acids. A product (XXV) was obtained which melted at 147° (corr.), and was shown to have the composition represented by $C_8H_{14}N_2O_3$. This compound was readily soluble in acetone, and reacted vigrously in the cold with thionyl chloride to yield, after subsequent hydrolysis, hydantoin XVI. The latter was also obtained from XXV by reaction with a solution of hydrogen bromide in glacial acetic acid. These facts are evidence that XXV is 5-methyl-5-(2-hydroxy-2 methylpropyl)hydantoin.



XIII XXV XVI XX

Insight into the structure of the $C_8H_{14}N_2O_3$ compound (XXII), of m.p. 210°, was gained by its ready conversion into XXV. This transformation was accomplished by heating the former with 10% sodium hydroxide on the steam-bath for two hours, with subsequent neutralization with hydrochloric acid (under similar conditions a typical hydantoin, such as 5-isobutyl-5-methyl-hydantoin (XVIII) is unchanged). This behavior, together with the data concerning the behavior of XXII towards thionyl chloride and mineral acids is best explained on the assumption that XXII is α,γ-dimethyl-α-ureido-γ-valerolactone.



XXII, m.p. 210° XXV, m.p. 147°

In order to obtain additional information about the production of the ureido lactone (XXII), diacetone alcohol (II) was mixed with potassium cyanide and ammonium carbonate, as in the Bucherer synthesis, except that the solution was allowed to stand for two days at room temperature; a 20.3% yield of (XXI) and a 26.4% yield of XIII were isolated, but no ureido lactone could be detected. In contrast, diacetone alcohol cyanhydrin (XXIII) was prepared and then mixed with a diluted alcohol solution of ammonium carbonate at 58° for from seventeen to fifty-one hours; acidification was omitted and directly from the reaction mixtures was obtained the ureido lactone (XXII) in 16% yield and dimethylhydantoin (XXI) in 8% yield, but no α-hydroxy-α,γ-dimethyl-γ-valerolactone (XIII). Thus, since this reaction mixture was not acidified, this hydroxy lactone (XIII) in previous experiments must arise from acid hydrolysis of the cyanhydrin (XXIII). On the other hand, the production of the ureido

lactone (XXII) shows that the latter can be formed in the Bucherer synthesis and does not depend on acid hydrolysis for its production. The isolation of XXI indicates that the cyanhydrin dissociates into diacetone alcohol which in turn decomposes to form acetone.

We desire to acknowledge our indebtedness to the Research Institute of the University of Texas for financial support of this investigation.

EXPERIMENTAL

5-Methyl-5-(2-methylpropenyl)hydantoin (XVI). Ninety-eight grams (1 mole) of mesityl oxide was placed in a 2-liter flask, equipped with a mechanical stirrer and a reflux condenser, together with 1 liter of 50% aqueous alcohol, 87 g. (1.3 mole) of potassium cyanide, and 342 g. (3 moles) of ammonium carbonate (cubes). The flask was kept at 58° for fifty hours. After three hours the mixture was homogeneous and the stirring was discontinued. On cooling to 5°, 53.5 g. of inorganic material crystallized. The filtrate was acidified and after evaporation 17 g. of organic material, m.p. 189–194°, was obtained. Purification with charcoal and crystallization from diluted alcohol yielded 16 g. (9.5% yield) of white crystals melting at 194° (corr.).

Anal. Calc'd for $C_8H_{12}N_2O_3$: Mol. wt. 168.19; C, 57.12; H, 7.19; N, 16.66.

Found: Mol. wt. (b.p. elevation of acetone) 175; C, 57.30, 57.09; H, 7.40, 7.39; N, 16.80, 16.80.

Isolation of 3-hydroxy-3,5,5-trimethyl-2-pyrrolidone (XV). After the removal of XVI, as described above, further concentration and chilling of the filtrate yielded only inorganic material, a total of 240 g. being obtained. Finally, the residue was dissolved in ethanol, filtered from a few grams of inorganic material, and the filtrate was concentrated to a thick syrup on the steam-bath. Heating to 150° removed the last traces of solvent and yielded 150 g. of amorphous, hygroscopic solid. When heated to 200° under 5 mm. pressure, white solid material collected on the cold-finger type condenser. After recrystallization from ethyl acetate, 9.5 g. (6.6% yield) of white crystals, m.p. 209–210° (corr.) was obtained. This material did not lower the m.p. of an authentic sample of XV.

Anal. Calc'd for $C_7H_{13}NO_2$: Mol. wt. 143.18; C, 58.72; H, 9.15; N, 9.78.

Found: Mol. wt. (b.p. elevation of acetone) 150; C, 58.60; H. 9.29; N, 9.80.

One-tenth gram of the pyrrolidone (XV), isolated as above, was heated with 4 cc. of acetyl chloride for one hour under a reflux condenser. The sample was slow to dissolve. The excess of acetyl chloride was evaporated to leave a residue which was crystallized from benzene-petroleum ether, wt. 0.1 g. (78% yield); m.p. 138°. Mixed with an authentic sample of the acetate of XV it showed no lowering of the melting point.

Anal. Calc'd for $C_9H_{15}NO_3$: N, 7.56. Found: N, 7.70.

Twenty and one-half grams (0.1 mole) of diacetoneamine hydrogen oxalate (11) was dissolved in 100 cc. of water and a solution of 11.1 g. (0.1 mole) of calcium chloride in 20 cc. of water was added. The precipitated calcium oxalate was removed and the filtrate concentrated to 25 cc. on the steam-bath. Six grams of liquid hydrogen cyanide was added to the chilled solution which was maintained at 0° for three hours and then at room temperature for twenty-four hours. An equal volume of concentrated hydrochloric acid was added and the mixture heated under a reflux condenser for six hours. After evaporation to dryness on the steam-bath the residue was subjected to vacuum sublimation. A white powder was collected and crystallized from ethyl acetate. The yield of *3-hydroxy-3,5,5-trimethyl-2-pyrrolidone* (XV) of melting point 209–210° (corr.), was 1 g. (7%).

The yield of XV was increased by the following, better method. Twenty-five and one-half grams of diacetoneamine hydrogen oxalate was dissolved in 100 cc. of water and 6.5 g. (0.1 mole) of potassium cyanide in 50 cc. of water was added. After standing at room temperature for twenty-four hours, an equal volume of concentrated hydrochloric acid was added and the mixture heated with refluxing for six hours. The solution was concentrated on a steam-bath under an air jet, 150 cc. of ethanol was added, the organic salts

were filtered, and the filtrate concentrated by evaporation. The residue was dried on a porous plate, and extracted (Soxhlet) with acetone. On evaporation, the acetone solution left a viscous, semi-solid mass which was subjected to vacuum sublimation. The light brown sublimate was crystallized from ethyl acetate; m.p. 209–210° (corr.); yield 4 g. (28%).

5-Isobutyl-5-methylhydantoin (XVIII). A. From isobutyl methyl ketone (XVII). Thirty-three grams of XVII [b.p. 115–116° (745 mm.)] was dissolved in 330 cc. of 50% aqueous alcohol to which 28.6 g. of potassium cyanide and 112 g. of ammonium carbonate had been added. The mixture was warmed at 58° for ten hours; after acidification and removal of alcohol, 45.3 g. of product was obtained. Concentration of the filtrate yielded an additional 7 g.; total yield 93%. After recrystallization from diluted alcohol, m.p. 144.5° (corr.).

Anal. Calc'd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46.
Found: C, 56.68; H, 8.39; N, 16.56.

B. Hydrogenation of 5-methyl-5-(2-methylpropenyl)hydantoin (XVI). One gram of XVI was dissolved in 40 cc. of ethanol and shaken under 70 cm. of hydrogen in the presence of 50 mg. of the Adams' platinum catalyst. The conversion was complete in one and one-half hours. The melting point of the product was 144.5° (corr.) and was unchanged by mixing with an authentic sample of XVIII.

Bromination of XVI. Six grams of the hydantoin (XVI) was dissolved in 125 cc. of glacial acetic acid and, with cooling in ice-water, a 28% solution of bromine in glacial acetic acid was added slowly until the color persisted; the time of addition was one hour. Excess bromine and the acetic acid were removed on the steam-bath under a current of air. The residue was crystallized from aqueous alcohol to give 9 g. (77% yield) of white, fluffy crystals of XIX, m.p. 185° (dec.).

Anal. Calc'd for $C_8H_{12}Br_2N_2O_2$: Br, 48.73; N, 8.54.
Found: Br, 48.52; N, 8.63.

Addition of hydrogen bromide to XVI. Fifteen grams of XVI was dissolved in 85.5 g. of a 16.2% solution of hydrogen bromide in glacial acetic acid; there was no heat of reaction and the mixture was allowed to stand for eight hours. Crystalline material separated and additional amounts were obtained by concentration of the mother liquor. The combined material, weighing 16.5 g. (76° yield), was recrystallized from glacial acetic acid as colorless, glistening, mica-like crystals (XX) melting at 193° to a clear liquid with evolution of gas. A mixture of XVI and XX melted at 170° (dec.). A sample of XX dissolved in glacial acetic acid did not discharge the color of a bromine solution.

Anal. Calc'd for $C_8H_{13}BrN_2O_2$: Br, 32.08; N, 11.25.
Found: Br, 31.74; N, 11.32.

Attempt to convert XX into 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin (XXV). Two grams of XX in 10 cc. of water was treated with 3.3 cc. of 0.2436 *N* sodium hydroxide. The mixture was warmed on a steam-bath for one hour, to complete solution, and then allowed to stand overnight. Upon concentrating and cooling, 1 g. of 5-methyl-5-(2-methylpropenyl)hydantoin (XVI) was obtained. The product alone and mixed with authentic XVI melted at 194° (corr.).

Another attempt was carried out by vigorously stirring 1 g. of XX with 1 g. of silver oxide in 50 cc. of benzene and 0.5 cc. of water for ten hours on the steam-bath. After removal of the benzene by evaporation, addition of 20 cc. of water, filtration from silver bromide, concentration and cooling, 0.5 g. of XVI (m.p. 194°) was recovered.

Finally, 0.5 g. of XX was mixed with 1.5 g. of sodium acetate and 25 cc. of water. The mixture was allowed to stand at room temperature for three days. From the concentrated solution there crystallized 0.2 g. of XVI (m.p. 194°).

Diacetone alcohol in the Bucherer synthesis. A. One hundred sixteen grams (1 mole) of diacetone alcohol (II) was dissolved in 1000 cc. of 50% alcohol containing 87 g. (1.3 mole) of potassium cyanide and 342 g. (3 moles) of ammonium carbonate (cubes) and warmed for fifty hours at 58°. The solution was acidified with concentrated hydrochloric acid, concentrated to small volume under reduced pressure on a steam-bath and diluted with 300 cc.

of ethanol. After chilling, 96 g. of inorganic material was removed and the alcoholic filtrate yielded a viscous oil upon concentration. The addition of 300 cc. of benzene caused granular solid material to separate. This material was subjected to extraction with benzene in a Soxhlet apparatus.

Upon concentrating and cooling the combined benzene extracts, a total of 16 g. of solid was obtained, which on crystallization from isoamyl alcohol and from water melted at 175–176° (corr.). The m.p. of a mixture with an authentic sample of 5,5-*dimethylhydantoin* (XXI) showed no depression.

Anal. Calc'd for $C_5H_8N_2O_2$: Mol. wt. 128.13; N, 21.87.

Found: Mol. wt. (b.p. elevation in acetone) 132; N, 21.92.

The benzene filtrate, which resulted from removal of XXI, was subjected to distillation under diminished pressure; 30 g. of colorless product was collected, b.p. 109–110° (10 mm.), which on crystallization from benzene-petroleum ether melted at 65° (corr.). A mixture with an authentic sample of α-hydroxy-α,γ-dimethyl-γ-valerolactone (XIII) showed no depression in melting point.

Conversion of 3-hydroxy-3,5,5-trimethyl-2-pyrrolidone (XV) into XIII. This was carried out essentially according to Kohn's modification (18) of Tafel's method (19). Two grams of XV was dissolved in a mixture of 10 cc. of water and 10 cc. of concentrated hydrochloric acid, and with cooling in an ice-bath, a solution of 3 g. of sodium nitrite in 5 cc. of water was slowly added. After the reaction subsided, the solution was made alkaline with 50% sodium hydroxide solution. One gram of unreacted XV separated and the filtrate was acidified with dilute sulfuric acid and heated under a reuflx condenser for two hours. The acidic solution was repeatedly extracted with ether and the extract dried over anhydrous sodium sulfate. The residue which remained after evaporation of the ether was crystallized from a benzene-petroleum ether mixture. The yield was 0.1 g. of material melting at 65–66° (corr.)[4], which did not lower the melting point of an authentic sample of α-hydroxy-α,γ-dimethyl-γ-valerolactone (XIII).

The residue which remained after removal of XX and XIII was extracted with acetone in a Soxhlet apparatus. On concentrating and chilling the extract, 16 g. of solid was obtained. Recrystallization from isoamyl alcohol and finally from acetone gave a colorless, crystalline product (XXII) which melted at 209–210°.

Anal. Calc'd for $C_8H_{14}N_2O_3$: Mol. wt. 186.21; C, 51.60; H, 7.58; N, 15.05.

Found: Mol. wt. (b.p. elevation in acetone) 195; C, 51.65; H, 7.62; N, 15.19.

B. The same quantities of materials as noted in *A* were maintained at 58° for thirty-six hours. The reaction mixture was cooled and acidified before being acidified and concentrated under diminished pressure. Again, inorganic salts separated and were removed by filtration. Now, 300 cc. of benzene was added to the syrupy residue and the mixture was heated to boiling. After cooling, the precipitated solid was filtered and 250 cc. of acetone was added to redissolve the organic material leaving some insoluble inorganic salts. Concentration of the acetone extract yielded 30 g. of XXI, m.p. 175° (corr.). From the benzene filtrate was obtained an additional 21 g. of XXI, m.p. 175°. Distillation of the final benzene mother liquor produced 35 g. of XIII; b.p. 108–110°; m.p. 62–64°. The residue from the distillation was dissolved in ethanol-benzene from which 5 g. of XXI was obtained. Thus a total of 56 g. (0.44 mole) of XXI and 35 g. (0.243 mole) of XIII were recovered from the molar quantity of II used.

Fifty-eight grams (0.50 mole) of II dissolved in 250 cc. of alcohol, 36 g. (0.555 mole) of potassium cyanide in 250 cc. of water, and 144 g. (1.5 mole) of ammonium carbonate were mixed and placed in a stoppered flask and permitted to stand at room temperature for two days. The solution was filtered from undissolved ammonium carbonate and acidified with concentrated hydrochloric acid while the temperature was maintained below 15°. The acidic solution was evaporated at room temperature to a thick slurry, 200 cc. of alcohol

[4] Kohn (18) reported m.p. 66–68°.

was added and, on cooling, 20 g. of inorganic salt separated. The alcoholic filtrate was concentrated to a thick syrup. The latter was stirred and heated under reflux condenser with 150 cc. of benzene for one hour, then allowed to stand overnight before being filtered. The residue was extracted with acetone from which was obtained 26 g. (0.203 mole) of XXI. The benzene filtrate yielded 19 g. (0.132 mole) of XIII.

Interaction of diacetone alcohol cyanhydrin with ammonium carbonate. One hundred twelve grams (0.97 mole) of diacetone alcohol was dissolved in a solution of 100.8 g. (0.97 mole) of sodium sulfite and 225 cc. of water by stirring at room temperature for one hour. To this solution of the bisulfite addition product was gradually added with cooling and stirring a solution of 63.1 g. (0.097 mole) of potassium cyanide in 125 cc. of water. After one hour the mixture was poured into a separatory funnel and the upper layer of cyanhydrin (143 g.) withdrawn. Without further purification, the latter was dissolved in 500 cc. of alcohol, mixed with 186.2 g. (1.94 mole) of ammonium carbonate cubes and maintained at 58° for seventeen hours.

One-half of the solution was withdrawn and concentrated to about 100 cc. on the steam-bath. On cooling, crystals formed which were filtered and washed with acetone; yield, 12 g. of XXII; m.p. 209–210°. The filtrate was concentrated to a syrup, two volumes of benzene was added and the mixture was stirred and warmed until homogeneous. On cooling, crystals formed and were filtered and washed with a mixed solvent (1 ethanol:3 benzene); yield, 4 g. of XXI; m.p. 174–175°. The mother liquor was concentrated and gave crystalline material upon cooling; after washing with acetone, 2.5 g.; m.p. 209–210°. Further concentration and dilution with benzene yielded 2 g.; m.p. 173–174°.

The remaining half of the original reaction mixture was held at 58° for twenty-four hours longer, and treated in the same manner as the initial portion. There was thus obtained 13.2 g. of material melting at 209–210° and 9.8 g. of solid of m.p. 173–175°. The material of m.p. 174–175° was shown to be 5,5-dimethylhydantoin (XXI). The substance melting at 209–210° (corr.) is identical with a solid (XXII) isolated from interaction of diacetone alcohol with potassium cyanide and ammonium carbonate by the Bucherer procedure and shown to be of composition $C_8H_{14}N_2O_3$, that is, α,γ-dimethyl-α-ureido-γ-valerolactone (XXII).

Treatment of XXII with acid. Two grams of XXII was mixed with 2 g. of water and 3 g. of sulfuric acid and heated on the steam-bath for one day; at first solution was complete, but after one hour crystals began to form. An equal volume of water was added, and the mixture cooled and filtered, giving 1.2 g. of solid melting with decomposition at 200–202°. After crystallization from water the substance melted at 203° with evolution of gas to yield a clear liquid which did not solidify on cooling. The material is acidic to litmus and gives a neutralization equivalent of 202 when titrated in the cold. If, however, the sample is dissolved in water with warming and then cooled to room temperature, the neutralization equivalent is higher (264). The analytical data are in agreement with those calculated for α-carbamino-α,γ-dimethyl-γ-valerolactone (XXIV).

Anal. Calc'd for $C_8H_{13}NO_4$: Mol. wt. 187.19; C, 51.33; H, 7.00; N, 7.49.
Found: Neut. equiv. 202; C, 51.18; H, 7.15; N, 7.45.

In another experiment, 2 g. of XXII was dissolved in 30 cc. of concentrated hydrochloric acid and heated for twenty hours at 100°. After evaporation to dryness and crystallization, there was obtained 1 g. of XXIV melting at 203° (dec.).

Treatment of XXII with thionyl chloride. Three-tenths of a gram of XXII was mixed with 3 cc. of thionyl chloride and heated at 90°; the solid dissolved and heating was continued under water-pump vacuum to remove excess thionyl chloride. After adding 3 cc. of water and concentrating to 0.5 cc., 0.3 g. of crystals separated. The material was shown to be unchanged lactone (XXII).

Preparation of 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin (XXV). A. From α-amino-α,γ-dimethyl-γ-valerolactone[5] *(XII).* Fourteen and three-tenths grams (0.1 mole)

[5] Prepared from diacetone alcohol (II) according to directions of Kohn (15).

of XII was dissolved in 15 cc. of water and treated with 19.7 g. (0.2 mole) of 37% hydrochloric acid. With cooling in an ice-bath and vigorous stirring 14.8 g. (0.2 mole) of potassium cyanate was added in small portions during about thirty minutes. After standing at 0° for two hours crystals separated and were recrystallized from isoamyl alcohol. The yield was 4.5 g. (24%) of hydantoin melting at 147° (corr.)[6].

B. From α,γ-dimethyl-α-ureido-γ-valerolactone (XXII). One and eighty-six hundredths grams of the lactone XXII was dissolved in 25 cc. of 10% sodium hydroxide solution and heated on the steam-bath for two hours. After acidification with concentrated hydrochloric acid and evaporation to dryness, the residue was extracted with 40 cc. of hot ethanol, this extract was evaporated to dryness and the solid crystallized from isoamyl alcohol. The yield was 1 g. of hydantoin melting at 146–147° (corr.). This material did not depress the m.p. of XXV prepared from XII and cyanic acid.

In another experiment, 3.8 g. of XXII was heated under reflux condenser for sixteen hours in 35 cc. of 30% alcoholic potassium hydroxide solution. After the acidification and subsequent treatment outlined above, 2.5 g. (70% yield) of XXV, m.p. 146–147°, was obtained.

Conversion of 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin (XXV) into 5-methyl-5-(2-bromo-2-methylpropyl)hydantoin (XX). One and four-tenths grams of XXV (m.p. 147°) was dissolved in 20 g. of glacial acetic acid (from which XXIV crystallizes unchanged) and treated with 24.4 g. of a 12.3% solution of hydrogen bromide in glacial acetic acid. After standing at room temperature for sixteen hours, the solution was concentrated at 100° to a volume of 15 cc. under an air-jet. Upon cooling, 1.1 g. of mica-like crystals formed and were found to decompose at 193°. No depression of m.p. occurred as a result of mixing this sample of XX with that prepared by interaction of hydrogen bromide and XVI.

Conversion of 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin (XXV) into 5-methyl-5-(2-methylpropenyl)hydantoin (XVI). Two grams of XXV (m.p. 147°) was treated with 5 cc. of thionyl chloride. After the initial vigorous reaction had subsided the mixture was heated to reflux for thirty minutes on the steam-bath. Excess thionyl chloride was decomposed with ethanol and finally 10 cc. of water was added. The solution was concentrated to about 3 cc. and cooled. A yield of 1.2 g. of brown colored crystals, melting at 182–185°, was collected. After vacuum sublimation, 0.8 g. of white powder was obtained; melting point and mixed m.p. with an authentic sample of XVI, 192.93°.

In another experiment, 0.7 g. of hydroxyhydantoin (XXV) was heated with 5 cc. of 40% hydrobromic acid for fifteen hours on the steam-bath, and then placed in a desiccator containing (solid) potassium hydroxide. In three days, most of the liquid had evaporated to leave a slurry of brown crystals. An attempt was made to recrystallize the material from glacial acetic acid but no crystals were obtained. On evaporation of the acid, dissolving the residue in 10 cc. of water, and concentration of this solution, crystals appeared on cooling; wt. 0.5 g. Vacuum sublimation yielded a white powder; m.p. alone or mixed with XVI, 193–194° (corr.).

SUMMARY

1. The behavior of mesityl oxide and diacetone alcohol, respectively, towards a hydroalcoholic solution of potassium cyanide and ammonium carbonate (Bucherer procedure for hydantoin formation) has been studied. The results noted differ widely from those reported by Marsh and Lazzell for these two carbonyl compounds under the same conditions.

2. Utilization of mesityl oxide led to the isolation of 3-hydroxy-3,5,5-trimethyl-2-pyrrolidone and 5-methyl-5-(2-methylpropenyl)hydantoin, m.p. 194° (corr.). The structure of the latter was confirmed through its reduction to form 5-isobutyl-5-methylhydantoin.

[6] Marsh and Lazzell (3) report m.p. 180–181° (corr.).

3. Treatment of the propenylhydantoin with bromine or hydrogen bromide in glacial acetic acid produced dibromo and monobromo derivatives respectively.

4. Diacetone alcohol yielded 5,5-dimethylhydantoin, α-hydroxy-α,γ-dimethyl-γ-valerolactone and α,γ-dimethyl-α-ureido-γ-valerolactone.

5. 5-Methyl-5-(2-hydroxy-2-methylpropyl)hydantoin was prepared from interaction of α-amino-α,γ-dimethyl-γ-valerolactone and cyanic acid, and also from α,γ-dimethyl-α-ureido-γ-valerolactone by action of dilute sodium hydroxide solution. The structure of this hydantoin was proved by its conversion into 5-methyl-5-(2-methylpropenyl)hydantoin and 5-methyl-5-(2-bromo-2-methylpropyl)hydantoin.

6. The structure of a compound melting at 210° (corr.), isolated from utilization of diacetone alcohol in the Bucherer procedure, and isomeric with 5-methyl-5-(2-hydroxy-2-methylpropyl)hydantoin was postulated as being α,γ-dimethyl-α-ureido-γ-valerolactone.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. XI. SYNTHESIS OF β-SUBSTITUTED-$\Delta^{\alpha,\beta}$-BUTENOLIDES FROM METHYL KETONES

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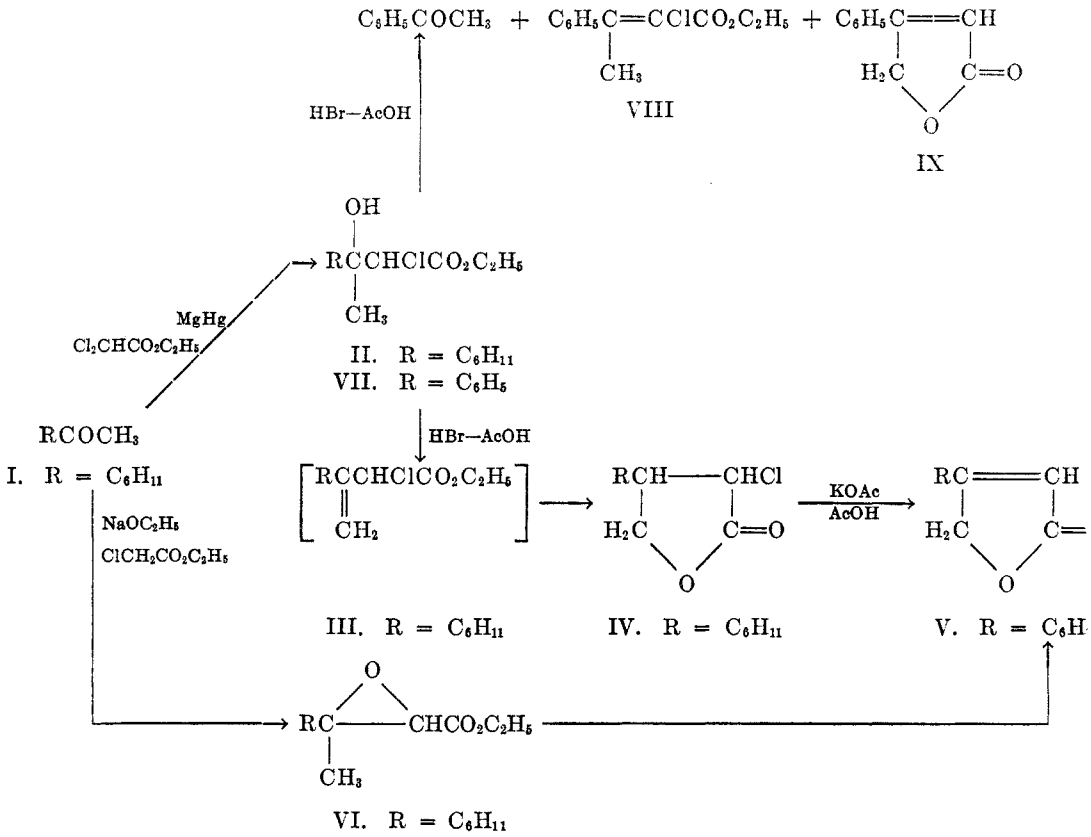
In previous communications, two general syntheses for β-substituted-$\Delta^{\alpha,\beta}$-butenolides have been described (1, 2). From the standpoint of over-all yield, accessibility of starting materials, number of steps involved, etc., these left something to be desired. In both of the earlier syntheses the double bond of the lactone was formed by removal of a β-substituent, which in turn was introduced by means of a Reformatzky reaction between ethyl bromoacetate and an alkoxy- or acyloxy-methyl ketone. In the present communication we wish to present our experience with the elimination of an α-substituent of a β-substituted butyro lactone as a means for introducing the desired double bond. The work has been confined to the preparation of simple model butenolides which are analogous to the cardiac aglycones and in which the substituent is cyclohexyl or phenyl.

Cyclohexyl methyl ketone (I) readily undergoes the Darzens (3) condensation with ethyl dichloroacetate in the presence of magnesium amalgam to yield ethyl α-chloro-β-hydroxy-β-cyclohexylbutyrate (II). When the latter is treated with a solution of hydrogen bromide in glacial acetic acid, ring closure ensues and α-chloro-β-cyclohexylbutyrolactone (IV) results in good yield. This rather novel lactone formation apparently proceeds through the intermediate unsaturated ester III, which is formed by dehydration of II, but which could not be isolated. Lactonization on the double bond then occurs in the known manner (4) after hydrolysis of the ester group. Elimination of the chlorine in the α-chloro lactone presented considerable difficulty. When the conventional method for accomplishing this by boiling the chloro lactone with quinoline was applied, extensive resinification took place. Use of the lower-boiling dimethylaniline resulted in only partial removal of hydrogen chloride and led to a mixture of unsaturated lactone and unchanged chloro lactone, together with condensation products of obscure nature. Pyridine was without action on the chloro lactone. Aqueous sodium hydroxide partially converted the chloro lactone to the corresponding hydroxy lactone. However, when the chloro lactone was heated with anhydrous potassium acetate in acetic acid, the desired removal of hydrogen chloride was accomplished yielding β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide (V).

Cyclohexyl methyl ketone also condensed smoothly with ethyl monochloroacetate in the presence of sodium ethoxide when the reaction was carried out by the method of Yarnall and Wallis (5), to yield the glycidic ester, VI. This ester, on treatment with a solution of hydrogen bromide in acetic acid, gave a small yield of β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide. However, the synthesis was

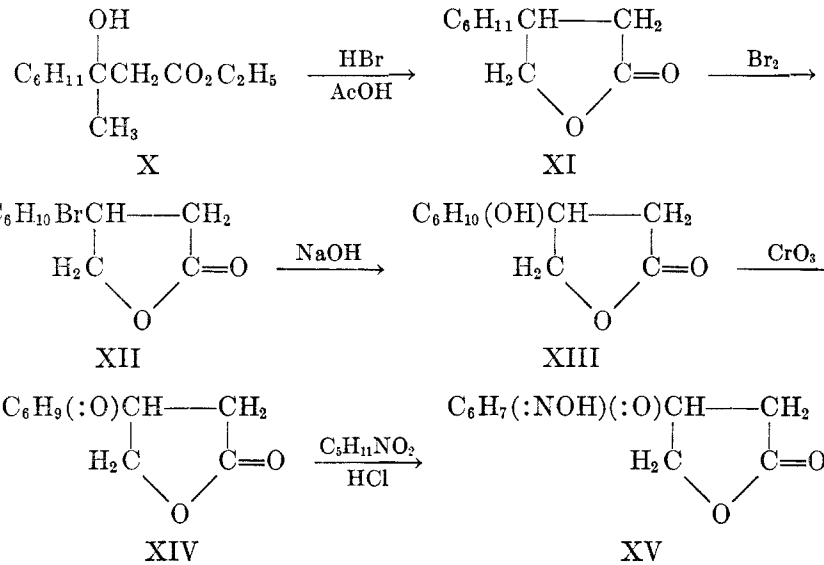


abandoned because of the poor yields and the difficulty encountered in separating the butenolide from contaminating by-products of the reaction.

In the phenyl series, acetophenone was condensed with ethyl dichloroacetate according to Darzens (3), yielding ethyl α-chloro-β-hydroxy-β-phenylbutyrate (VII) together with a small amount of acetophenone pinacol. The presence of the aromatic substituent in VII, contrasted with the cyclohexyl substituent in II, resulted in the formation of a more complex mixture of products when the ester VII was treated with hydrogen bromide in acetic acid. From the product of the reaction we have isolated acetophenone, apparently formed by a reversal of the Darzens condensation, ethyl α-chloro-β-phenylcrotonate (VIII), formed by α,β-dehydration of VI, and β-phenyl-$\Delta^{\alpha,\beta}$-butenolide (IX), formed by β,γ-dehydration of VII and subsequent lactonization and dehydrochlorination.

In view of the difficulty encountered in removing hydrogen chloride from α-chloro-β-cyclohexylbutyrolactone by the use of organic bases, it was felt that substitution of the more reactive bromine might lead to a smoother reaction. When ethyl β-hydroxy-β-cyclohexylbutyrate (X) was heated with hydrogen bromide in acetic acid, β-cyclohexylbutyrolactone (XI) was formed in excellent yield. It was then planned to brominate the saturated lactone, XI, whereby

α-bromo-β-cyclohexylbutyrolactone should be expected. However, while the lactone, XI, was readily brominated in acetic acid solution, investigation of the resulting bromo derivative disclosed that bromination had occurred on the cyclohexane ring, although the exact position taken by the bromine has not been demonstrated. The bromine atom in XII was replaced by a hydroxyl group by means of aqueous sodium hydroxide solution to yield α,β-(*x*-hydroxycyclohexyl)butyrolactone (XIII), the *p*-nitrobenzoate of which was not identical with the *p*-nitrobenzoate of α-hydroxy-β-cyclohexylbutyrolactone prepared from α-chloro-β-cyclohexylbtuyrolactone, IV. That the hydroxyl group in XIII is secondary was shown by oxidation to a ketone (XIV) without degradation. The possibility that bromination had occurred in the γ-position of the lactone was excluded on the basis of saponification values obtained with the keto lactone. Only one saponifiable group was found, whereas had bromination in the lactone ring



taken place, an anhydride requiring two equivalents of alkali in saponification, would have been formed by the above series of reactions. Furthermore, the keto lactone, XIV, yielded an isonitroso derivative when treated with isoamyl nitrite. The formation of such a derivative can only take place provided an unsubstituted methylene group is adjacent to the carbonyl group, a condition met only on the assumption that the ketone group in question, and hence its precursor bromine, is located on the cyclohexane ring.

EXPERIMENTAL

All melting and boiling points are corrected for stem exposure.

Ethyl α-chloro-β-hydroxy-β-cyclohexylbutyrate (II). Magnesium amalgam was prepared by heating 12.5 g. (0.5 mole) of magnesium turnings with 625 g. of dry mercury in a one-liter round-bottom flask. It was found to be unnecessary to carry out the amalgamation under an atmosphere of hydrogen as suggested by Darzens (3). To the well cooled amal-

gam was added a mixture of 400 cc. of anhydrous ether, 63 g. (0.5 mole) of cyclohexyl methyl ketone, and 90 g. (0.58 mole) of ethyl dichloroacetate all at one time. The stoppered flask was then shaken by hand until the amalgam had completely dissolved, the temperature being controlled so that it did not rise above 30°. Mechanical shaking for one hour completed the reaction. The solution was then poured into an excess of ice and concentrated hydrochloric acid and the resulting mixture was extracted with ether. After washing the ether extract free from acid, first with sodium carbonate solution and then with water, and drying over anhydrous magnesium sulfate, the residue, after evaporation of the ether, was distilled under reduced pressure. The yield of ethyl α-chloro-β-hydroxy-β-cyclohexylbutyrate boiling at 110–135° at 1.8 mm. was 84.5 g., or 68%. n_D^{25} 1.4776.

Anal. Calc'd for $C_{12}H_{21}ClO_3$: C, 57.9; H, 8.5; Cl, 14.3.
Found: C, 57.9; H, 8.5; Cl,14.5

α-Chloro-β-cyclohexylbutyrolactone (IV). A solution of 90 g. of ethyl α-chloro-β-hydroxy-β-cyclohexylbutyrate in 120 cc. of glacial acetic acid which had been previously saturated with dry hydrogen bromide at 0°, and 350 cc. of glacial acetic acid, was refluxed. After about half an hour a low-boiling liquid began to condense, and the reflux condenser was replaced by one set downward for distillation. Forty-eight grams of distillate, boiling up to 62°, was collected. Alternate refluxing and distilling were then continued for 24 hours, during which, at the end of 16 hours, 25 cc. more of glacial acetic acid, saturated with hydrogen bromide, was added. The residual mixture was then poured into a large amount of ice and water and extracted with ether. After washing the ether extract free from acid and drying, the residue, after removal of the solvent, was distilled under reduced pressure yielding 39 g., or 48% of α-chloro-β-cyclohexylbutyrolactone. The chloro lactone is a heavy, mobile, yellow oil which boiled at 131–135° at 0.9 mm. On standing, the chloro lactone crystallized as stout white prisms which were very soluble in the usual organic solvents. After crystallization from isopentane, the substance melted at 131–131.5°.

Anal. Calc'd for $C_{10}H_{15}ClO_2$: C, 59.2; H, 7.5.
Found: C, 59.2; H, 7.6.

α-Hydroxy-β-cyclohexylbutyrolactone. Five and six-tenths grams of α-chloro-β-cyclohexylbutyrolactone was refluxed for 4 hours with 100 cc. of 4% sodium hydroxide solution. The alkaline solution was extracted with ether to remove a slight amount of insoluble material and then acidified with hydrochloric acid. The acidified solution was warmed on a steam-bath for 4 hours, during which the lactone separated as a heavy yellow oil as relactonization proceeded. After concentrating to about 25 cc. the solution was extracted several times with chloroform. After washing and drying the extract and removing the solvent, 2.7 g. of material which boiled at 122–127° at 0.4 mm., was obtained. This distillate crystallized on scratching, and was found to consist, for the most part, of α-chloro-β-cyclohexylbutyrolactone. About 200 mg. of α-hydroxy-β-cyclohexylbutyrolactone was separated by fractional crystallization of the distillate from petroleum ether (Skellysolve B), in which the chloro lactone is much more soluble than the hydroxy lactone. The hydroxy lactone formed white monoclinic needles which melted at 144°.

Anal. Calc'd for $C_{10}H_{16}O_3$: C, 65.2; H, 8.7.
Found: C, 65.0; H, 8.8.

The p-*nitrobenzoate* of the above lactone crystallized as clusters of light yellow needles from 50% alcohol and melted at 154–154.5°.

Anal. Calc'd for $C_{17}H_{19}NO_6$: C, 61.2; H, 5.8.
Found: C, 61.0; H, 6.1.

β-Cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide (V). A mixture of 6 g. of α-chloro-β-cyclohexylbutyrolactone, 12 g. of anhydrous potassium acetate, and 15 cc. of glacial acetic acid was heated to boiling under reflux. A copious precipitate of potassium chloride separated almost immediately and heating was continued for 12 hours. The mixture was then poured into ice and water and extracted with ether. After washing and drying the extract, the solvent was removed and the residue was distilled under reduced pressure, yielding 2.4 g. or 49% of β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide which boiled at 115–117° at 0.1 mm. The lactone gave no

Beilstein test for halogen and gave the characteristic red nitroprusside reaction; n_D^{25} 1.5002; d_4^{25} 1.044; M_D^{25} obs. 46.32; M_D^{25} calc'd 45.17.

Anal. Calc'd for $C_{10}H_{14}O_2$: C, 72.2; H, 8.5.
Found: C, 72.2; H, 8.7.

Inasmuch as these values do not agree any too well with the previously reported ones of n_D^{25} 1.5059 and d_4^{25} 1.0985 (1), the compound was further identified by conversion to the semicarbazone of methyl β-cyclohexyl-β-formylpropionate by treating it with an alcoholic solution of potassium hydroxide, followed by methylation with diazomethane and treatment of the resulting product with semicarbazide. The semicarbazone thus obtained melted at 118–119° and gave no depression with a sample prepared from the lactone according to Paist, Blout, Uhle, and Elderfield (6).

Ethyl α,β-oxido-β-cyclohexylbutyrate (VI). Dry, freshly prepared sodium ethoxide, prepared from 12.7 g. (0.55 mole) of clean sodium and 350 cc. of freshly distilled absolute alcohol according to Yarnall and Wallis (5), was added in three portions to a mixture of 67.4 g. (0.55 mole) of ethyl monochloroacetate and 63.1 g. (0.50 mole) of cyclohexyl methyl ketone at −80°. A tan-brown mush was obtained which, after standing at −80° for 10 min., was brought to room temperature and left overnight. The next day the paste was heated on the steam-bath for 2.5 hrs. and poured into a mixture of ice and ether. After the alkaline solution had been extracted, it was acidified with hydrochloric acid and further extracted with ether. The combined ether extracts were then washed until neutral, dried over anhydrous magnesium sulfate, and the ether removed. Distillation yielded 23.4 g. or 22% of the theoretical yield of ethyl α,β-oxido-β-cyclohexylbutyrate boiling at 86–90° at 0.3 mm.; n_D^{25} 1.4588.

Anal. Calc'd for $C_{12}H_{20}O_3$: C, 67.9; H, 9.6.
Found: C, 67.5; H, 9.3.

Lactonization of the glycidic ester. A mixture of 10 g. of ethyl α,β-oxido-β-cyclohexylbutyrate, 25 cc. of glacial acetic acid previously saturated with dry hydrogen bromide at 0°, and 25 cc. of glacial acetic acid was alternately refluxed and distilled for 2 hrs. A small amount of low-boiling distillate was collected. After removal of the acetic acid under reduced pressure, the residue was taken up in ether, washed free of acid with sodium bicarbonate solution, dried, and the solvent removed. Distillation yielded 4 g. of material boiling at 134–140° at 0.5 mm.; n_D^{25} 1.4888. This material had an odor similar to β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide and gave a red nitroprusside reaction, but was evidently contaminated with other substances of approximately the same boiling point. It was not investigated further.

Ethyl α-chloro-β-hydroxy-β-phenylbutyrate (VII) was prepared essentially according to Darzens (3) except that the amalgam was not made under hydrogen. Yields of from 45 to 60% were obtained. The ester boiled at 124–126° at 1.5 mm.

In addition to the ester, we have isolated from 5 to 10% of a by-product which boiled at 140–144° at 1.5 mm. and melted at 122°. This substance gave analytical figures and a melting point corresponding to those for acetophenone pinacol. Cimiacian and Silber (7) report the melting point of this pinacol to be 122°.

Anal. Calc'd for $C_{16}H_{18}O_2$: C, 79.3; H, 7.5.
Found: C, 79.6; H, 7.6.

Action of hydrobromic-acetic acid on ethyl α-chloro-β-hydroxy-β-phenylbutyrate. A solution of 20 g. of the above chloro ester was heated with a mixture of hydrobromic and acetic acids in a manner similar to that used with the analogous cyclohexyl compound. The crude product was isolated as in the previous case and fractional distillation at reduced pressure yielded three fractions.

Fraction I weighed 3 g. and boiled at 53–56° at 0.3 mm. and was identified as acetophenone through its 2,4-dinitrophenylhydrazone, which melted at 233–233.5° and gave the following analytical figures:

Anal. Calc'd for $C_{14}H_{12}N_4O_4$: N, 18.7. Found: N, 18.8.

Fraction II amounted to 4 g. and boiled at 103° at 0.5 mm. The analytical figures ob-

tained corresponded to ethyl α-chloro-β-phenylcrotonate (VIII), which obviously resulted from α,β-dehydration of the hydroxy ester.

Anal. Calc'd for $C_{12}H_{13}ClO_2$: C, 64.1; H, 5.8.
Found: C, 64.4; H, 5.9.

Fraction III amounted to 3.8 g. and boiled at 126–136° at 0.5 mm. On trituration with petroleum ether the oil set, for the most part, to a white crystalline substance. After recrystallization from ether-isopentane the substance formed stout prisms which melted at 93°. It was identified as β-phenyl-$\Delta^{\alpha,\beta}$-butenolide by mixed melting point with a known sample prepared by the method of Linville and Elderfield (2).

Anal. Calc'd for $C_{10}H_8O_2$: C, 75.0; H, 5.1.
Found: C, 75.1; H, 5.1.

β-Cyclohexylbutyrolactone (XI). A mixture of 100 g. of ethyl β-hydroxy-β-cyclohexylbutyrate, prepared by the usual Reformatzky reaction from cyclohexyl methyl ketone and ethyl bromoacetate, as described by Rubin (8), 100 cc. of glacial acetic acid previously saturated with dry hydrogen bromide at 0°, and 300 cc. of glacial acetic acid was heated to boiling under reflux. At the end of half an hour a low-boiling fraction was removed by distillation and the residue was refluxed for a total of 4 hrs. After pouring into ice and water the mixture was extracted with ether. The ether extract, after washing free from acid, drying and removal of the solvent, left a residue which on distillation under reduced pressure gave 62 g., or 79% of β-cyclohexylbutyrolactone. The lactone boiled at 124–126° at 1.2 mm. and corresponded in all respects with that prepared by catalytic reduction of β-cyclohexyl-$\Delta^{\alpha,\beta}$-butenolide (6); n_D^{25} 1.4794.

Anal. Calc'd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.6.
Found: C, 71.5; H, 9.6.

The butyro lactone was also obtained in 78% yield by refluxing a mixture of 20 g. of ethyl β-hydroxy-β-cyclohexylbutyrate with a mixture of 20 cc. of conc'd sulfuric acid, 35 cc. of glacial acetic acid, and 50 cc. of water. After 5 hrs. the original two phases had merged into one and the mixture was worked up in a manner similar to that used above.

Bromination of β-cyclohexylbutyrolactone (XII). A solution of 40 g. (0.25 mole) of dry bromine in 350 cc. of glacial acetic acid was added slowly, and with stirring, to a solution of 33.7 g. (0.2 mole) of β-cyclohexylbutyrolactone in 150 cc. of glacial acetic acid. The reaction was started by the addition of 2 drops of acetic acid saturated with hydrogen bromide, and the mixture was kept at steam-bath temperature during the course of the reaction. The bromine was absorbed promptly and the reaction was complete in about an hour. After pouring onto ice, the mixture was extracted with chloroform and the chloroform extracts were washed free from acid and dried with anhydrous sodium sulfate. Distillation of the residue, after removal of the solvent, yielded 38.3 g., or 77.5% of the bromo-β-cyclohexylbutyrolactone, which boiled at 130–135° at 1 mm. The bromo lactone crystallized on standing and formed fine white needles which melted at 63–63.5° after recrystallization from isopentane. We propose that this substance be designated as β-(*x*-bromocyclohexyl)butyrolactone. Such nomenclature indicates that the bromine is on the cyclohexane ring, although its exact position remains to be determined.

Anal. Calc'd for $C_{10}H_{15}BrO_2$: C, 48.6; H, 6.1; Br, 32.3.
Found: C, 48.9; H, 6.2; Br, 32.2.

β-(x-Hydroxycyclohexyl)butyrolactone (XIII). A mixture of 10 g. of the above bromo lactone, 30 cc. of alcohol, and 100 cc. of 2 *N* sodium hydroxide solution was shaken for 15 hrs. at room temperature, at the end of which time a homogeneous solution was formed. The solution was acidified with hydrochloric acid and warmed for 3 hrs. on the steam-bath in order to complete relactonization. The alcohol was removed by concentration to 75 cc. and the resulting aqueous suspension of a heavy yellow oil was extracted with ether. The residue, after removal of the ether, yielded 5.5 g., or 74% of β-(*x*-hydroxycyclohexyl)-butyrolactone, which boiled at 140–152° at 0.7 mm.; n_D^{25} 1.4946.

Anal. Calc'd for $C_{10}H_{16}O_3$: C, 65.2; H, 8.7.
Found: C, 65.1; H, 8.7.

The p-*nitrobenzoate* of the above hydroxy lactone crystallized from alcohol in small, light yellow needles which melted at 163–164.5°.

Anal. Calc'd for $C_{17}H_{19}NO_6$: C, 61.2; H, 5.8; N, 4.2.
Found: C, 61.3; H, 6.0; N, 4.5.

When this p-*nitrobenzoate* was mixed with p-*nitrobenzoate* of α-hydroxy-β-cyclohexylbutyrolactone described above, the melting point of the mixture was depressed. It softened at 131° and melted at 148°.

β-(x-Ketocyclohexyl)butyrolactone (XIV). A solution of 2.3 g. of chromic acid in 25 cc. of 90% acetic acid was slowly added to a solution of 8.5 g. of the above hydroxy lactone in 75 cc. of 90% acetic acid, the temperature being kept below 30°. After standing for 20 min. at room temperature, the excess chromic acid was decomposed by the addition of 3 cc. of alcohol. After concentrating the mixture under reduced pressure to 15 cc., 500 cc. of water was added and the solution was extracted with 5 portions of ether. Removal of the ether from the washed and dried extracts and distillation of the residue yielded 3.5 g. of a heavy oil which boiled at 118–125° at 0.1 mm.; n_D^{25} 1.4960. Concentration of the aqueous solution from the ether extract to a small volume and extraction of this with chloroform yielded 2.5 g. of crystalline material which formed clusters of white needles after recrystallization from 50% methanol, and melted at 82–83.5°. When the oil obtained above was seeded with the crystals, about one-half of it crystallized. This failure to crystallize may be accounted for by the presence of two racemic mixtures, one of which crystallizes readily and the other does not. The total yield of keto lactone was 6 g., or 73%.

Anal. Calc'd for $C_{10}H_{14}O_3$: C, 65.9; H, 7.7.
Found: For the oily substance, C, 65.9; H, 8.0.
For the crystalline substance, C, 65.9; H, 8.0.

The p-*nitrophenylhydrazone* prepared from the oily material formed yellow monoclinic prisms from alcohol, which softened at 184° and melted at 187–188° with decomposition.

Anal. Calc'd for $C_{16}H_{19}N_3O_4$: C, 60.6; H, 6.1; N, 13.2.
Found: C, 60.5; H, 6.2; N, 13.5.

That the ketone group formed in the above oxidation, and hence its precursor hydroxyl group, is located on the cyclohexane ring, was further indicated by the behavior of the keto lactone on saponification. When 29.1 mg. of the keto lactone was saponified in 5 cc. of neutral alcohol with 6 cc. of 0.1 *N* sodium hydroxide, and the excess alkali then titrated back, the neutralization equivalent found was 188. Calc'd for one lactone, 182. If by an unlikely possibility the ketone and hydroxyl groups were in the γ-position of the lactone ring, the keto lactone would be a cyclohexylsuccinic anhydride and its neutralization equivalent would be 91.

Isonitroso derivative of β-(x-ketocyclohexyl)butyrolactone (XV). Freshly prepared isoamyl nitrite (0.92 cc.) was added dropwise with shaking to a solution of 920 mg. of crystalline keto lactone in 3 cc. of absolute alcohol, 3 cc. of ether, and 0.1 cc. of conc'd hydrochloric acid (9). After standing at room temperature for 24 hrs., the acid solution was neutralized with dilute sodium bicarbonate solution and evaporated almost to dryness. After addition of 15 cc. of 25% alcohol the solution was extracted with ether. The ether extract, on drying and concentration, yielded a sticky yellow gum which crystallized on trituration with ethyl acetate. Recrystallization from ethyl acetate and petroleum ether yielded clusters of very pale yellow prisms which melted at 160–161° with decomposition.

Anal. Calc'd for $C_{10}H_{13}NO_4$: C, 56.9; H, 6.2.
Found: C, 57.1; H, 6.3.

Action of potassium acetate on β-(x-bromocyclohexyl)butyrolactone. A mixture of 10 g. of the bromo lactone, 15 g. of anhydrous potassium acetate, and 30 cc. of glacial acetic acid was heated under reflux for 8 hrs. During this time a copious precipitate of potassium bromide was formed. An additional 5 g. of potassium acetate was then added and refluxing was continued for another 12 hrs. The reaction mixture was poured into water and the product was extracted with ether. Distillation of the product gave 5.5 g. of a substance

which boiled at 110–114° at 0.2 mm. The analytical figures obtained with this corresponded to a mixture of acetoxycyclohexylbutyrolactone and cyclohexenylbutyrolactone, the latter obviously having been formed by removal of hydrogen bromide. The mixture, however, gave no color reaction with sodium nitroprusside, again substantiating the view that the bromine had been introduced on the cyclohexane ring.

Anal. Calc'd for $C_{12}H_{18}O_4$: C, 63.7; H, 8.0.
Calc'd for $C_{10}H_{14}O_2$: C, 72.2; H, 8.5.
Found: C, 68.8; H, 8.1.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. β-Substituted butyro lactones have been prepared from β-substituted, β-hydroxybutyrates.

2. A new synthesis for β-substituted-$\Delta^{\alpha,\beta}$-butenolides from methyl ketones, has been described.

3. Bromination of β-cyclohexylbutyrolactone takes place on the cyclohexane ring.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. XII. THE CONDENSATION OF ETHYL OXALATE WITH ETHYL γ-CYCLOHEXYLCROTONATE AND A METHOD FOR PREDICTING THE PRODUCTS FROM SUCH CONDENSATIONS

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The synthesis of 5-methyl- and 5-ethyl-α-pyrone by ring closure of the appropriate γ-oxalyl unsaturated acids followed by decarboxylation, has been described previously (1). It was hoped that these reactions might be utilized for the preparation of 5-substituted α-pyrones containing cyclic substituents which would bear close resemblance to the natural cardiac aglycones of the squill, toad venom group. However, the attempted condensation of ethyl γ-cyclohexylcrotonate and ethyl oxalate to yield the necessary substituted γ-oxalylcrotonic ester, which was to serve as a model, was unsuccessful under the action of bases which accomplished the condensation of crotonic esters containing straight chain aliphatic substituents in the γ-position.

In continuing this investigation, we now find that ethyl oxalate condenses smoothly with ethyl γ-cyclohexylcrotonate in the presence of potassium ethoxide and pyridine according to the observation of Kuhn and Grundmann (2) that the presence of pyridine promotes this type of condensation. However, the condensation under discussion did not take the expected course. The only product isolated was that formed by condensation of ethyl oxalate in the α-position, namely the potassium salt of the enol form of ethyl 3-carbethoxy-5-cyclohexyl-4-pentene-2-one-1-oate (I). On acidification the diester (II) was readily formed. In contrast to the behavior of the analogous γ-oxalyl esters previously described (1), when II was boiled with concentrated hydrochloric acid in acetic acid solution, decarboxylation, as well as hydrolysis, ensued, leading to 5-cyclohexyl-4-pentene-2-one-1-oic acid (III). The γ-oxalyl esters merely underwent hydrolysis of the ester groups with no decarboxylation. However, it was possible to isolate the diacid (IX) and its half ester (X) by gentle treatment with hydrochloric acid in acetic acid solution.

Definite proof that the condensation of ethyl oxalate and ethyl cyclohexylcrotonate had taken place on the α-carbon atom of the latter, was secured by the following series of transformations. The diester, II, on catalytic reduction gave ethyl 3-carbethoxy-5-cyclohexylpentane-2-ol-1-oate (IV), which after saponification of the ester groups yielded the substituted malic acid (V). The same malic acid was also prepared by a series of reactions which leave no doubt as to its structure. Ethyl γ-cyclohexylbutyrate (VI), prepared by reduction of ethyl γ-cyclohexylcrotonate, was condensed with ethyl oxalate, yielding the potassium salt of the enol form of ethyl 3-carbethoxy-5-cyclohexylpentane-2-one-1-oate (VII), from which VIII was readily obtained on acidification.

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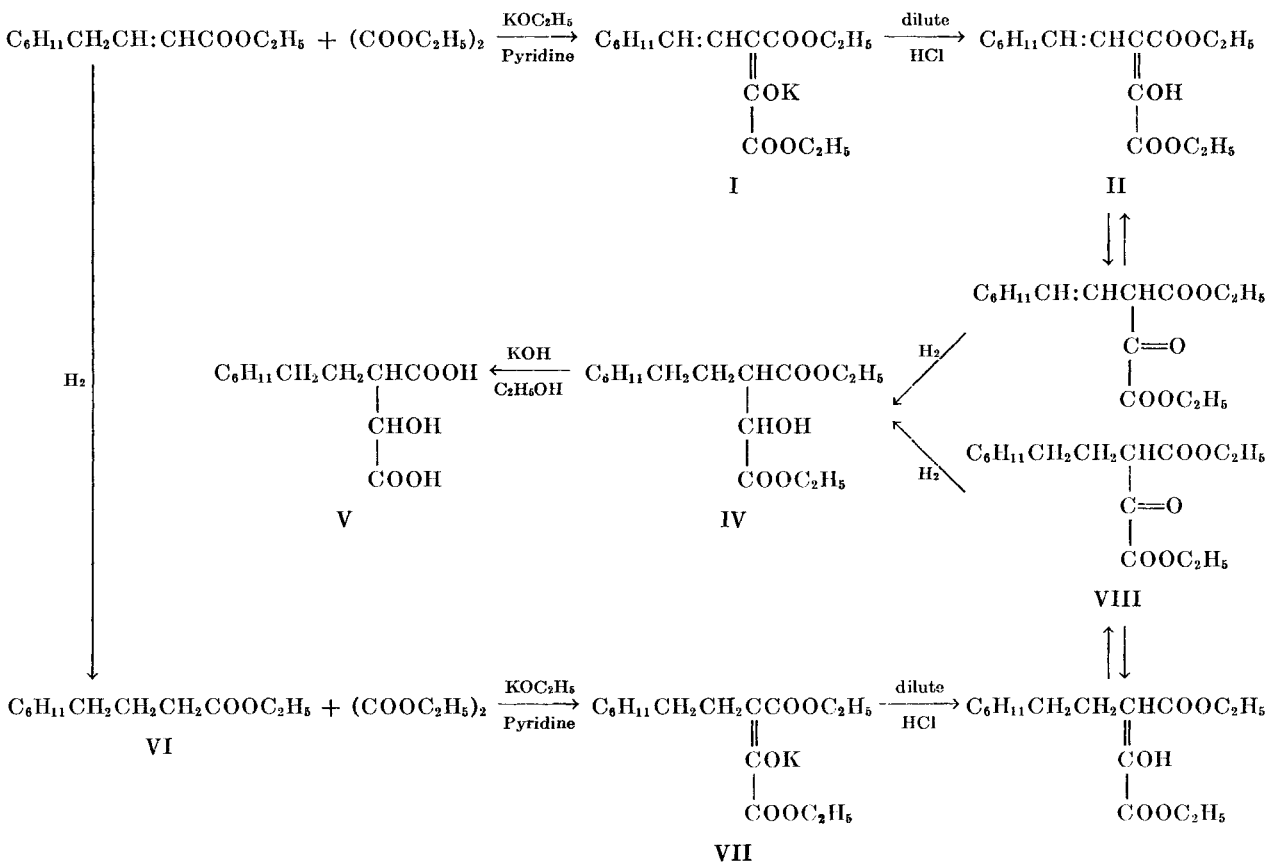
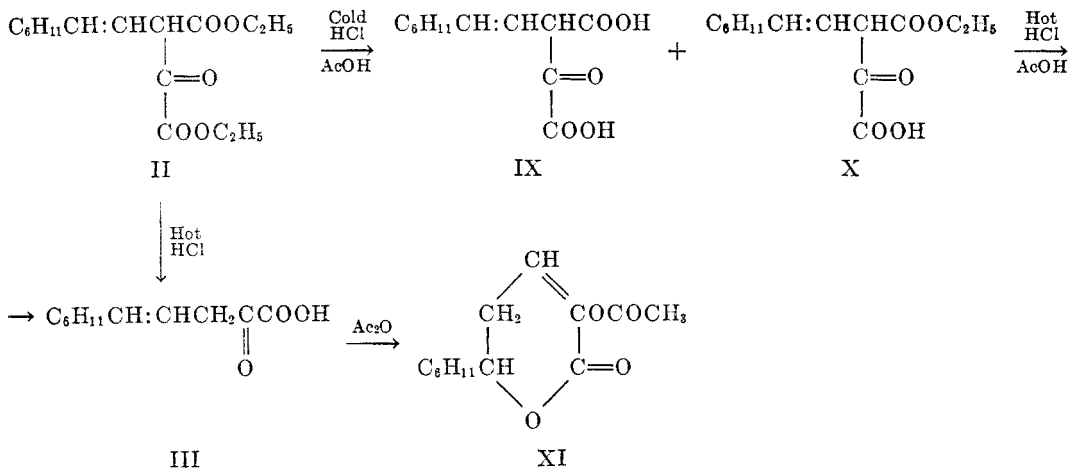

C6H11CH2CH:CHCOOC2H5 + (COOC2H5)2
KOC2H5
Pyridine
C6H11CH:CHCCOOC2H5
COK
COOC2H5
I
dilute
HCl
C6H11CH:CHCCOOC2H5
COH
COOC2H5
II
C6H11CH:CHCHCOOC2H5
C=O
COOC2H5
H2
C6H11CH2CH2CHCOOC2H5
C=O
COOC2H5
VIII
H2
C6H11CH2CH2CHCOOC2H5
CHOH
COOC2H5
IV
KOH
C2H5OH
C6H11CH2CH2CHCOOH
CHOH
COOH
V
H2
C6H11CH2CH2CH2COOC2H5 + (COOC2H5)2
VI
KOC2H5
Pyridine
C6H11CH2CH2CCOOC2H5
COK
COOC2H5
VII
dilute
HCl
C6H11CH2CH2CHCOOC2H5
COH
COOC2H5

Catalytic reduction of VIII followed by saponification of the ester groups in the reduced product gave 3-carboxy-5-cyclohexylpentane-2-ol-1-oic acid (V), which was identical in all respects with the substance prepared from the condensation product of the unsaturated ester with ethyl oxalate. The identity of the acids prepared by the two methods was confirmed by preparation of their di-*p*-bromophenacyl esters, which likewise showed no differences.

With the experience gained in the present work and in previous work (1), together with the observations of other workers, *e.g.*, Kuhn and Grundmann (2) and Boese and Major (3), it is now possible to predict with a reasonable degree of certainty, the products which can be obtained from condensations involving ethyl oxalate and γ-substituted $\Delta^{\alpha,\beta}$-crotonic esters, $\Delta^{\beta,\gamma}$-crotonic esters and their vinylogs. In the first place, the position originally occupied by the double bond of the crotonic ester appears to be of little importance, and the controlling factor in such condensations is the electronic nature of the



substituent in the γ-position. If this substituent is hydrogen, condensation will take place in the γ-position (3). If the γ-substituent is a straight chain alkyl group, condensation takes place on the γ-carbon atom with progressively poorer yields obtained as the inductive effect of the substituent increases, *i.e.*, as one goes from methyl to ethyl, etc. as substituents. When the electron-donating capacity of the γ-substituent is still further enhanced, as in the case of the cyclohexyl group, then condensation takes place on the α-carbon atom. As would be expected, aryl substituents, such as phenyl, lead to condensation in the α-position (4). That the course of the condensation is not influenced by the solvent effect of the pyridine used in the present work was demonstrated by a repetition of the condensation of ethyl oxalate with ethyl $\Delta^{\alpha,\beta}$-hexenoate (1) under the newer conditions. The product isolated was that formed by γ-condensation as described previously, and the yield was almost doubled.

Finally, treatment of the keto acid (III) with acetic anhydride has yielded a lactone acetate (XI). This is assigned the tentative structure of the acetate

of α-hydroxy-δ-cyclohexyl-$\Delta^{\alpha,\beta}$-valerolactone on the basis of its empirical composition and saponification equivalent. It apparently is formed by acetylation of the enolized ketone group followed by lactonization of the carboxyl group on the γ,δ double bond of III in accordance with known reactions (5,6).

EXPERIMENTAL

Ethyl γ-cyclohexylcrotonate was prepared according to Fried and Elderfield (1). It distilled at 96–98° at 1 mm.; n_D^{25} 1.4687.

Ethyl 3-carbethoxy-5-cyclohexyl-4-pentene-2-one-1-oate (II). To a potassium ethoxide solution prepared from 7.8 g. (0.2 mole) of clean potassium and 34 cc. of absolute alcohol in 50 cc. of anhydrous ether at 0° was added slowly with shaking a solution of 29.2 g. (0.2 mole) of diethyl oxalate in 20 cc. of dry ether. After standing 15 min. at 0°, 39.2 g. (0.2 mole) of ethyl γ-cyclohexylcrotonate in 40 cc. of dry pyridine was added dropwise with constant shaking. Almost immediately a red color, which deepened as the addition proceeded, developed. After 13 hrs. in the refrigerator, a light yellow crystalline precipitate formed. To the solution an additional 25 cc. of dry pyridine was added with shaking. Seven hours later when crystallization was complete, an equal volume of petroleum ether (Skellysolve B) was added, and the salt removed by filtration, and thoroughly washed with petroleum ether. After drying over paraffin the salt weighed 15.6 g., representing 23% yield. Acidification of the potassium salt with ice-cold dilute hydrochloric acid produced the diester, II, as a heavy yellow oil which could not be crystallized or distilled without decomposition. It gave a purple ferric chloride test in alcoholic solution.

The *2,4-dinitrophenylhydrazone* of the above keto ester crystallized as bright yellow needles from alcohol and melted at 76–77°.

Anal. Calc'd for $C_{22}H_{28}N_4O_8$: C, 55.7; H, 5.9; N, 11.8.
Found: C, 55.9; H, 6.1; N, 11.8.

3-Carbethoxy-5-cyclohexyl-4-pentene-2-one-1-oic acid (X). The diester from 5 g. of the above potassium salt was added to 30 cc. of conc'd hydrochloric acid, and then just enough acetic acid (22 cc.) was added to make an extremely fine suspension. This solution was then shaken vigorously at room temperature on the mechanical shaker for 18 hrs., at the end of which small white crystalline globules had precipitated, which were filtered off, washed with conc'd hydrochloric acid and dried over potassium hydroxide, yielding 3 g., or 75% of the half ester, X. On recrystallization from petroleum ether the ester formed clumps of white needles which melted at 83.5–84°. It gave a blood-red ferric chloride test in alcohol.

Anal. Calc'd for $C_{14}H_{20}O_5$: C, 62.7; H, 7.5.
Found: C, 62.8; H, 7.5.

The p-*bromophenacyl ester* of the above acid crystallized from alcohol in flat platelets which melted at 108–109°. It gave a very weak yellow color with ferric chloride in alcoholic solution.

Anal. Calc'd for $C_{22}H_{25}BrO_6$: C, 56.8; H, 5.4.
Found: C, 56.7; H, 5.4.

3-Carboxy-5-cyclohexyl-4-pentene-2-one-1-oic acid (IX). Evaporation of the mother liquors from the half ester, X, to 25 cc. resulted in the precipitation of 0.8 g. of white needles which gave analytical figures corresponding to 3-carboxy-5-cyclohexyl-4-pentene-2-one-1-oic acid. On recrystallization from a mixture of ether and petroleum ether the diacid formed needles which started to decompose at 135° but did not completely melt until 217°, a gas being evolved during this time.

Anal. Calc'd for $C_{12}H_{16}O_5$: C, 60.0; H, 6.7.
Found: C, 60.3; H, 6.8.

5-Cyclohexyl-4-pentene-2-one-1-oic acid (III). To the diester (II) from 1 g. of potassium salt, a solution of 20 cc. of glacial acetic acid and 30 cc. of conc'd hydrochloric acid was added and the mixture was refluxed for 1 hr., during which the solution turned red and

some black droplets precipitated. After boiling with decolorizing carbon for 1 min., the yellow solution was filtered and evaporated to dryness under reduced pressure, yielding 220 mg. of 5-cyclohexyl-4-pentene-2-one-1-oic acid.

On recrystallization from chloroform and petroleum ether the acid separated as clusters of colorless, long, rectangular platelets which melted at 93–94° and gave a red color with ferric chloride in alcoholic solution.

Anal. Calc'd for $C_{11}H_{16}O_3$: C, 67.3; H, 8.2.
Found: C, 67.1; H, 8.0.

The above acid was also obtained from the crystalline half ester (X) in a manner similar to that outlined above.

The acidic nature of the above compound was shown by titration with .01 *N* sodium hydroxide. One equivalent of alkali was absorbed immediately. Neutralization equivalent calc'd: 196; found: 199.

Action of acetic anhydride on 5-cyclohexyl-4-pentene-2-one-1-oic acid. The lactone (XI). A solution of 330 mg. of 5-cyclohexyl-4-pentene-2-one-1-oic acid in 5 cc. of redistilled acetic anhydride was refluxed for 2 hrs. The solvent was removed under reduced pressure and, on scratching, the tan residual gum crystallized. On recrystallization from petroleum ether, yellow rods were formed which melted at 87–88°. The yield was practically quantitative. The substance was neutral and did not give a ferric chloride test in alcoholic solution.

Anal. Calc'd for $C_{13}H_{18}O_4$: C, 65.5; H, 7.6.
Found: C, 65.5; H, 7.8.

Titration of the above compound with alkali indicated that it was an acetate of the enolic form of an α-keto lactone. With an excess of .01 *N* sodium hydroxide cold, one equivalent of alkali was absorbed after 3 hrs., showing the presence of a readily hydrolyzed lactone or ester linkage. Saponification equivalent calc'd for one hydrolyzable group: 238; found: 239, 234. With 0.1 *N* sodium hydroxide solution, on boiling for 30 min., two equivalents were absorbed. Saponification equivalent calc'd for two hydrolyzable groups: 119; found: 116.

3-Carboxy-5-cyclohexylpentane-2-ol-1-oic acid (V). The crude diester from 3 g. of the potassium salt of ethyl 3-carbethoxy-5-cyclohexyl-4-pentene-2-one-1-oate was reduced in absolute alcoholic solution in the presence of 150 mg. of Adams' platinum oxide catalyst, and 80% of the calculated amount for 2 moles of hydrogen was absorbed within an hour. The reduced ester was not isolated, but 1.5 g. of potassium hydroxide in 5 cc. of water was added to the alcoholic solution after filtration from the catalyst. The mixture was refluxed for 2 hrs., acidified with dilute hydrochloric acid, and most of the alcohol evaporated. Water was added, and the solution extracted with ether. The ethereal solution was extracted with sodium bicarbonate solution, the extracts acidified, and again extracted with ether. After drying and removal of the solvent, the substituted malic acid crystallized readily. On recrystallization from ethyl acetate and petroleum ether, clusters of colorless prisms were obtained which melted at 126–127°.

Anal. Calc'd for $C_{12}H_{20}O_5$: C, 58.9; H, 8.2.
Found: C, 58.9; H, 8.2.

The *di*-p-*bromophenacyl ester* of the above acid crystallized from alcohol as needles which melted at 143–144°. Mixtures of this ester with the ester prepared as subsequently described showed no depression in melting point.

Ethyl γ-cyclohexylbutyrate (VI). Reduction of 12.4 g. of ethyl γ-cyclohexylcrotonate in absolute alcoholic solution in the presence of 200 mg. of Adams' catalyst required 15 min. for the absorption of the calculated amount of hydrogen for one double bond. After filtering off the catalyst and evaporating the alcohol, 10.2 g. of ethyl γ-cyclohexylbutyrate was obtained, which distilled at 86–87° at 0.6 mm. It is a colorless oil with an odor reminiscent of ethyl γ-cyclohexylcrotonate; n_D^{25} 1.4482.

Anal. Calc'd for $C_{12}H_{22}O_2$: C, 72.7; H, 11.2.
Found: C, 72.5; H, 11.2.

Ethyl 3-carbethoxy-5-cyclohexylpentane-2-one-1-oate (VIII). This ester was prepared from ethyl oxalate and ethyl γ-cyclohexylbutyrate as described above for the corresponding unsaturated ester. The yield of crystalline, very pale yellow potassium salt was 30%. The free enol ester, obtained by hydrolysis of the potassium salt with ice-cold dilute hydrochloric acid, was an almost colorless oil which did not crystallize. It gave a purple color with ferric chloride in alcoholic solution.

The *2,4-dinitrophenylhydrazone* of the above ester was crystallized from alcohol or petroleum ether. It formed clusters of fine yellow needles which melted at 81–82.5°.

Anal. Calc'd for $C_{22}H_{30}N_4O_8$: C, 55.2; H, 6.3.
Found: C, 55.5; H, 6.3.

Reduction and hydrolysis of ethyl 3-carbethoxy-5-cyclohexylpentane-2-one-1-oate. The reduction and subsequent hydrolysis of the diethyl ester were carried out as described for the unsaturated ester (II). One molecular equivalent of hydrogen was absorbed. The diacid, on recrystallization from ethyl acetate and petroleum ether, formed long, colorless platelets which melted at 126–127°. Mixed melting points with the diacid prepared by the reduction and subsequent hydrolysis of the condensation product of diethyl oxalate and ethyl γ-cyclohexylcrotonate, showed no depression. The latter condensation, therefore, occurred in the α-position.

The *di*-p-*bromophenacyl ester* of the above acid recrystallized from alcohol as needles and melted at 143–144°.

Anal. Calc'd for $C_{28}H_{30}Br_2O_7$: C, 52.7; H, 4.7.
Found: C, 52.9; H, 4.8.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. Condensation of ethyl oxalate with ethyl γ-cyclohexylcrotonate has been shown to proceed on the α-carbon atom of the latter.

2. Generalizations have been formulated by which the products of the condensation of ethyl oxalate with γ-substituted $\Delta^{\alpha,\beta}$-crotonic esters, $\Delta^{\beta,\gamma}$-crotonic esters, and their vinylogs may be predicted.

3. A convenient method for the preparation of α-hydroxy-β-substituted succinic (substituted malic) acids, has been described.

4. A new substituted $\Delta^{\alpha,\beta}$-valerolactone has been prepared.

NEW YORK, N. Y.

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(6) LINSTEAD AND RYDON, *J. Chem. Soc.*, 580, (1933).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

REACTIONS OF PHENANTHRAQUINONE AND RETENEQUINONE WITH AMINES UNDER PRESSURE

GERALD M. JAFFE[1] AND ALLAN R. DAY

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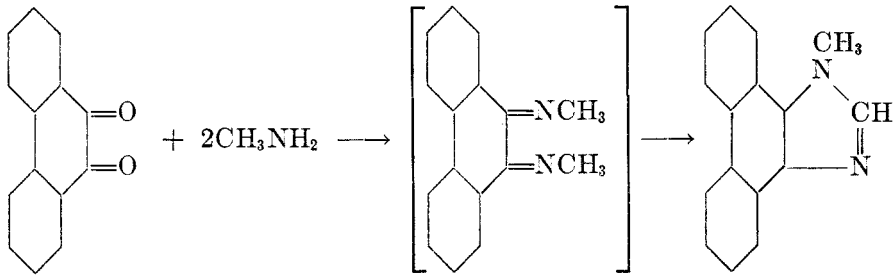
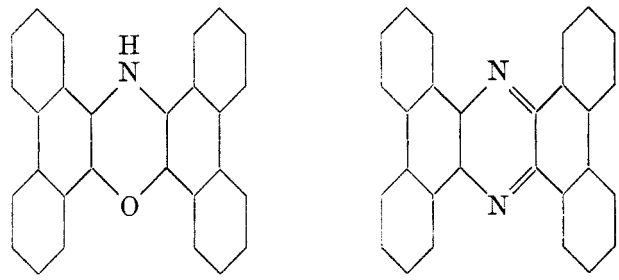
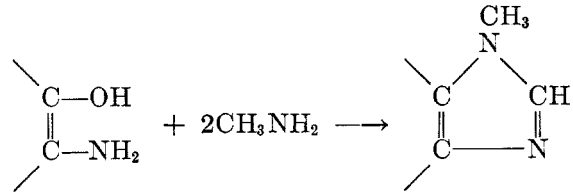
Zincke and Hof (1) first carried out a reaction between phenanthraquinone and methylamine under pressure, but were unable to formulate their products. Later Japp and Davidson (2) studied the same reaction and obtained 1-methylphenanthrimidazole.



However, when benzylamine was used, 2-phenylphenanthroxazole was isolated but no corresponding imidazole was found. In both cases, a mixture of the insoluble phenanthroxazine and phenanthrazine was reported.



Vahlen (3) prepared 1-methylphenanthrimidazole by the action of methylamine on 9,10-aminophenanthrol hydrochloride in the presence of sodium acetate and under pressure.



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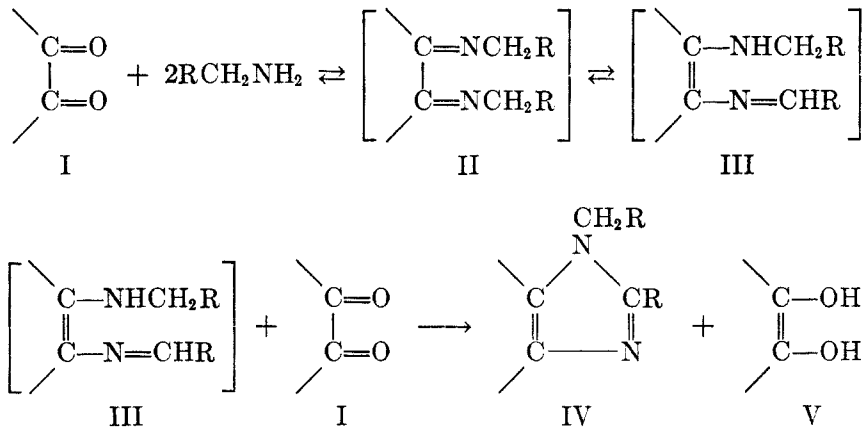
Pschorr (4) made a critical study of Vahlen's work and reported that the first stage of the reaction involved the splitting out of ammonia from the aminophenanthrol to form the hydroquinone. The latter then reacted with two equivalents of methylamine to form the imidazole. This does not appear to be a very logical explanation of the course of reaction.

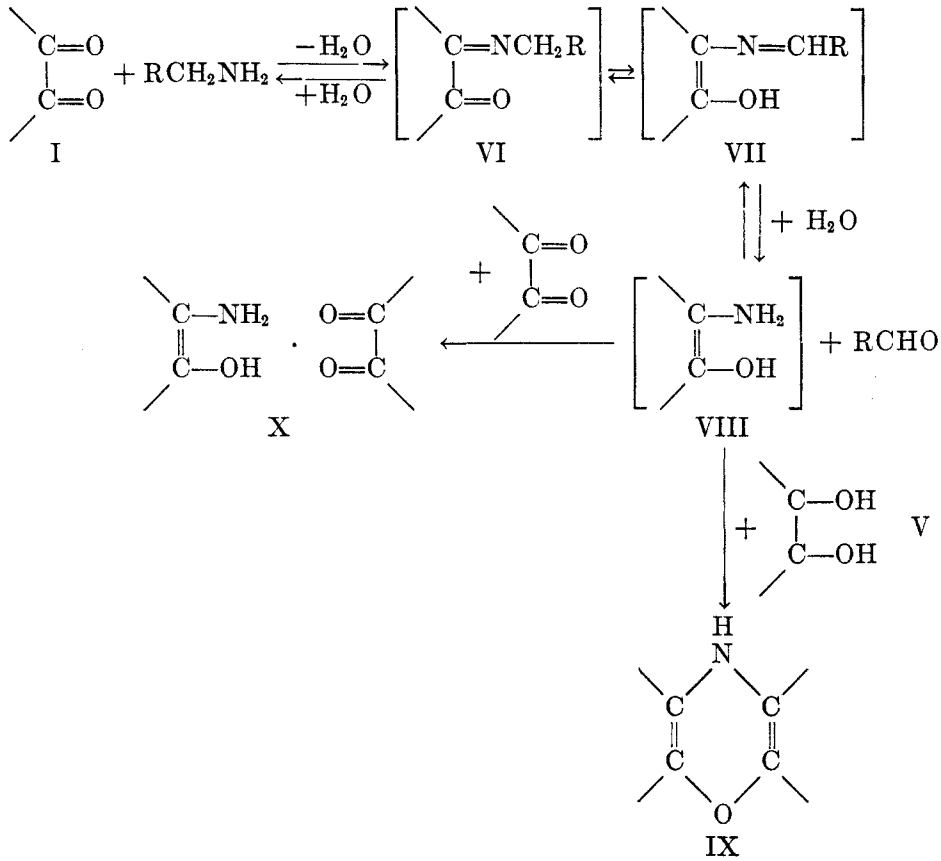
In view of the fact that it has been shown in this laboratory (5) that amines with two hydrogen atoms on the alpha carbon atom react with phenanthraquinone or retenequinone at atmospheric pressure to form the corresponding 2-substituted oxazoles, it appeared desirable to confirm and extend the findings of Japp and Davidson. This study was undertaken primarily to find some correlation between the variety of products formed and the course of reaction.

It has been found that the wholly aliphatic amines, methyl, ethyl, and *n*-butylamines gave similar results. Methylamine yielded 1-methylphenanthrimidazole, ethylamine gave 1-ethyl-2-methylphenanthrimidazole, and *n*-butylamine gave 1-butyl-2-*n*-propylphenanthrimidazole. These imidazoles were obtained in low yields due to the occurrence of side reactions. The imidazoles may be assumed to be formed by steps I–V:



The Schiff's base (III) could result from two hydrogen shifts in the two adjacent triad systems (6) of the N,N′-dialkylphenanthraquinone di-imine (II) formed by the interaction of phenanthraquinone (I) and two equivalents of the amine. The Schiff's base then undergoes an oxidative ring closure to the imidazole. This last step is similar to the reaction reported by Traube and Nithack (7). The latter workers used ferric chloride in the oxidative ring closure of 1,3-dimethyl-4-amino-5-benzalaminouracil to the corresponding imidazole.

Phenanthroxazine and a quinhydrone type of compound, involving 9,10-aminophenanthrol and phenanthraquinone, were isolated from all of the runs using aliphatic amines. These products may be assumed to result from the series of reactions, following.



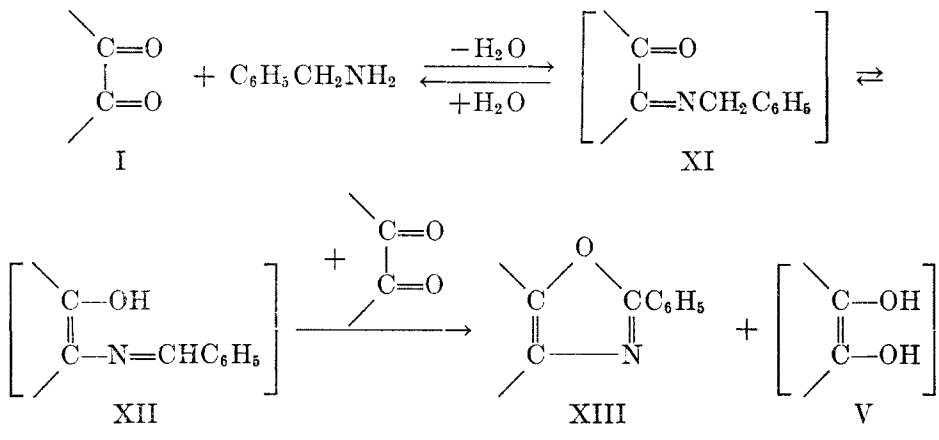
The formation of phenanthroxazine and the quinhydrone type of compound may be explained by the fact that the N-alkylphenanthraquinonimine (VI), the product of phenanthraquinone and one equivalent of amine, rearranges in part to the Schiff's base (VII) before the second equivalent of amine reacts with the other carbonyl group. Subsequent hydrolysis of the Schiff's base would yield 9,10-aminophenanthrol (VIII) and the latter could react with phenanthrahydroquinone (V) to form the oxazine (IX) or with phenanthraquinone (I) to form the quinhydrone compound (X).

In addition to the above reaction products, there was formed in every case a brown, difficultly soluble, amorphous compound which melted above 360°. De and Ghosh (8) reported phenanthroxazole and 2-methylphenanthroxazole to be brown, high-melting, insoluble, amorphous solids. They prepared them from the interaction of 9,10-aminophenanthrol with formic acid and acetic acid respectively. The nitrogen values for the brown compounds obtained in the present work agreed with those calculated for the corresponding 2-alkylphenanthroxazole, but the carbon and hydrogen values did not agree. It is very doubt-

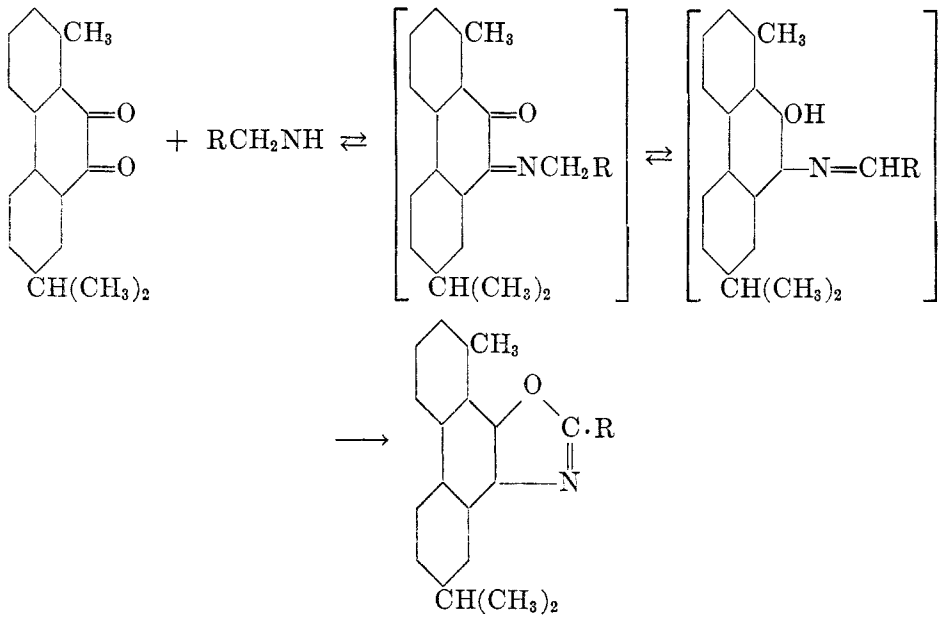
ful that the compounds reported by De and Ghosh were oxazoles, for one would expect 2-alkylphenanthroxazoles to be colorless, crystalline, low-melting solids. 2-*n*-Propylphenanthroxazole has been prepared by Stein and Day (9) and obtained as colorless needles, melting at 84–86°. This product was soluble in most organic solvents. These properties are quite different from those reported by De and Ghosh. It is not possible to assign formulas to these derivatives at the present time.

It may be noted at this point that no phenanthrazine was isolated from any of the experiments. This is contrary to the work of Japp and Davidson and it may be that the formation of the azine in their work was due to the presence of ammonia as an impurity in the amines used. This supposition is based on the work of Bamberger and Grob (10) and Foresti (11) who reported the formation of the azine by the action of ammonia on the corresponding oxazine.

The behavior of benzylamine with phenanthraquinone differed from that of the wholly aliphatic amines, for 2-phenylphenanthroxazole (XIII) was formed but no corresponding imidazole. The formation of the oxazole probably follows the same course of reaction as that suggested first by McCoy and Day (5):



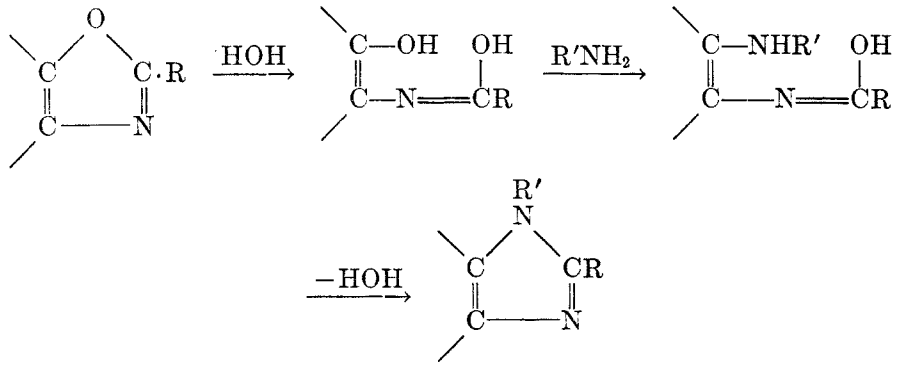
Apparently in this reaction there is a more rapid shift of the methylene hydrogen in XI due to the activating influence of the phenyl group, thus preventing the reaction between the second molecule of amine and the other carbonyl group. As a result, compound XII is rapidly oxidized to the oxazole by the phenanthraquinone. In these runs the second equivalent of amine was recovered almost quantitatively from the reaction mixtures. Phenanthroxazine (IX) and the quinhydrone (X) type of compound were also formed in this reaction. A course of reaction explaining the formation of these two products was suggested earlier in the paper. Evidence for this mechanism was obtained by the isolation and identification of benzaldehyde from the reaction mixture.



When retenequinone was used in place of the phenanthraquinone somewhat different results were obtained. Reactions were carried out under pressure using the same five amines but in no case could any imidazole be isolated, only oxazoles being obtained.

These results indicate steric hindrance in the retene molecule. This effect may be caused by the proximity of the methyl group to the 9 and 10 positions, which prevents a second molecule of the amine from reacting with the second carbonyl group. This hindrance is also indicated by the non-formation of retenoxazine and the corresponding quinhydrone type of compound.

The fact that the wholly aliphatic amines yield imidazoles with phenanthraquinone under pressure, but give only the corresponding oxazoles at atmospheric pressure (5), suggested another course of reaction for imidazole formation. For example, the oxazole may be formed first and then undergo an aminolysis, at the temperature and pressure used, to form the imidazoles.



Hence it became necessary to eliminate this possibility in order to establish the validity of the course of reaction previously suggested.

The investigations of Sircar and his associates (12) indicated that the course of the reaction with phenanthraquinone or acenaphthoquinone, aromatic aldehydes, and ammonia depended primarily on the temperature at which the reactions were carried out. At higher temperatures, imidazole formations usually predominated and at lower temperatures, oxazole formation predominated. The assumption that oxazoles were formed first and imidazoles resulted from the ammonolysis of the oxazoles, however, was not experimentally demonstrated by these workers.

The assumption that imidazoles may be formed through the ammonolysis of oxazoles was tested by Kreps and Day (13). They subjected 2-phenylretenoxazole and concentrated aqueous ammonia to a temperature of 170–180° and a pressure of five hundred pounds for forty-nine hours, but observed no conversion to the corresponding imidazole. Similar results were obtained with 2-(2′-hydroxyphenyl)retenoxazole. However, this work can not be assumed to apply to the unsubstituted phenanthrene series, for it has been shown in the course of the present work that where phenanthraquinone reacted to form 1,2-disubstituted phenanthrimidazoles, retenequinone formed only oxazoles. Consequently, if oxazoles can be converted into imidazoles it would not be expected in the retene series, because of a probable steric hindrance effect which prevents the formation of imidazoles.

Similar results were obtained in the present study when attempts were made to convert 2-phenylphenanthroxazole and 2-(2′-hydroxyphenyl)phenanthroxazole to imidazoles. The oxazoles were treated with ammonia or methylamine, under various conditions of temperature and pressure, but no conversion to imidazole was noted. Even the addition of sodium hydroxide to these mixtures failed to cleave the oxazole ring. It would appear, therefore, that oxazoles can not be regarded as intermediates in the formation of imidazoles, in the phenanthrene and retene series. This conclusion can not be applied to benzoxazoles and naphthoxazoles, for there is evidence (14) that the oxazole ring in these compounds may be readily cleaved.

EXPERIMENTAL

Analysis and melting points. The semi-micro Kjeldahl method was used for the nitrogen determinations and the semi-micro combustion method was used for carbon and hydrogen. The recorded melting points are corrected values.

Molecular weights. The Rast method of determining molecular weights by the depression of the m.p. of *d*-camphor, triphenylmethane, or naphthalene was used according to the directions of Shriner and Fuson (15).

Phenanthraquinone. It was prepared by the chromic acid oxidation of phenanthrene (technical grade) in glacial acetic acid (16). The crude product was purified by the bisulfite method of Courtot (17) and finally recrystallized from 50% acetic acid, yield 60%, m.p. 208–209.5°.

Retenequinone. Retenequinone was prepared by the method of Kreps and Day (13). It was recrystallized from chloroform, yield 50%, m.p. 197–199°.

Reactions of phenanthraquinone with amines. Preliminary work showed that where these reactions were carried out at temperatures higher than 100°, the imidazoles were formed in lower yields, and larger amounts of intractable gums were obtained.

I. With methylamine. Eight grams (0.0385 mole) of phenanthraquinone, 3.1 g. (0.1 mole) of methylamine and 25 cc. of benzene were heated under pressure for 6 hours at 100°. The reaction mixture was extracted with hot benzene, leaving 0.30 g. of a brown solid. The latter on recrystallization from nitrobenzene gave green, micro crystals of phenanthroxazine, m.p. above 360°.

Anal. Calc'd for $C_{28}H_{17}NO$: N, 3.94. Found: N, 3.86.

The benzene extract was evaporated and the residue extracted with hydrochloric acid. The brown, gummy solid, left after the acid extraction, was washed thoroughly with alcohol and refluxed with ethyl acetate. The hot mixture was filtered to remove a small amount of brown powder. The addition of alcohol to the filtrate precipitated 0.5 g. of yellow, micro crystals of the quinhydrone type of compound, formed from 9,10-aminophenanthrol and phenanthraquinone. The product melts with decomposition over a wide range, 150–214°. On oxidation with chromic acid, phenanthraquinone was obtained as the sole product.

Anal. Calc'd for $C_{28}H_{19}NO_3$: C, 80.57; H, 4.55; N, 3.36, Mol. wt., 417.
Found: C, 80.82; H, 4.74; N, 3.53, Mol. wt., 407.

The brown residue remaining after the ethyl acetate extraction could not be identified. The analytical values for carbon, hydrogen, and nitrogen did not agree with any probable formula.

The hydrochloric acid extract, from above, on neutralization with sodium bicarbonate yielded 5.65 g. (63%) of crude 1-methylphenanthrimidazole. It was recrystallized from alcohol with the aid of Darco, m.p. 196°, picrate m.p. 288–289°.

Anal. Calc'd for $C_{16}H_{12}N_2$: N, 12.07. Found: N, 11.87.

II. With ethylamine. A mixture of 6.24 g. (0.03 mole) of phenanthraquinone, 2.93 g. (0.065 mole) of ethylamine, and 33.5 g. of benzene was heated under pressure at 100° for 6 hours. The reaction mixture was worked up by the method described under methylamine. The following products were isolated: phenanthroxazine, m.p. above 360° (*Anal.* Calc'd for $C_{28}H_{17}NO$: N, 3.94. Found: N, 3.82); quinhydrone type compound (*Anal.* Calc'd for $C_{28}H_{19}NO_3$: N, 3.36. Found: N, 3.28); and a 5.4% yield of 1-ethyl-2-methylphenanthrimidazole. The latter was purified by recrystallization from alcohol, with the aid of Darco, m.p. 193.5–194.5°, picrate m.p. 222–242° (decomp.).

Anal. Calc'd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.77.
Found: C, 82.70; H, 6.13; N, 10.72.

III. With n-*butylamine.* A mixture of 6.24 g. (0.03 mole) of phenanthraquinone, 4.95 g. (0.065 mole) of *n*-butylamine and 35 cc. of benzene was heated under pressure at 100° for 6 hours. The reaction mixture was worked up by the procedure described previously and the following products isolated: phenanthroxazine (0.31 g.); quinhydrone type compound 0.11 g. (*Anal.* Calc'd for $C_{28}H_{19}NO_3$: N, 3.36. Found: 3.25); and a 2% yield of 1-*n*-butyl-2-*n*-propylphenanthrimidazole. The latter was recrystallized from alcohol, with the aid of Darco, m.p. 59–62°, picrate m.p. 199–200°.

Anal. Calc'd for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.68.
Found: C, 83.33; H, 7.75; N, 8.67.

IV. With benzylamine. A mixture of 6.24 g. (0.03 mole) of phenanthraquinone, 6.42 g. (0.06 mole) of benzylamine and 25 cc. of benzene was heated under pressure at 100° for 6 hours. The reaction mixture was extracted with boiling benzene, leaving 2 g. of a dark yellow powder, consisting of a mixture of phenanthroxazine and the quinhydrone type compound. The quinhydrone was removed by extraction with dioxane, and the residue on recrystallization from nitrobenzene yielded 1.25 g. of the oxazine, m.p. above 360°.

Anal. Calc'd for $C_{28}H_{17}NO$: N, 3.94. Found: N, 3.96.

The dioxane extract was concentrated and a little alcohol added to precipitate the yellow, micro crystals of the quinhydrone type compound, yield 0.5 g., m.p. 150–192° (decomp.).

Anal. Calc'd for $C_{28}H_{19}NO_3$: N, 3.36. Found: 3.11.

The benzene extract from above was evaporated until crystals of 2-phenylphenanthroxazole began to separate. After cooling, the crude oxazole was removed by filtration, yield 4.5 g. (51%). It was purified by recrystallization from a mixture of dry alcohol and benzene (3:1), with the aid of Darco, m.p. 206.5–207°. The pure product gave no depression in a mixed melting point determination with an authentic sample.

The benzene filtrate from the oxazole was evaporated to dryness and the gummy residue extracted with hydrochloric acid. The acid extract on evaporation yielded only benzylamine hydrochloride. The residue from the acid extraction was dissolved in alcohol and treated with semicarbazide hydrochloride and sodium acetate. The precipitate obtained from this reaction proved to be benzaldehyde semicarbazone, m.p. 217–218°.

Reactions of retenequinone with amines. I. With methylamine. A mixture of 2.64 g. (0.01 mole) of retenequinone, 0.80 g. (0.026 mole) of methylamine and 35 cc. of benzene was heated under pressure at 100° for 3 hours. The reaction mixture was extracted with hot benzene and filtered to remove a trace of a gummy solid. The benzene extract was evaporated to dryness and the residue extracted with methyl alcohol. Evaporation of the alcohol gave 0.92 g. (33% yield) of 2-methylretenoxazole. It was recrystallized from methyl alcohol with the aid of Darco, colorless needles, m.p. 108°. No imidazole could be isolated.

Anal. Calc'd for $C_{19}H_{17}NO$: C, 82.95; H, 6.23; N, 5.09.
Found: C, 82.78; H, 6.37; N, 4.91.

II. With ethylamine. The above procedure, using ethylamine in place of methylamine, gave 2.15 g. (74.5% yield) of 2-ethylretenoxazole. The crude product was recrystallized from ethyl alcohol, with the aid of Darco, colorless needles, m.p. 127.5–128.5°.

Anal. Calc'd for $C_{20}H_{19}NO$: C, 83.08; H, 6.63; N, 4.82.
Found: C, 82.87; H, 6.73; N, 4.88.

III. With n-*butylamine.* The above procedure, using *n*-butylamine in place of methylamine, gave 2.1 g. (66% yield) of 2-propylretenoxazole. It was recrystallized from ethyl alcohol with the aid of Darco, m.p. 100–101.5°. This value agrees with the m.p. reported by Stein and Day (9). A mixed m.p. determination gave no depression.

IV. With benzylamine. Five grams (0.019 mole) of retenequinone, 4.10 g. (0.038 mole) of benzylamine, and 15 cc. of dry alcohol were heated at 100° for 6 hours under pressure. The reaction mixture was digested with dry alcohol and filtered. Concentration of the filtrate yielded 2.66 g. (40%) of 2-phenylretenoxazole. It was recrystallized from ethyl alcohol, m.p. 172°. The m.p. agrees with the value reported by Kreps and Day (13).

Attempts to convert phenanthroxazoles to phenanthrimidazoles by aminolysis. I. 2-Phenylphenanthroxazole. (a) In boiling p-*cymene.* One gram of the oxazole was dissolved in *p*-cymene and ammonia passed through the refluxing solution for 4 hours. Evaporation of the solution gave a quantitative recovery of the starting compound, m.p. 206.5–207°.

(*b*) *In the presence of sodium hydroxide.* A solution containing 1.48 g. of 2-phenylphenanthroxazole and 0.25 g. of sodium hydroxide in 100 cc. of alcohol was refluxed for 7 hours while ammonia was passed through the solution. Evaporation of the solution gave a quantitative recovery of the oxazole, m.p. 206.5–207°.

(*c*) *With methylamine under pressure.* Two grams (0.00678 mole) of 2-phenylphenanthroxazole, 0.25 g. (0.00807 mole) of methylamine, and 30 cc. of absolute alcohol were heated at 100° for 6 hours under pressure. The starting material was recovered almost quantitatively, m.p. 205–206°.

II. 2-(2′-Hydroxyphenyl)phenanthroxazole. This compound was prepared by the method of Stein and Day (9). It was recrystallized from pyridine, m.p. 243–243.5°. (*a*) *In alcoholic solution.* A sample (0.50 g.) of 2-(2′-hydroxyphenyl)phenanthroxazole was refluxed in 100 cc. of dry alcohol for 2.5 hours while ammonia was passed through the suspension. On cooling, the starting material was recovered quantitatively, m.p. 243–243.5°.

(*b*) *In the presence of sodium hydroxide.* A solution of 0.50 g. (0.00161 mole) of 2-(2′-hydroxyphenyl)phenanthroxazole and 0.13 g. (0.00322 mole) of sodium hydroxide in 100 cc. of alcohol and 10 cc. of water was refluxed for 4 hours while ammonia was passed through the

solution. Neutralization of the solution with dilute hydrochloric acid yielded 0.48 g. of the starting oxazole, m.p. 243–243.5°.

(*c*) *With ammonium hydroxide under pressure.* A mixture of 0.78 g. of 2-(2′-hydroxyphenyl)phenanthroxazole and 25 cc. of concentrated ammonium hydroxide was heated at 100° for 5 hours under a pressure of 130 lbs. At the end of this period, the solid was washed with water and recrystallized from pyridine, m.p. 243–243.5°. The recovery of starting material was quantitative.

A similar run was carried out at 200° and 550 lbs. pressure. Some oxazole was recovered together with decomposition products, but no conversion to imidazole was noted.

SUMMARY

1. The interaction of primary amines with phenanthraquinone under pressure has been studied. The wholly aliphatic amines gave 1,2-disubstituted phenanthrimidazoles, whereas benzylamine yielded only 2-phenylphenanthroxazole. By-products of each reaction were phenanthroxazine and a quinhydrone type compound of 9,10-aminophenanthrol and phenanthraquinone. A mechanism has been postulated for the formation of these compounds.

2. The reaction of retenequinone and primary amines under pressure has been studied. The only product isolated in each case was the corresponding 2-substituted retenoxazole.

3. 2-Arylphenanthroxazoles were subjected to aminolysis and simultaneous hydrolysis and aminolysis. No conversion to imidazole was obtained, thus eliminating the possibility of intermediate oxazole formation in the preparation of imidazoles.

PHILADELPHIA, PA.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CINCINNATI]

POLYNITRO COMPOUNDS OF FLUORENE

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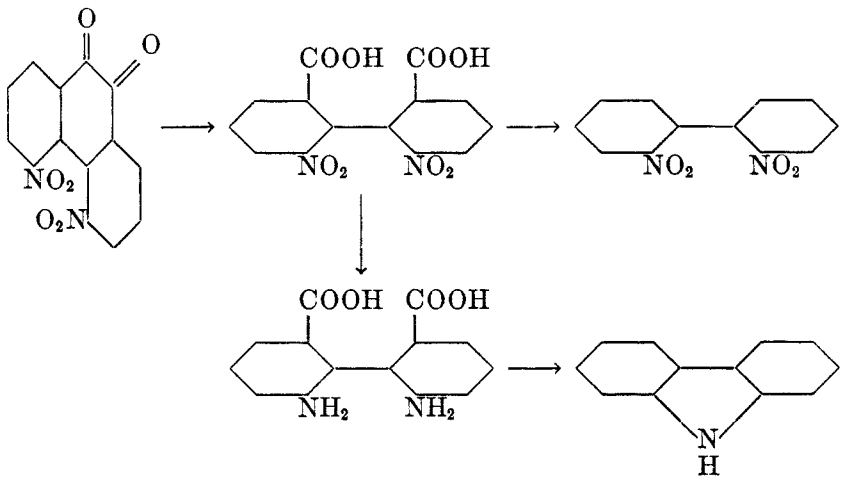
Schmidt and Bauer (1) reported the preparation of 4,5-dinitrofluorenone from 4,5-dinitrophenanthrenequinone and characterized it as *not melting at 350°*. The oxime melted at 267–268°, the phenylhydrazone melted at 244° (dec.), and the semicarbazone melted at 238° (dec.).

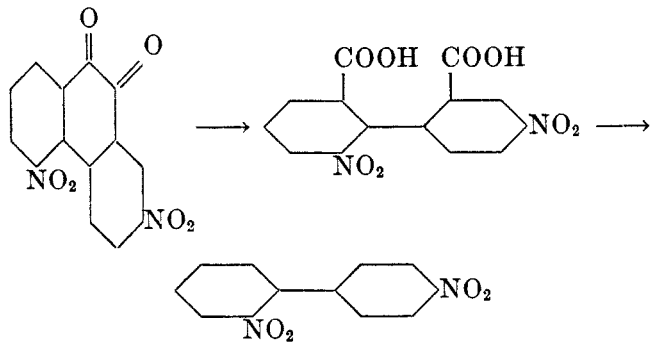
The structure of 4,5-dinitrofluorenone depends on the structure of the corresponding 4,5-dinitrophenanthrenequinone. Schmidt and Kämpf (2) claimed that they had converted the latter to "*beta*-dinitrodiphenic acid" (3) which was in turn converted into 2,2′-dinitrobiphenyl. They also claimed to have obtained carbazole in rather good yield by distillation of the barium salt of "*beta*-diaminodiphenic acid."



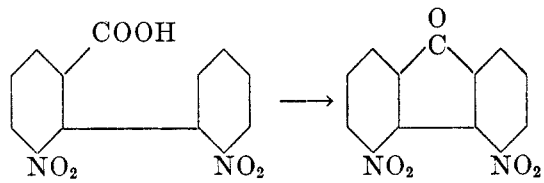
In repeating Schmidt and Bauer's alleged preparation of 4,5-dinitrofluorenone we obtained 2,5-dinitrofluorenone (m.p. 241°), the oxime of which melted at 265° (S. and B., 267–268°), and the phenylhydrazone at 237–241° (S. and B., 241°). Further purification of the latter raised the melting point of the phenylhydrazone to 252–253°.

The literature revealed that Schmidt and Kämpf had reported that when their supposed 4,5-dinitrophenanthrenequinone was mixed with sand and distilled at 300° under reduced pressure, 2,2′-dinitrobiphenyl was produced, together with a small quantity of a sparingly soluble compound melting at 240°. These workers mentioned that this latter product was very probably a dinitrofluorenone. If they had really been using 4,5-dinitrophenanthrenequinone the dinitrofluorenone obtained should have been the 4,5 compound which Schmidt and Bauer (1) had previously claimed did not melt even at 350°. Schmidt apparently did not notice this discrepancy.

Additional evidence which confirms our identification of this compound as 2,5-dinitrofluorenone is found in the work of Kenner and Stubbings (4), Christie and Kenner (5), and Christie, Holderness, and Kenner (6). In 1926 Christie and Kenner, while attempting to obtain a tetranitration product of phenanthrenequinone, found that the same trinitrophenanthrenequinone, melting point 209°, could be obtained from both 2,7-dinitrophenanthrenequinone and Schmidt and Kämpf's (2) alleged 4,5-dinitrophenanthrenequinone. Oxidation of the trinitrophenanthrenequinone to the corresponding trinitrodiphenic acid, in each case, revealed on resolution into optically active forms by fractional crystallization of the quinidine and of the quinine salts a very close correspondence between the physical constants of the various salts. This was further confirmed by mixed melting points between the two diphenic acids, as well as between the quinoxaline derivatives of the trinitroquinones prepared from the two different dinitroquinones. These results caused Christie, Holderness, and Kenner (6) to reinvestigate the "*beta*-acid" of Schultz (3). The outcome of their experiments led them to believe that it was not 6,6′-dinitrodiphenic acid, but rather 4,6′-dinitrodiphenic acid. Consequently the dinitrophenanthrenequinone from which this "*beta*-acid" was derived must be 2,5-dinitrophenanthrenequinone. This may best be shown by the following series of reactions.



The actual 4,5-dinitrofluorenone being, therefore, unknown, we decided to synthesize it by a method leaving no doubt as to its structure. This we were able to accomplish by heating 2,2′-dinitro-6-carboxybiphenyl (7) with concentrated sulfuric acid.

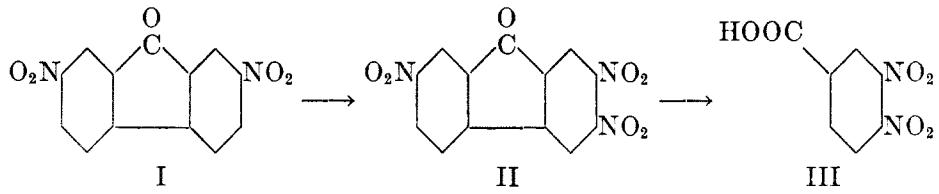


4,5-Dinitrofluorenone
VIII

The resulting 4,5-dinitrofluorenone melted sharply at 273.5°. We must conclude, therefore, that this is the first preparation of 4,5-dinitrofluorenone, VIII.

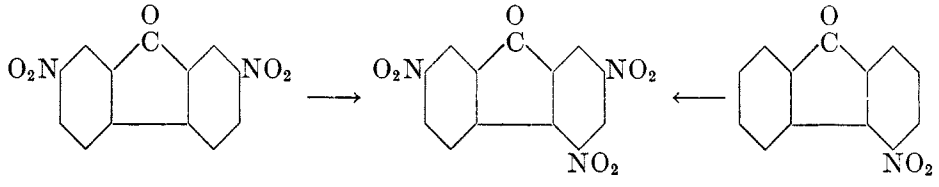
2,4,7-TRINITROFLUORENONE AND 2,4,5,7-TETRANITROFLUORENONE

In 1905 Schmidt and Bauer (8) reported the preparation of a trinitrofluorenone, melting at 180–181°, by boiling fluorenone with fuming nitric acid. The structure assigned to it was based on two facts, namely, that it could be obtained by the nitration of 2,7-dinitrofluorenone, I, and that it could be oxidized with acid permanganate to 3,4-dinitrobenzoic acid, m.p. 165°, III. As a result of these data they assigned to it the structure 2,6,7-(or 2,3,7-)trinitrofluorenone, II.



I II III

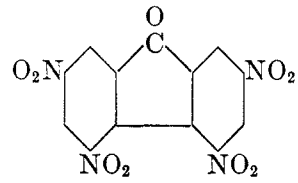
Bell (9) was led to reinvestigate this compound for the following reasons: (a) It is unusual for a nitro group to go ortho to another nitro group rather than meta. (b) It is unusual in view of the observation of Morgan and Thomason (10), namely, that the second nitro group is directed by the phenylene radical, thus directing nitration to the ortho and para positions, *i.e.*, positions 5 and 7. Consequently, since two of the nitro groups were known to occupy the 2,7 positions, it would seem logical for the third nitro group to occupy the 4 position, *i.e.*, the position ortho to the phenylene linkage. Bell (9), therefore, dinitrated 4-nitrofluorenone, V, and obtained a compound which did not differ from that derived from the 2,7-dinitrofluorenone. Its melting point (176°), however, differed from that reported by Schmidt and Bauer (180°). Oxidation gave a product melting between 165–170°. Bell, therefore, concluded that this product could not be 3,4-dinitrobenzoic acid, m.p. 164–165°, since recrystallization of his impure material should raise its melting point. Although this reasoning is not very conclusive, the synthesis from both 2,7-dinitrofluorenone and 4-nitrofluorenone establishes the trinitro compound as 2,4,7-trinitrofluorenone, IV.



I IV V

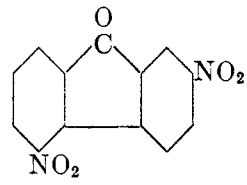
A tetranitro compound of fluorenone was prepared by Schmidt, Retzlaff, and Haid (11) in 1912 by vigorous nitration of fluorenone as well as by the further nitration of the trinitrofluorenone of Schmidt and Bauer (8). To the tetranitration product thus obtained was assigned the structure 2,3,6,7-tetranitrofluorenone. However, in view of the evidence presented by Bell for

the structure of the trinitrofluorenone it would seem reasonable to expect that the tetranitro compound would have the structure 2,4,5,7-tetranitrofluorenone, VI. Even if Bell's work is accepted as conclusive, only the 2,4,7-positions in this compound would be settled.

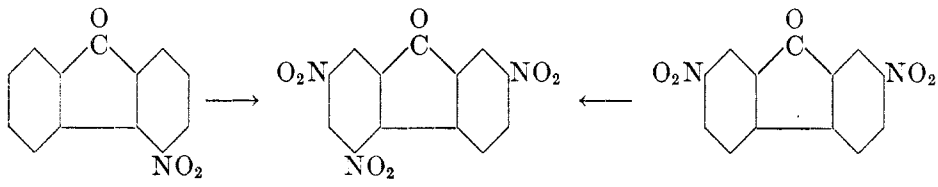


VI

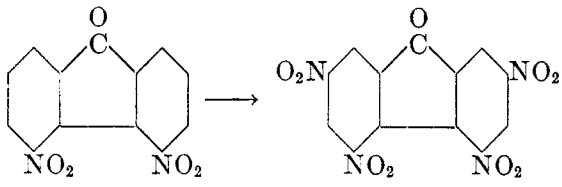
In the present work it was decided to prepare the trinitrofluorenone by an entirely new synthesis from 2,5-dinitrofluorenone, VII.



VII



V IV I



VIII VI

The identical trinitro compound was obtained by us from both 2,5- and 2,7-dinitrofluorenone, thus verifying conclusively the structure assigned to the trinitrofluorenone by Bell. The same melting point (176°) was obtained for

this product by both methods. This agrees with Bell's value (176°) rather than with Schmidt's value (180–181°).

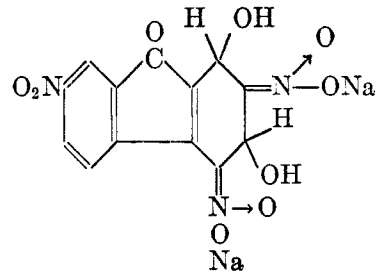
Oxidation of 2,4,7-trinitrofluorenone could not possibly give rise to the dinitrobenzoic acid reported by Schmidt and Bauer unless very deep-seated changes had occurred. A trial oxidation of the trinitrofluorenone, using the exact conditions specified by Schmidt and Bauer, gave, after removal of the manganese dioxide residue, a product melting at 155°. We were led to try mixed melting points with some of the crude original 2,4,7-trinitrofluorenone melting at 163–165°, because of the marked similarity of the two substances in appearance. Instead of a depression of the melting point, which would have been expected if the oxidation product were a dinitrobenzoic acid, the mixture melted at 160–162°.

A recheck of the analytical data given by Schmidt and Bauer showed that the percentage compositions for nitrogen in the trinitrofluorenone and in their reported dinitrobenzoic acid were within 0.1 of each other. It must be concluded, therefore, that these investigators were working with the original trinitrofluorenone rather than with the supposed 3,4-dinitrobenzoic acid. This conclusion also offers a plausible explanation for the results obtained by Bell on oxidation of his trinitro compound. The fact that he obtained a product melting at 165–170°, on the oxidation of his trinitrofluorenone of m.p. 176°, makes the aforementioned conclusion seem even more inevitable.

Because the trinitro compound resisted oxidation with acid permanganate it was decided to oxidize it with permanganate in pyridine solution. The resulting product was a black tarry material of an acidic nature. A second attempt was made using Caro's acid (12), but the original material was recovered unchanged. The difficulty experienced in trying to oxidize the trinitro compound in the presence of acid indicates that it is remarkably stable to oxidation under these conditions.

The fact that alkaline permanganate oxidation of this compound gives for the most part a tar, indicates that the trinitrofluorenone is changed remarkably by such conditions. This is further borne out if attention is paid to the effect of alkali alone upon the trinitro compound; thus when it was treated with alkali, solution occurred. A light brown color developed, which became progressively darker as more material dissolved and a deep chocolate brown solution was finally attained. Heating hastened the formation of the brown color. Neutralization with acid caused a light yellow precipitate to form. In view of these properties it is not too difficult to see how Schmidt and Bauer were misled into thinking that the oxidation product was a dinitrobenzoic acid.

The color changes brought about by the action of alkali on 2,4,7-trinitrofluorenone are remarkably similar to those which have been noted to occur with sodium nitrophenoxides. Davis and Richmond (13) have proposed an hypothesis which assigns hydrated quinoid structures to the *o*-, *m*-, and *p*-nitrophenoxide ions, which is, at the same time, in harmony with the known facts concerning *m*-quinone and the oxidation of *m*-diphenols. Reasoning by analogy the following structure, IX, may be written.



IX

As 2,4-dinitrofluorenone is also soluble in alkali, but neither the 2,7- nor the 4,5-dinitrofluorenones dissolve, it is clear that the two nitro groups must be in the same ring to react with alkali.

The trinitro compound from which the tetranitrofluorenone was prepared has its three nitro groups located in the 2,4,7 positions. It follows, therefore, that the resulting tetranitrofluorenone also has three of its nitro groups in these positions. The fourth nitro group should be expected to occupy the 5 position. No proof of this has been presented thus far, hence we decided to follow Ray and Rieveschl's suggestion (14) and attempt to synthesize it from 4,5-dinitrofluorenone, VIII. This we accomplished. The tetranitrofluorenone thus obtained melted at 252–253°, whereas that reported by Schmidt and co-workers melted at 248–249°. When we prepared it from the trinitro compound it first melted at 248–249°, but recrystallization from acetic anhydride gave a product which melted at 252–253°. No depression of the melting point was observed when the two different preparations were mixed, hence we must conclude that the remaining nitro group occupies the 5 position and, consequently, that the tetranitrofluorenone possesses the structure 2,4,5,7-tetranitrofluorenone, VI.

EXPERIMENTAL PART

Conversion of 2,5-dinitrophenanthrenequinone to 2,5-dinitrofluorenone. Two hundred cubic centimeters of 10% potassium hydroxide solution was heated to boiling on a hot-plate and 10 g. of potassium permanganate added while stirring mechanically. To this solution was added slowly 2 g. of 2,5-dinitrophenanthrequinone. Stirring and heating was continued for 20 minutes. About 0.5 cc. of 95% alcohol was added cautiously, to decompose the excess potassium permanganate. This hot mixture was allowed to cool and was then filtered. Digestion of the insoluble residue containing manganese dioxide with excess hydrochloric acid gave 1.3 g. of a pale yellow, granular product, m.p. 240–245°. Recrystallization from glacial acetic acid gave fine, yellow needles melting at 243°. A mixed melting point with authentic 2,5-dinitrofluorenone (10), m.p. 241°, gave no depression of the melting point.

From the filtrate, on acidification, we obtained 0.2 g. of 4,6′-dinitrodiphenic acid, m.p. 306–307°. The literature gives the melting point as 303° (6, 3).

Oxime of 2,5-dinitrofluorenone. This was obtained by refluxing 0.3 g. of the ketone, suspended in alcohol, with a concentrated aqueous solution containing 0.2 g. of hydroxylamine hydrochloride for one and one-half hours on the water-bath. The crude product melted at 261°. Several recrystallizations from alcohol caused it to melt at 265°. This agrees with Schmidt and Bauer's (1) value.

Phenylhydrazone of 2,5-dinitrofluorenone. Three-tenths of a gram of this ketone was

suspended in 20 cc. of alcohol and refluxed on the water-bath, for 1.5 hours with 0.15 g. of phenylhydrazine hydrochloride. Red needles melting at 220–224° were obtained. Recrystallization from glacial acetic acid caused it to melt at 252–253° (dec.). Evaporation of the original mother liquor gave a product which after one recrystallization from glacial acetic acid melted at 241°. This agrees with the value obtained for the phenylhydrazone of Schmidt's supposed 4,5-dinitrofluorenone.

2,2'-Dinitro-6-carboxybiphenyl was prepared by the method of Adams and Hale (7).

4,5-Dinitrofluorenone. Seven-tenths gram of 2,2'-dinitro-6-carboxybiphenyl and 3 cc. of concentrated sulfuric acid were maintained at 190 ± 5° for 10 minutes. On cooling, the dark reaction product was poured into cold water and filtered with suction. The dark colored, powdery product was boiled with glacial acetic acid and Darco carbon for 15 minutes and filtered hot. The filtrate on cooling gave long, slender, orange needles, m.p. 273.5°. Concentration of the mother liquor gave another crop of the same material, m.p. 272–273°; the over-all yield was 0.236 g.

Anal. Calc'd for $C_{13}H_6N_2O_5$: C, 57.78; H, 2.22; N, 10.37.
Found: C, 57.54, 57. 77; H, 2.77, 2.75; N, 10.50, 10.32.

2,4,7-Trinitrofluorenone was prepared from 2,7-dinitrofluorenone (10) according to the method of Schmidt and Bauer (1). Recrystallization from glacial acetic acid gave orange-yellow needles, m.p. 176°.

Anal. Calc'd for $C_{13}H_5N_3O_7$: N, 13.38. Found: N, 13.35, 13.25.

2,4,7-Trinitrofluorenone was also prepared from 7.1 g. of 2,5-dinitrofluorenone (10), which was nitrated in the same manner as 2,7-dinitrofluorenone. The yield of crude material was 6.8 g., m.p. 167–170°. Purification yielded 3.2 g. of a product melting at 174–175°. The mixed melting point with the product obtained from 2,7-dinitrofluorenone was 175.5°. One recrystallization of the product melting at 174–175° was accomplished from benzene by the dropwise addition of ligroin. The trinitrofluorenone thus obtained melted sharply at 175°.

Attempted oxidation of 2,4,7-trinitrofluorenone with acid permanganate. Two grams of crude 2,4,7-trinitrofluorenone (m.p. 163–165°) was finely mixed with 5 cc. of concentrated sulfuric acid in a mortar and then gradually diluted with 100 cc. of water, so that a thin paste resulted. To this hot, mechanically stirred mixture was added, over a period of two hours, a solution of 5 g. of potassium permanganate in 500 cc. of water. Refluxing was continued for an additional two hours and the mixture was filtered hot. The clear filtrate deposited a flocculent yellow precipitate, m.p. 155°. Mixture with the original material raised the melting point to 160–162°. In alkali it gave a brown solution identical with that of pure 2,4,7-trinitrofluorenone.

2,4,5,7-Tetranitrofluorenone. We were unable to prepare the desired tetranitrofluorenone from 2,4,7-trinitrofluorenone in any degree of purity using the directions of Schmidt, Retzlaff, and Haid (11), but the following procedure was found to give satisfactory results. Five grams of the trinitrofluorenone, m.p. 175°, was added to a mixture of 60 cc. of fuming nitric acid (sp. g. 1.59–1.60) and 70 cc. of concentrated sulfuric acid and allowed to reflux for five hours. The reaction mixture, on cooling, was poured into 1500 cc. of water and allowed to stand for two hours. The flocculent precipitate was washed well with water. It melted at 235–240°. Recrystallization from 90 cc. of glacial acetic acid gave 3.0 g. of fine yellow needles, m.p. 248–249°. Recrystallization of this product from acetic anhydride caused it to melt at 252–253°.

Anal. Calc'd for $C_{13}H_4N_4O_9$: N, 15.55. Found: N, 15.57, 15.52.

2,4,5,7-Tetranitrofluorenone. 4,5-Dinitrofluorenone (0.112 g.) was added to a mixture of 24 cc. of red fuming nitric acid (sp. g. 1.59–1.60) and 25 cc. of concentrated sulfuric acid and refluxed for four hours. On cooling, the reaction mixture was poured into 350 cc. of cold water. The flocculent yellow material was collected at the pump and dried. It melted at 250–252° and weighed 0.108 g. One recrystallization from glacial acetic acid caused it to melt at 252–253°. No depression of the melting point was observed when the substance was mixed with the tetranitrofluorenone derived from 2,4,7-trinitrofluorenone.

It is moderately soluble in glacial acetic acid and acetic anhydride. It is somewhat more soluble in dioxane. It appears to react with tetrahydronaphthalene to give a red addition compound.

ACKNOWLEDGMENT

We wish to express our thanks to the Barrett Co. for their assistance in this research.

SUMMARY

A synthesis and proof of structure for the previously unknown 4,5-dinitrofluorenone has been effected.

The preparation of 2,4,5,7-tetranitrofluorenone from 4,5- and 2,7-dinitrofluorenones has determined its structure.

The structure of 2,4,7-trinitrofluorenone has been confirmed.

The supposed 4,5-dinitrophenanthrenequinone of Schmidt and Bauer has been shown to be in reality 2,5-dinitrophenanthrenequinone by its conversion to 2,5-dinitrofluorenone.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

THE ADDITION OF TRIPHENYLMETHYLSODIUM AND PHENYLLITHIUM TO CINNAMIC ESTER AND BENZALACETOPHENONE

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Although the addition of diphenylmethylsodium to methyl cinnamate and to benzalacetophenone was carried out by Bergmann (1), no mention appears in the literature of the reaction of triphenylmethylsodium with these conjugated systems. Such addition was found to occur, leading to the formation of compounds hitherto unreported in the literature. The yields, however, are not very high, varying from 25% to 35%, as considerable polymerization with the formation of tars seems to occur. The reactions must be carried out at low temperatures in complete absence of any moisture or enolizable hydrogen, to obtain the addition product. These conditions account for the non-mention of our products by Hauser and Abramovitch (2), who carried out experiments with triphenylmethylsodium in the presence of both methyl cinnamate and benzalacetophenone. In their studies, however, either ethyl acetate or ethyl isobutyrate was invariably present to compete for the triphenylmethylsodium, and was invariably successful. Our experiment with methyl crotonate, a molecule containing both an enolizable hydrogen and a conjugated system, shows clearly that there is very little, if any, addition in such a case.

The addition of phenyllithium to conjugated systems has been widely studied. Gilman and Kirby (3) have carried out its addition to benzalacetophenone, obtaining 13% 1,4-addition and 69% 1,2-addition. In our experiments, by using excess phenyllithium, the 1,2-addition product, diphenylstyryl carbinol, was obtained in good yield, as well as a more complicated addition compound, 1,1,2,3,3-pentaphenylpropanol. The reaction between phenyllithium and methyl cinnamate was found to yield this interesting product also. Neither the propanol nor the 1,1,2,3,3-pentaphenylpropylene, its dehydration product, were found to have been reported in the literature.

EXPERIMENTAL PART

I. CONDENSATIONS WITH TRIPHENYLMETHYLSODIUM

A. *With methyl cinnamate.* Triphenylmethylsodium was prepared by shaking 6.3 g. (0.023 mole) of triphenylchloromethane in a Schlenk tube with 210 g. of 1% sodium amalgam in 150 cc. of anhydrous ether for three hours according to the method of Schlenk (4). The red triphenylmethylsodium solution so obtained was forced by pressure of dry nitrogen to drip into 5 g. (0.032 mole) of methyl cinnamate in 30 cc. of anhydrous ether under dry

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nitrogen at −20°. The red solution immediately decolorized on mixing with the ester to give a pale yellow solution out of which, on standing, a yellow solid separated. After 12 hours the solid was separated by filtration, washed with light petroleum and dried; yield 5 g. It was shown to contain sodium. It was suspended in ether and hydrolyzed wth dilute hydrochloric acid. The ether layer was washed with bicarbonate solution and water and dried over calcium chloride. The ether was removed on the steam-bath and crystallization occurred. The product, 3,4,4,4-tetraphenylbutyric acid methyl ester, was recrystallized from dry methanol in small white prisms, m.p. 170.5–171°; yield 3 g.

Anal. Calc'd for $C_{29}H_{26}O_2$: C, 85.7; H, 6.5.
Found: C, 86.0; H, 7.0.

A 0.2-g. sample of this 3,4,4,4-tetraphenylbutyric acid methyl ester was hydrolyzed by refluxing for one hour with 0.05 g. of potassium hydroxide in 10 cc. of alcohol. Acidification and recrystallization from ether gave an acid, 3,4,4,4-tetraphenylbutyric acid, m.p. 227–228°; yield 0.15 g.

Anal. Calc'd for $C_{28}H_{24}O_2$: C, 85.7; H, 6.2.
Found: C, 85.3; H, 6.5.

By heating some of this acid in methanol with a trace of hydrochloric acid, a white crystalline product was obtained, m.p. 170.5–171°, the original methyl ester.

One gram of the methyl ester was destructively distilled at atmospheric pressure. At about 280–310° material began to sublime over; this was crystallized from methanol, m.p. 92°. A mixed melting point with a known sample of triphenylmethane, m.p. 93°, gave no depression, *i.e.*, m.p. 92°.

Another portion of the pyrolyzed ester was hydrolyzed by refluxing with alcoholic potash for an hour. On dilution with water solid material separated and was removed by filtration. The filtrate was acidified with dilute hydrochloric acid and the resulting crystalline compound recrystallized from ether-petroleum ether mixture. It melted at 133° and gave no depression in a mixed melting point with a known sample of cinnamic acid, m.p. 133°.

B. *With ethyl cinnamate.* Triphenylmethylsodium prepared as described above from 6.3 g. (0.023 mole) of triphenylchloromethane was added slowly to 6 g. (0.034 mole) of ethyl cinnamate in 25 cc. of anhydrous ether under dry nitrogen. Reaction occurred and the solution became yellow. On addition of 50 cc. of dry petroleum ether considerable solid separated. The mixture was allowed to stand overnight before filtering. The yellow salt obtained was washed with petroleum ether and dried. It was found to contain sodium; yield 2.7 g. It was suspended in ether and hydrolyzed with dilute hydrochloric acid. The ether layer was washed with water and bicarbonate solution and dried over calcium chloride. On removal of the ether, crystalline 3,4,4,4-tetraphenylbutyric acid ethyl ester was obtained and was recrystallized from methanol, m.p. 127–127.5°; yield 2 g.

Anal. Calc'd for $C_{30}H_{28}O_2$: C, 85.7; H, 6.7.
Found: C, 85.4; H, 7.0.

By refluxing for an hour with 0.05 g. of potassium hydroxide in 10 cc. of alcohol, 0.1 g. of this ethyl ester was hydrolyzed. On acidification an acid was obtained which melted at 228° after recrystallization from ether. A mixed melting point with the acid obtained from the methyl ester in (A) m.p. 228° gave no depression.

The ether filtrate from the solid sodium salt described above was examined, and 0.5 g. of triphenylmethane, m.p. 93°, was isolated, as well as 0.3 g. of cinnamic acid, m.p. 133°. A considerable amount of non-crystalline material was also found, similar in appearance to the material described by Michael (5) in his investigation of the action of sodium on cinnamic ester.

C. *With methyl crotonate.* Tritylsodium prepared from 6.3 g. (0.023 mole) of triphenylchloromethane was slowly added to 4 g. (0.04 mole) of methyl crotonate in 30 cc. of anhydrous ether under dry nitrogen at −20°. Reaction was instantaneous, giving a yellow solution containing some yellow solid which was separated by filtration (2 g.). Its hydrolysis with dilute hydrochloric acid yielded only tarry material which could not be crystallized. On removal of the ether from the filtrate, however, crystalline material was obtained which

was recrystallized from methanol to give white needles, m.p., 93°. This was shown to be triphenylmethane by a mixed melting point with a known sample, which gave no depression; yield 4.8 g. (0.021 mole).

D. *With benzalacetophenone.* Triphenylmethylsodium prepared from 6.3 g. (0.023 mole) of triphenylchloromethane was added to 4.8 g. (0.023 mole) of benzalacetophenone in anhydrous ether under dry nitrogen. The red solution became yellow but very little solid appeared. After two hours the whole mixture was hydrolyzed with dilute hydrochloric acid. The ether layer was washed with bicarbonate and water, then dried over calcium chloride. It yielded a sticky material on removal of the ether, which was crystallized by scratching with methanol. The 2,3,3,3-tetraphenylpropyl phenyl ketone was recrystallized from hot ligroin in the form of fine white needles, m.p. 169.5–170°; yield 4 g.

Anal. Calc'd for $C_{34}H_{28}O$: C, 90.3; H, 6.2.
Found: C, 90.2; H, 6.7.

II. CONDENSATIONS WITH PHENYLLITHIUM

A. *With methyl cinnamate.* Using the method of Evans and Allen (6), phenyllithium was prepared from 3.5 g. (0.5 mole) of lithium and 40 g. (0.25 mole) of bromobenzene in 150 cc. of anhydrous ether. To it at −20° was added slowly 40 g. (0.25 mole) of methylcinnamate in 100 cc. of anhydrous ether. The mixture was allowed to stand overnight. It was then hydrolyzed with dilute acetic acid and the ether layer washed with bicarbonate solution and water, then dried over calcium chloride. On removal of the ether on the steam-bath an oil resulted which crystallized on scratching with ligroin. The 1,1,2,3,3-pentaphenylpropanol was recrystallized from ligroin in the form of white prisms, m.p. 160.5–161°.

Anal. Calc'd for $C_{33}H_{28}O$: C, 90.0; H, 6.4; Mol. wt., 440.
Found: C, 90.5; H, 6.6; Mol. wt. (camphor), 439.

Some of the crude product was placed in a distilling flask and heated at 180–200° for 4 hours at 4 mm. pressure. The resulting decomposition product was extracted with hot benzene, from which it separated on cooling as white crystals. This material, 1,1,2,3,3-pentaphenylpropylene was recrystallized from benzene, and melted at 214–215°.

Anal. Calc'd for $C_{33}H_{26}$: Mol. Wt. 422; C, 93.8; H, 6.2.
Found: Mol. Wt. (camphor) 410; C, 93.8; H, 6.1.

Lithium cinnamate. This salt, a conceivable by-product of the above reaction between phenyllithium and methylcinnamate, was prepared by refluxing 0.5 g. of lithium in a mixture of 25 cc. of water and 25 cc. of alcohol until it had completely reacted. Fifteen grams of ethylcinnamate was then added and the mixture refluxed for two hours. On cooling, lithium cinnamate separated in the form of white plates, and was recrystallized from alcohol. It melted at 303–305° with decomposition; yield, 10 g.

Anal. Calc'd for $C_9H_7LiO_3$: C, 70.1; H, 4.6.
Found: C, 70.0; H, 4.8.

B. *With benzalacetophenone.* Ten grams (0.05 mole) of benzalacetophenone was added to a solution of phenyllithium prepared from 2.1 g. (0.3 mole) of lithium and 22.8 g. of bromobenzene in 125 cc. of anhydrous ether, giving a wine red solution which was refluxed an hour and allowed to stand overnight. It was decomposed with dilute acetic acid. The ether layer was washed with bicarbonate solution and water and then dried over calcium chloride. On evaporation of the ether, crystallization occurred. The material was recrystallized from ligroin to give 11.5 g. of diphenylstyrylcarbinol, melting at 110–111° as described by Luttringhaus, Jr. (7).

From the ligroin filtrate a small amount of material was obtained which melted at 159° and gave no depression in a mixed melting point with a known sample of 1,1,2,3,3-pentaphenylpropanol. Repetition of the above experiment using varying proportions of materials failed to increase the yield of this by-product.

All melting points are corrected.

SUMMARY

1. Triphenylmethylsodium has been found to add to ethyl cinnamate, methyl cinnamate, and benzalacetophenone, resulting in the formation of three compounds hitherto unreported in the literature. The two esters were hydrolyzed to the same acid.

2. Phenyllithium was added to methyl cinnamate and benzalacetophenone, giving, besides the expected products, 1,1,2,3,3-pentaphenylpropanol. This was dehydrated to the corresponding propylene derivative.

3. Lithium cinnamate was prepared.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

HIGHLY HINDERED STILBENES

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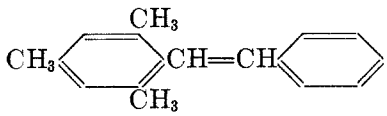
The hindering influence of *ortho* substituents is generally associated with reactions that are additive in type and has been noted frequently in studies of aldehydes, ketones, esters, nitriles, and other compounds in which the functional group contains a multiple linkage between carbon and a negative element. Very little attention, however, has been given to the influence of *ortho* substituents on the addition reactions of the carbon-to-carbon multiple linkages. To this end a study has been made of the effect of *ortho* substituents on the reactions of stilbene.

Three new stilbenes containing *ortho* substituents have been prepared and treated with reagents known to react with the central linkage of stilbene. The compounds selected for the work were 1-mesityl-2-phenylethylene (I), 1,2-dimesitylethylene (II), and 1-phenyl-2-(2,4,6-triisopropylphenyl)ethylene (III).



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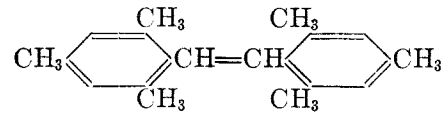

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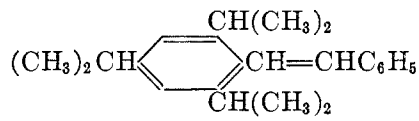


III

REACTIONS OF THE STILBENES

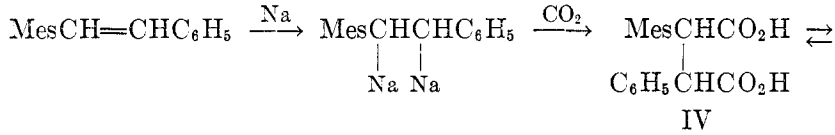
The three new stilbenes were found to undergo hydrogenation to the corresponding 1,2-diarylethanes when treated with hydrogen in the presence of Raney nickel.

Ozone cleaved the hindered stilbenes to produce the corresponding acids. From mesitylphenylethylene and dimesitylethylene small amounts of mesitol were also obtained. This unexpected result is reminiscent of the production of phenols by the autoxidation of certain vinyl alcohols (1).

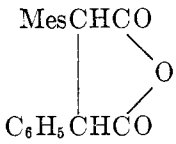
Perbenzoic acid converted 1-mesityl-2-phenylethylene to the epoxide, which could be reconverted to the olefin by treatment with hydriodic acid in glacial acetic acid. A similar result could not be obtained with dimesitylethylene. The action of perbenzoic acid on the mesityl compounds appeared to be complex, and it was suspected that the mesityl radical was attacked. As a test of this suggestion, mesitylene itself was treated with perbenzoic acid. A large part of the mesitylene was acted upon by the reagent and from the products mesitol could be isolated.

Perhaps the most interesting reaction of the stilbenes was with metallic sod-

ium. It had been shown that *trans*-stilbene, when treated successively with sodium, carbon dioxide, and water, yielded α,β-diphenylsuccinic acid (2). 1-Mesityl-2-phenylethylene behaved in a similar manner, yielding α-mesityl-β-phenylsuccinic acid (IV). The hexamethyl and the triisopropyl stilbenes failed to react under these conditions. The corresponding succinic acids were prepared from these olefins, however, by the use of a liquid sodium-potassium alloy, followed by carbonation. The anhydride (V) of α-mesityl-β-phenylsuccinic acid was prepared by heating with acetyl chloride. The acid was regenerated by treating the anhydride with water.



IV



V

Solutions of potassium permanganate were decolorized slowly by the hindered olefins. The triisopropyl stilbene reacted less rapidly than the trimethyl and the hexamethyl was most sluggish of all. Stilbene itself was more reactive than any of the hindered olefins. These results are in harmony with the observation that 1,1-dineopentylethylene is not oxidized by permanganate solutions (3).

Treatment of 1,2-dimesitylethylene with silver benzoate and iodine by the method of Prévost (4) followed by hydrolysis yielded a mixture of the corresponding glycols. 1-Mesityl-2-phenylethylene appeared to react in a similar manner.

SYNTHESIS OF THE STILBENES

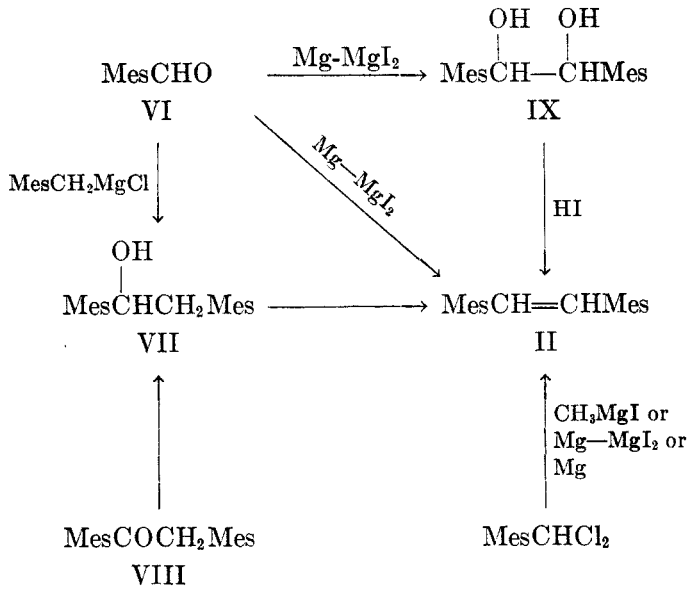
1,2-Dimesitylethylene. The hexamethylstilbene (I) was first made by the coupling action of methylmagnesium iodide on mesital chloride. It was to be expected by analogy with the coupling of benzal chloride (5) that the stilbene dichloride would be formed. However, the only product that could be isolated was 1,2-dimesitylethylene. The yield was about 30%.

The new stilbene was assumed to be the *trans* form because of its close resemblance to *trans*-stilbene. Moreover, other methods of synthesis yielded this form, suggesting that it is the more stable modification. One of the methods consisted in effecting the coupling of mesital chloride with the binary mixture, Mg-MgI_2 (6). Magnesium alone was found to produce the stilbene also, but the product of this reaction was difficult to purify.

The most satisfactory method for preparing the hexamethylstilbene was by the dehydration of 1,2-dimesitylethanol (VII). The dehydration was effected in nearly quantitative yields by treating the alcohol with acetic anhydride in

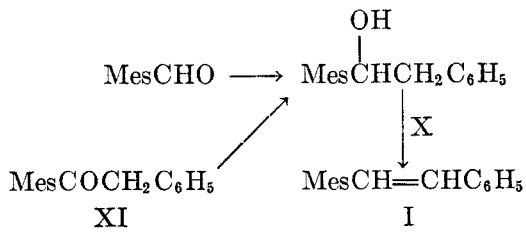
the presence of a small amount of hydrogen chloride. When the dehydration was carried out with sulfuric acid or phosphorus pentoxide the product was contaminated with a high-melting solid which appeared to be the di(α,β-dimesitylethyl) ether. Acetic anhydride alone produced the acetate of the alcohol.

1,2-Dimesitylethanol (VII) was prepared by high-pressure hydrogenation of desoxymesitoin (VIII) and by the condensation of mesitaldehyde (VI) with 2,4,6-trimethylbenzylmagnesium chloride.



Another method of preparing the stilbene (II) consisted in treating mesitaldehyde with the binary mixture, Mg-MgI_2 (7). The principal product of the reduction, dimesitylethylene glycol (IX), could also be converted to the stilbene by treatment with hydrogen iodide in glacial acetic acid.

1-Mesityl-2-phenylethylene. The trimethylstilbene (I) was prepared by dehydration of 1-mesityl-2-phenylethanol (X). This alcohol in turn could be produced either by high-pressure hydrogenation of benzyl mesityl ketone (XI) or by the condensation of mesitaldehyde with benzylmagnesium chloride.



The dehydration was effected in high yield by treatment with sulfuric acid. By analogy with stilbene, this hydrocarbon was assigned the *trans* configuration.

1-Phenyl-2-(triisopropylphenyl)ethylene (III). The triisopropylstilbene was prepared by dehydration of the corresponding alcohol. It was assumed to have the *trans* configuration. Experience has shown that the 2,4,6-triisopropylphenyl group offers much more hindrance than the mesityl radical. 1-Phenyl-2-(triisopropylphenyl)ethylene would accordingly be expected to be much less reactive than the mesityl analog.

EXPERIMENTAL

1,2-Dimesitylethylene (from mesital chloride). This hydrocarbon was made by coupling mesital chloride, prepared by the method of Asinger and Lock (8). The coupling was carried out by three different reagents—methylmagnesium iodide, the binary mixture (Mg-MgI_2), and magnesium alone. The yields are nearly the same with the three reagents but the use of the Grignard reagent is to be preferred because it gives a product that is easily purified.

A. *Methylmagnesium iodide.* The method was essentially that used with benzal chloride (5). From 30 g. of mesital chloride was obtained 5.8 g. of the ethylene. It was purified by recrystallization from ethanol; m.p. 132.5–133.5°.

Anal[1]. Calc'd for $C_{20}H_{24}$: C, 90.84; H, 9.16.
Found: C, 90.74; H, 9.21.

Removal of the solid olefin left 12.79 g. of a red oil; it was not investigated further.

B. *The binary mixture, Mg-MgI_2.* The reagent was prepared from 2.6 g. of magnesium and 12.79 g. of iodine in the usual manner (6). A solution of 10 g. of mesital chloride in 10 cc. of ether was added dropwise over a period of thirty minutes. The heat liberated caused the solution to boil. The mixture was stirred throughout the addition of the chloride and for two hours longer. During the last hour, refluxing was maintained by heating. An iodine color developed, then faded; a solid separated from the solution.

The reaction mixture was poured on a mixture of ice and hydrochloric acid, the ether-benzene layer was removed, and the water layer was extracted once with ether. The ether-benzene was united with the ether extract and washed once with sodium bicarbonate solution, twice with sodium bisulfite solution, and finally with water. The solution was dried over magnesium sulfate and concentrated to a small volume by heating on a steam-cone. The concentrate was mixed with ethanol and cooled; 2.1 g. of the ethylene was deposited. Concentration of the mother liquors produced 5 g. of a dark viscous oil.

C. *Magnesium.* A solution of 10 g. of mesital chloride in 50 cc. of dry ether was added dropwise over a period of one hour to a mixture of 2.5 g. of magnesium turnings and 75 cc. of dry ether. The reaction was initiated by the addition of a few drops of methyl iodide along with the first few drops of the mesital chloride solution. The reaction liberated heat and caused a precipitate to form. Stirring was continued during the mixing and for two hours longer. An additional 50 cc. of ether was added to facilitate stirring. After the addition was completed, the mixture was maintained at room temperature for an hour, then heated under reflux for an hour. It was poured on an ice-hydrochloric acid mixture, and the product isolated in a manner similar to that already described. The ethylene was induced to crystallize by dissolving it in high-boiling petroleum ether and cooling the solution with solid carbon dioxide; m.p. 114–121°; yield 2 g. It was purified by recrystallization alternately from methanol and from high-boiling petroleum ether; m.p. 131–132°. Six recrystallizations were necessary.

1,2-Dimesitylethanol. A. *From desoxymesitoin.* A mixture of 28 g. of desoxymesitoin, 140 cc. of absolute ethanol, and 5 g. of copper chromite was subjected to a hydrogen pres-

[1] Microanalyses by Miss Margaret McCarthy, Miss Theta Spoor, and Miss Dorothy Schneider.

sure of 2000 lbs. at 125°.[2] A mole of the gas was absorbed in thirty minutes. The catalyst was removed by filtration and the filtrate treated with Norit. When concentrated to 80 cc. and allowed to stand in the ice-chest overnight, the solution deposited 26 g. of 1,2-dimesitylethanol; m.p. 128–129°.

Anal. Calc'd for $C_{20}H_{26}$: C, 85.06; H, 9.29.
Found: C, 84.92; H, 9.17.

B. *From mesitaldehyde and 2,4,6-trimethylbenzylmagnesium chloride.* The Grignard reagent was prepared by adding, over a period of two and one-half hours, a solution of 13 g. of 2,4,6-trimethylbenzyl chloride in 400 cc. of dry ether to a mixture of 18.8 g. of magnesium turnings, and 170 cc. of dry ether. The reaction mixture was stirred and kept at ice-bath temperature during the mixing and for two hours longer. It was then allowed to come to room temperature. A solution of 7.4 g. of mesitaldehyde in 200 cc. of dry ether was added, with stirring, over a period of one and one-fourth hours. Stirring was discontinued and the mixture allowed to stand overnight. It was poured on a mixture of ice and acetic acid. The ether layer was removed and the water layer extracted with ether. The two ether solutions were united, dried over magnesium sulfate, and concentrated to a small volume. When cooled, this solution deposited 15.4 g. of colorless solid material melting at 109–114°. Tedious fractional crystallization from methanol separated it into 1,2-dimesitylethanol and 1,2-dimesitylethane.

1,2-Dimesitylethyl acetate. A mixture of 2 g. of 1,2-dimesitylethanol and 20 cc. of acetic anhydride was heated overnight under reflux, cooled, and poured into water. The acetate was isolated by filtration and purified by recrystallization from methanol; m.p. 117.5–118°; yield 1.6 g.

Anal. Calc'd for $C_{22}H_{28}O_2$: C, 81.43; H, 8.70.
Found: C, 81.28; H, 8.82.

The acetate also was made by acetylation with acetyl chloride.

Dimesitylethylene (from 1,2-dimesitylethanol). The dehydration of the ethanol could not be effected by heat alone. The alcohol was unchanged after two hours at 220°.

A. *Sulfuric acid.* A mixture of 2 g. of the ethanol, 10 cc. of concentrated sulfuric acid, and 10 cc. of water was heated on the steam-cone, with occasional shaking, for eighteen hours. It was cooled and poured on 200 g. of ice and water. The solid product was removed by filtration and recrystallized from 500 cc. of methanol. It was then recrystallized successively from high-boiling petroleum ether, ethanol, and a mixture of dioxane and ethanol; m.p. 177–180°. It was believed to be di(α,β-dimesityl)ethyl ether.

Anal. Calc'd for $C_{40}H_{50}O$: C, 87.91; H, 9.15.
Found: C, 87.83; H, 8.94.

The original methanolic filtrate was concentrated to a volume of 50 cc. and cooled; 1.0 g. of impure 1,2-dimesitylethylene (m.p. 127–128°) separated.

B. *Phosphorus pentoxide.* A mixture of 5 g. of the ethanol, 15 g. of phosphorus pentoxide, and 150 cc. of benzene was heated under reflux for three and one-half hours. The pentoxide was removed by filtration and the solvent evaporated. The residue was extracted with 1 liter of boiling ethanol. One gram of solid remained undissolved and, from its melting point (155–165°), was assumed to be the ether. When the ethanol solution was concentrated to a volume of 300 cc. and cooled, 2.5 g. of impure 1,2-dimesitylethylene (m.p. 122–128°) was obtained.

C. *Acetic anhydride and hydrochloric acid.* A mixture of 10 g. of the ethanol, 2 cc. of concentrated hydrochloric acid, and 50 cc. of acetic anhydride was heated under reflux for seven hours and poured into water. The ethylene was isolated by filtration and recrystallized from ethanol; yield 8 g.; m.p. 128–130°.

1-Mesityl-2-phenylethanol. A. *From mesitaldehyde and benzylmagnesium chloride.* The Grignard reagent was prepared by adding a solution of 49.2 g. of benzyl chloride in 50 cc.

[2] The high-pressure hydrogenations were carried out by Mr. J. C. Robinson, Jr. and Mr. John M. Stewart.

of dry ether to a mixture of 9.3 g. of magnesium turnings and 50 cc. of dry ether. A solution of 44.4 g. of mesitaldehyde in 50 cc. of dry ether was added to this, with stirring. In order to facilitate stirring, 50 cc. more of dry ether was added. The mixture was then heated under reflux for thirty minutes. It was cooled and 100 cc. of ice-cold dilute hydrochloric acid was added to it dropwise, with stirring. The layers were separated and the aqueous layer extracted with ether. The combined ether extracts were washed successively with dilute hydrochloric acid, water, and 10% sodium hydroxide solution. The ether solution was dried over magnesium sulfate and the solvent removed by heating on a steam-cone. The oily residue was diluted with an equal volume of high-boiling petroleum ether and cooled. Scratching the beaker induced the precipitation of 52.1 g. of a white solid; m.p. 62–66°. This melted at 65–66° after two recrystallizations from dilute methanol.

Anal. Calc'd for $C_{17}H_{20}O$: C, 85.00; H, 8.33.
Found: C, 85.10; H, 8.30.

B. *By catalytic reduction of benzyl mesityl ketone.* To a solution of 47.6 g. of the ketone in methanol made up to 150 cc. was added 6 g. of copper chromite. The mixture was subjected to a hydrogen pressure of 1,550 lbs. at 150° for three hours. The yield of the ethanol (m.p. 65–66°) was 27.3 g.

1-Mesityl-2-phenylethylene. A mixture of 75 g. of the ethanol, 375 cc. of sulfuric acid, and 375 cc. of water was heated, with occasional shaking, on a steam-cone for twenty-four hours. The olefin was isolated and purified by the method described for the hexamethylstilbene. The product melted at 55–56°; yield 86%.

Anal. Calc'd for $C_{17}H_{18}$: C, 91.81; H, 8.11.
Found: C, 91.69; H, 8.17.

1-Phenyl-2-(triisopropylphenyl)ethanol. This compound was prepared by the method outlined for 1-mesityl-2-phenylethanol. From 69.6 g. of 2,4,6-triisopropylbenzaldehyde was obtained 75 g. of product melting at 108–111°. After repeated recrystallization from high-boiling petroleum ether the alcohol melted at 117.5–118.5°.

Anal. Calc'd for $C_{23}H_{32}O$: C, 85.19; H, 9.88.
Found: C, 85.09; H, 9.68.

2-Phenyl-1-(triisopropylphenyl)ethylene. This hydrocarbon was prepared by dehydrating the alcohol with sulfuric acid as described for 1-mesityl-2-phenylethylene. Four grams of the ethanol yielded 2.5 g. of the olefin, melting at 79–80°. Repeated recrystallization produced a pure sample; m.p. 82.5–83.5°.

Hydrogenation. A mixture of 1 g. of 1,2-dimesitylethylene, 10 cc. of methylcyclohexane, and 1 g. of a Raney nickel catalyst was heated at 100° for one hour under a hydrogen pressure of 2000 lbs. The temperature was then raised to 150° and maintained at that point for one-half hour. The product was purified by repeated recrystallization from ethanol; m.p. 114–117°. It was shown by the mixed melting point method to be *1,2-dimesitylethane* (9).

Hydrogenation of 1-mesityl-2-phenylethylene at 100° by a similar procedure yielded *1-mesityl-1-phenylethane.* It crystallized from methanol in beautiful, white needles; m.p. 38–39°.

Anal. Calc'd for $C_{17}H_{20}$: C, 91.01; H, 8.98.
Found: C, 90.90; H, 9.22.

1-Phenyl-2-(2,4,6-triisopropylphenyl)ethylene was hydrogenated by the foregoing procedure. The *1-phenyl-2-(2,4,6-triisopropylphenyl)ethane* was purified by distillation followed by recrystallization from methanol; b.p. 155–161° (4 mm.); m.p. 33–34°.

Anal. Calc'd for $C_{23}H_{32}$: C, 89.54; H, 10.46.
Found: C, 89.55; H, 10.29.

Ozonolysis. A stream of oxygen containing approximately 1% ozone was passed for three hours into a solution of 2 g. of *1,2-dimesitylethylene* in 50 cc. of chloroform. The solvent was evaporated under reduced pressure and the residue treated with 100 cc. of 3% hydrogen peroxide solution. The mixture was boiled for five minutes; 10 cc. of 20% sodium hydroxide was then added slowly. The resulting solution was filtered and treated with solid carbon dioxide. The solid which formed was extracted with ether and purified by

low-pressure sublimation; m.p. 69–71°; yield 0.04 g. This compound was shown by the mixed melting point method to be *mesitol*.

The aqueous solution remaining after removal of the mesitol was freed from dissolved ether and acidified. The precipitated mesitoic acid weighed 0.7 g. It was recrystallized from high-boiling petroleum ether, then from water; m.p. 150–151°. The melting point was not depressed by admixture of the sample with a known specimen of mesitoic acid.

1-Mesityl-2-phenylethylene was ozonized by a similar procedure. By suitable methods the product was separated into three components: mesitol, mesitoic acid, and benzoic acid.

The mesitoic acid was obtained in pure form by extracting the mixture with hot water and recrystallizing the residue from high-boiling petroleum ether. The extract, when cooled, yielded a mixture of the two acids; m.p. 88–91°. Recrystallization of this material from water or from high-boiling petroleum ether did not raise the melting point. Benzoic acid was obtained pure by partially subliming the material at low pressure and recrystallizing the sublimate from high-boiling petroleum ether.

In a similar manner *1-phenyl-2-(2,4,6-triisopropylphenyl)ethylene* was converted by ozonolysis to a mixture of benzoic and 2,4,6-triisopropylbenzoic acids. The benzoic acid was extracted with hot water and the residual triisopropylbenzoic acid was recrystallized from high-boiling petroleum ether; m.p. 180–182°.

1-Mesityl-2-phenylethylene oxide. To a chloroform solution of perbenzoic acid, containing 0.06 mole of the reagent, was added 6.7 g. (0.03 mole) of the ethylene. After being allowed to stand in the ice-box for twenty-four hours, the solution was washed with water solutions of sodium thiosulfate and potassium bicarbonate. Removal of the solvent left the crude oxide as an oil, which solidified on cooling. One recrystallization from methanol gave 4.6 g. of yellow crystals melting at 64–66°. The color was removed with Norit. Recrystallization from dilute methanol yielded white plates; m.p. 67–68°.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.71; H, 7.56.
Found: C, 86.00; H, 7.75.

The oxide could be reduced to the olefin with hydrogen iodide. A solution of 1 g. of the oxide, 10 cc. of hydriodic acid (sp. gr. 1.5), and 30 cc. of glacial acetic acid was heated for ninety minutes on a steam-cone and poured into water. The product was the olefin; m.p. 53–54°.

Action of perbenzoic acid on mesitylene. Thirty-six grams (0.3 mole) of mesitylene was added to a chloroform solution of perbenzoic acid containing 0.15 mole of the reagent. After being allowed to stand 112 hours, the solution was washed with solutions of sodium thiosulfate and potassium carbonate and then with water. Repeated extraction with 10% sodium hydroxide solution gave 3.8 g. of *mesitol* melting at 67–70°. This was a yield of 18.6%.

α-Mesityl-β-phenylsuccinic acid. A mixture of 10 g. of powdered sodium, 4 g. of 1-mesityl-2-phenylethylene, and 200 cc. of ether was shaken for five hours. It developed a dark red color and finally deposited a finely divided red-brown precipitate. The introduction of solid carbon dioxide discharged the color and left a yellow precipitate. The solution and precipitate were decanted from the sodium into 300 cc. of water. Acidification of the water layer gave 1.9 g. of product melting at 210–215°. The α-mesityl-β-phenylsuccinic acid was recrystallized from dilute acetic acid; m.p. 217–219°.

Anal. Calc'd for $C_{19}H_{20}O_4$: C, 73.08; H, 6.41; neut. equiv., 156.
Found: C, 72.89; H, 6.69; neut. equiv., 153.

The *anhydride* was made by heating 0.5 g. of the acid for two and one-half hours with 10 cc. of acetyl chloride. After the volatile portion of the mixture had been distilled under reduced pressure the residue was induced to crystallize by allowing it to stand overnight with high-boiling petroleum ether. The anhydride was recrystallized from this solvent; m.p. 129–130°.

Anal. Calc'd for $C_{19}H_{18}O_3$: C, 77.55; H, 6.17.
Found: C, 77.42; H, 6.14.

Treatment with hot 2% sodium hydroxide solution, followed by acidification, regenerated the parent acid.

α,β-Dimesitylsuccinic acid. A solution of 4 g. of 1,2-dimesitylethylene in 250 cc. of dry ether was added to an alloy of 4 g. of sodium and 6 g. of potassium. The mixture was shaken for six hours; it developed a black color. A stream of carbon dioxide was passed in until the black color had been completely discharged. The ether and suspended white solid were decanted from the excess alloy and washed twice with water. The aqueous solution was heated to drive off dissolved ether and acidified with hydrochloric acid. The crude acid melted at 250–270° and weighed 4.6 g. It was recrystallized from ethyl benzoate; m.p. 283–285°.

Anal. Calc'd for $C_{22}H_{26}O_4$: C, 74.58; H, 7.40; neut. equiv., 177.
Found: C, 74.65; H, 7.71; neut. equiv., 177.5.

α-Phenyl-β-(2,4,6-triisopropylphenyl)succinic acid. By the procedure outlined for the dimesitylsuccinic acid, 4 g. of 1-phenyl-2-(2,4,6-triisopropylphenyl)ethylene was converted to 3.6 g. of crude α-phenyl-β-(2,4,6-triisopropylphenyl)succinic acid. It was purified by recrystallization from glacial acetic acid; m.p. 195–198°.

Anal. Calc'd for $C_{25}H_{32}O_4$: C, 75.76; H, 8.08; neut. equiv., 196.
Found: C, 75.61; H, 8.22; neut. equiv., 197.

Action of potassium permanganate solutions on the stilbenes. The tests were made by adding 0.1 cc. of a 2% solution of potassium permanganate in water to a solution of 0.05 g. of the stilbene in 4 cc. of acetone and allowing to stand. The time required for discharging the permanganate color was less than one minute for stilbene, four and one-half hours for 1-mesityl-2-phenylethylene, 30 hours for 1-phenyl-2-(2,4,6-triisopropylphenyl)ethylene, and 60 hours for 1,2-dimesitylethylene. 1,2-Dimesitylethane was unaffected by the permanganate in 72 hours.

Action of the silver benzoate-iodine complex on 1,2-dimesitylethylene. The method of Prévost (4) was used. A solution of 3 g. of iodine in 50 cc. of dry benzene was added, with stirring, to a suspension of 5.7 g. of silver benzoate in 50 cc. of dry benzene. To the resulting mixture 2.64 g. of the ethylene in 50 cc. of dry benzene was added. The mixture was heated under reflux for 24 hours and cooled. The silver salts were removed by filtration and the solvent by evaporation. The residue was treated for four hours with a solution of 3 g. of potassium hydroxide in 30 cc. of ethanol and 10 cc. of water. The mixture was extracted twice with ether, and the ether solution dried over sodium sulfate. After evaporation of the solvent, the residue was dissolved in 50 cc. of hot high-boiling petroleum ether. When cooled, the solution deposited 1.1 g. of white crystals melting at 147–170°. Two recrystallizations from methanol yielded the pure high-melting hydromesitoin; m.p. 212–213°.

The solvent was evaporated from the methanol filtrates and the residue recrystallized from high-boiling petroleum ether. The low-melting hydrobenzoin melted at 158–159°. Both glycols were identified by mixed melting point determinations with known samples (7).

Action of the complex on 1-mesityl-2-phenylethylene. By use of the foregoing procedure 2.22 g. of the olefin was partially converted to a solid melting at 120–124°. Recrystallization of the solid from aqueous ethanol raised the melting point to 124–132°. The material was assumed to be a mixture of the expected glycols.

Anal. Calc'd for $C_{17}H_{20}O_2$: C, 79.64; H, 7.87.
Found: C, 79.58; H, 8.03.

SUMMARY

Three hindered stilbenes have been prepared and treated with reagents known to react with the olefin linkage. Reactions with hydrogen, permanganate, ozone, perbenzoic acid, sodium, sodium-potassium alloy, and a silver benzoate-

iodine complex were found to occur normally but often at much slower rates than with the unhindered stilbene.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

THE SYNTHESIS OF *CIS*- AND *TRANS*-3-(PENTADECENYL-8′)-VERATROLE, A DIHYDRO DERIVATIVE OF URUSHIOL DIMETHYL ETHER

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The question of the chemical nature of the vesicant principle in poison ivy (*Rhus toxicodendron*) has interested investigators as far back as 1858, when it was thought to be a volatile alkaloid (1). A big contribution to the solution of the problem was made by G. A. Hill *et al.* (2) in 1934, when he isolated the substance responsible for the poisonous activity of the plant, and showed that in its reduced form it contained a substance identical with hydrourushiol, the hydrogenated form of the toxic substance urushiol, isolated from Japanese lac (*Rhus vernicifera*) by R. Majima (3) in 1909. Apparently Hill did not carry his investigation on the structure of this substance any further.

From oxidative degradation studies on urushiol (4), Majima concluded thta it was probably a mixture of four compounds which he could not separate by distillation. This seemed to be an obvious conclusion from the variety of degradation products isolated. He postulated that urushiol was a mixture of catechols differing in the number of double bonds in a normal fifteen-carbon side chain in position three, and that one of the compounds carried a completely reduced side chain. His evidence indicated that each of the three olefinic compounds had an unsaturated linkage in position 8′ of the side chain. Quantitative hydrogenation of urushiol showed an average of two aliphatic double bonds.

Backer and Haack (5) in 1938 showed that the toxicity of *Semecarpus heterophylla* was also due to a urushiol type compound. They were able to isolate a pure compound which they named renghol, and showed that it was a dihydro derivative of urushiol, having a single double bond in the 10′ position of the side chain.

In the light of the above work, it seemed desirable to develop a method for synthesizing catechol compounds of this type. Majima's evidence appeared to locate the position of the double bond closest to the ring in urushiol as being in the 8′ position. For this reason it was decided to attempt the synthesis of 3-(pentadecenyl-8′)veratrole by a method that could be applied for the introduction of one or more double bonds in any desired position in the side chain. The method developed is described below.

1-Chloro-6-benzoxyhexane (II) was prepared from adipic acid. The acid was converted into its diethyl ester by the method of Rysselberg (6), and then reduced with hydrogen at high pressure in the presence of copper chromic oxide catalyst, following the Adkins technique (7), to yield 1,6-hexanediol. The monosodium salt of this glycol, made by using a ratio of three moles of glycol to one mole of sodium (8), yielded 6-benzoxy-*n*-hexanol (I), upon addition of benzyl chloride. 1-Chloro-6-benzoxyhexane (II) was obtained upon displace-

ment of the hydroxyl group of the alcohol (I), using thionyl chloride and dimethylaniline.

The benzoxy chloride was then used in the preparation of 3-(7′-bromoheptyl)-veratrole, by first treating it with magnesium in the usual manner, to yield 6-benzoxy-*n*-hexylmagnesium chloride. By adding an ethereal solution of *o*-veratraldehyde to the Grignard reagent, a secondary alcohol, 3-(7′-benzoxy-heptanol-1′)veratrole (III) was formed (9). This alcohol was converted to the olefin by splitting out water at 210° in the presence of potassium bisulfate, to yield 3-(7′-benzoxyheptenyl-1′)veratrole (IV). The double bond was saturated, and the benzyl ether split in compound (IV) by reduction and simultaneous hydrogenolysis with hydrogen at two atmospheres in the presence of palladium black catalyst, resulting in the formation of 3-(7′-hydroxyheptyl)veratrole (V). This was esterified with dry hydrogen bromide at 140–150°, and the phenolic hydroxyl groups on the benzene ring which were liberated under these drastic conditions, were remethylated with dimethyl sulfate according to the method of Perkin and Weizman (10), to yield 3-(7′-bromoheptyl)veratrole (VI).

A disubstituted acetylene was then prepared from the above bromide (VI) and hexyl bromide, using the liquid ammonia method of Hennion (11). The bromide (VI) was treated with sodium acetylide in liquid ammonia at room temperature in an autoclave, yielding a monosubstituted acetylene, 3-(nonynyl-8′)veratrole (VII). The sodium salt of this acetylene derivative (VII) was prepared in liquid ammonia by the addition of sodamide, and this was then converted to the disubstituted acetylene, 3-(pentadecynyl-8′)veratrole (VIII) by the addition of hexyl bromide, using the same conditions as in the preparation of (VII).

The method of Campbell and O'Connor (12) for the preparation of pure *cis* and *trans* olefins from the corresponding acetylenic compound was used to form the *cis* and *trans* olefin from (VIII). *cis*-3-(Pentadecenyl-8′)veratrole (IX) was made from the acetylene derivative (VIII) by partial reduction with hydrogen, in the presence of Raney nickel catalyst, at a pressure of one atmosphere. *trans*-3-(Pentadecenyl-8′)veratrole (X) was obtained as a result of the reduction of (VIII) with sodium in liquid ammonia at 0° in an autoclave.

To learn whether or not the double bond had shifted under the alkaline conditions of reduction in the autoclave, the *trans* olefin (X) was oxidized with potassium permanganate according to the method of Armstrong and Hilditch (13). *n*-Heptylic acid and *o*-veratric acid were isolated in small yield from the oxidation products. Other acids that could have resulted because of a shift of the double bond could not be detected. The isolation and identification of *n*-heptylic acid indicates the presence of a double bond in the 8′ position. The isolation and identification of *o*-veratric acid indicates the presence of an alkenyl group at position three in the ring. Due to the difficulty involved in isolating pure products from the resin-like reaction mass after the oxidation, it was not feasible to attempt a weight balance on the oxidative degradation. For this reason, the possibility still exists that isomerization of the double bond or the position of the alkenyl group may have taken place to a small extent. However, in view

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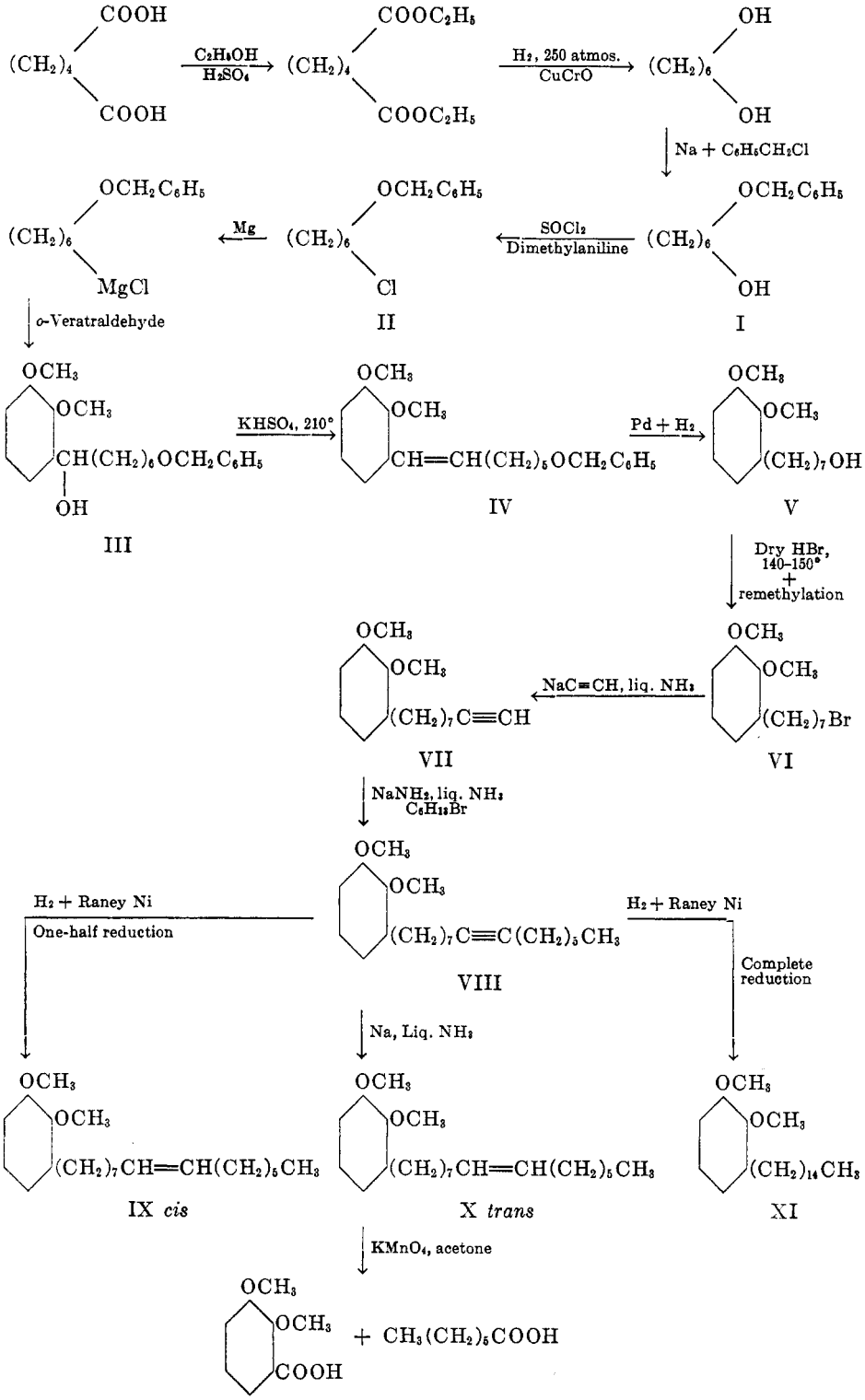

of the failure to detect other acids in the degradation products, the likelihood of such isomerization occurring to any appreciable extent is small.

Compound VIII was completely reduced with hydrogen at atmospheric pressure in the presence of Raney nickel catalyst, to 3-(pentadecyl)veratrole, (tetrahydrourushiol dimethyl ether, XI), whose melting point (36.8–37.0°) agreed with the data on a similar compound from natural sources, of R. Majima (4) and G. A. Hill (2). There was a sharp change in the rate of absorption of hydrogen at the 50% reduction stage, indicating the preferential hydrogenation of the acetylenic bond under these conditions, as previously shown in a variety of similar compounds studied by Campbell and O'Connor (12).

Urushiol dimethyl ether (XII), isolated from poison ivy bark by the method of G. A. Hill (2) was reduced to tetrahydrourushiol dimethyl ether (XIII) by hydrogen at one atmosphere, in the presence of Raney nickel catalyst. There was no sharp change in the rate of absorption of hydrogen at the 50% reduction stage as in VIII, indicating that the unsaturation in the natural product (XII) is not due to an acetylenic linkage in the side chain, but rather to olefinic bonds. A mixed melting point of this compound (XIII) with the synthetic tetrahydrourushiol dimethyl ether gave no melting point depression, indicating that they were identical.

An attempt to synthesize the olefins (IX) and (X) by the Boord olefin synthesis (14) from the bromide, (VI), resulted in an impure compound which could not be purified by distillation, or by the use of the Praevost reagent (15). Carbon and hydrogen analysis, quantitative hydrogenation, and methoxyl determination indicated no more than 56% of the desired olefinic compound in the mixture.

Compounds V, VIII, IX, and X were found to exhibit experimental molar refractivities that were from 1–1.2 units higher than the calculated theoretical values, whereas compounds I and II gave values within the experimental error of those calculated. To determine the cause of this exaltation, *o*-dimethoxytoluene in a high state of purity was prepared, and its molar refractivity determined. This compound was also found to exhibit an exaltation of 0.8 units. It would appear, therefore, that the high experimental values of molecular refractivity reported for the above compounds, are the result, in part at least, of exaltation due to the 3-alkyl veratrole type of structure.

As yet no serious attempt has been made to obtain the toxic 3-alkenyl catechols either by demethylation of the corresponding synthetic 3-alkenyl veratroles or by direct synthesis.

EXPERIMENTAL

The thermometers used in these experiments were calibrated against a Bureau of Standards thermometer. Values are uncorrected for exposed stem unless otherwise indicated.

Adipic acid was converted to diethyl adipate by the method of Rysselberg (6). Two runs, each consisting of 750 g. of du Pont adipic acid, 900 cc. of 95% ethyl alcohol, 2200 cc. of dry benzene, and 300 g. of concentrated sulfuric acid, were worked up. The product boiled at 106°/5 mm. (oil-bath at 146°), and totaled 1800 g. or a yield of 86.8%.

1,6-Hexamethyleneglycol. This was prepared from the above diethyl adipate by reduction with hydrogen at high pressure, using copper chromic oxide as catalyst, prepared in

the Columbia Preparations Laboratory. The procedure in Organic Syntheses (7) was followed, using a 1250 cc. capacity bomb.

Best yields were obtained by using 252 g. of diethyl adipate, and 20 g. of catalyst at 255° for fourteen hours. The bomb was charged at room temperature with a minimum initial pressure of hydrogen from the tank of 1750 lbs. per sq. in. Yields as high as 136 g. (94%) were thus obtained. Total yield from the various runs from 1800 g. of diethyl adipate was 886 g. (84%), b.p. 128–130°/6 mm.

6-Benzoxyhexanol (I). Using the method of Bennett (8), for the preparation of 3-benzoxypropanol, 373 g. of hexamethyleneglycol, covered with 200 cc. of dry xylene, in a 1-liter flask equipped with a stirrer, bulb condenser, and thermometer, was heated with stirring to 130°. Twenty-five grams of sodium in long strips was added through the top of the condenser, at such a rate as to maintain the inner temperature at 120–130°. After all the sodium had reacted the temperature was lowered to 120°, a dropping-funnel was substituted for the thermometer, and 150 g. of benzyl chloride was added dropwise with stirring. Reaction was indicated by the formation of fine white crystals of sodium chloride. The mixture was refluxed for one-half hour after the last addition of benzyl chloride. After cooling, 75 cc. of benzene was added, and the salt filtered off. Small amounts of the product and unreacted hexanediol were carefully removed from the salt cake by washing with a 50–50 mixture of benzene and ethyl alcohol. On distillation of the combined filtrates, the forerun of hexamethyleneglycol was saved for further use, and the product was taken at 150–160°/1.5 mm. (oil-bath at 200–250°). A total of 705 g. of glycol was worked up as described above, and the combined yields were redistilled at 154–158°/2.5 mm. cutting a middle fraction at 154°/2.5 mm. for analysis. Yields of 66–78.5% were obtained on the basis of reacted glycol. Total yield was 868 g. (71%) of clear colorless liquid; n_D^{25} 1.5048, d_4^{25} 0.9947, MR 62.1 (calc'd 61.8).

Anal. Calc'd for $C_{13}H_{20}O_2$: C, 75.0; H, 9.7.
Found: C, 74.8; H, 9.7.

1-Chloro-6-benzoxyhexane (II). Into a one-liter 3-neck flask equipped with stirrer, dropping-funnel, thermometer, and vent to the hood was placed 285 g. (1.38 moles) of the above benzoxyhexanol, and 185 g. (1.52 moles) of dry, redistilled dimethylaniline. One hundred seventy-one grams (1.23 moles) of purified thionyl chloride was added through the dropping-funnel slowly, with continuous stirring, keeping the inner temperature between 30–45° with a water-bath. When about one-half of the thionyl chloride had been added, the mixture turned into a yellow, difficultly stirred solid. On continued addition of the chloride over a period of two hours, the reaction mixture turned into a brown liquid. This was poured into 400 cc. of 9% hydrochloric acid, with stirring. The oil that separated was extracted with chloroform, and combined chloroform extracts washed with 250 cc. of 6% hydrochloric acid, to remove the excess dimethylaniline. After removal of the chloroform, the residue was dried by the addition and distillation of benzene. The resulting brown oil was fractionated using a Vigreux column, the main fraction being taken at 136–141°/1 mm. (oil-bath at 183°). A middle fraction for analysis was cut at 138°/1 mm. (oil-bath at 183°); yield, 268 g. (85.5%) of clear colorless liquid. A total of 868 g. of (I) was converted to 780 g. of (II) for an average yield of 81.8%; n_D^{25} 1.5027, d_4^{25} 1.0249, MR 65.4 (calc'd 65.1).

Anal. Calc'd for $C_{13}H_{19}ClO$: C, 68.9; H, 8.4.
Found: C, 69.1; H, 8.5.

3-(7'Benzoxyheptanol-1')veratrole (III). A two-liter 3-neck flask, equipped with a dropping-funnel and a bulb condenser was dried by flaming the flask while passing dry air through it. After cooling, 100 cc. of sodium-dried ether, 28.6 g. (1.18 moles) of magnesium turnings, 0.5 g. of methyl iodide, and a crystal of iodine were added. After the methylmagnesium iodide had formed, a solution of 268 g. (1.18 moles) of the above benzoxychloride in 230 cc. of dry ether was added through the dropping-funnel, at such a rate as to keep the reaction going vigorously. After four hours of addition and refluxing, a small amount of unreacted magnesium still remained. The flask was cooled in ice, and 156.5 g. (0.94 mole)

of *o*-veratraldehyde[1] dissolved in 400 cc. of dry ether was slowly added, with efficient stirring. The mixture turned white on addition of the aldehyde, but cleared after standing overnight. The mixture was hydrolyzed with 600 cc. of 6 *N* sulfuric acid, ether layer separated, washed with 10% sodium carbonate, and then with water. The ether was distilled and the remaining liquid dried by addition and distillation of benzene, leaving a yellow product (III), which was not further purified.

3-(7'Benzoxyheptenyl-1')veratrole (IV). The crude secondary alcohol from above was placed in a 500-cc. flask equipped with a Vigreux column. Five grams of potassium bisulfate was added and the flask slowly heated to 210°. The formation of water was indicated by much spattering. After fifteen minutes, the flask was cooled, and water was removed by distilling some xylene from the mixture. The operation was carried out three times using 15 g. of the bisulfate in all. After filtering off the salt, the brown liquid was distilled through the Vigreux column at 209–229°/1.8 mm. (Wood's metal-bath at 270–310°). A middle fraction for analysis was cut at 229°/1.8 mm. (Wood's metal-bath at 299°). The yield was 227 g. (71%) of yellow liquid with a decided bluish fluorescence; n_D^{25} 1.5528, d_4^{25} 1.0431, MR 103.7 (calc'd 101.0).

Anal. Calc'd for $C_{22}H_{28}O_5$: C, 77.5; H, 8.3.
Found: C, 77.5; H, 8.2.

A total of 780 g. of the benzoxychloride (II) yielded 616 g. of (IV) with yields from 71–80%, and an average yield of 74.2%.

3-(Heptanol-7')veratrole (V). The benzyl ether was split and the olefinic linkage reduced in compound (IV) by hydrogen at 2–3 atmospheres in the presence of palladium black and acetic acid. Seventy-five grams (0.221 mole) of (IV) with 0.5 g. of palladium black and 150 cc. of glacial acetic acid, was reduced on the Adams shaker for five hours. The theoretical amount of hydrogen (0.442 mole) was absorbed. The catalyst was removed and washed with acetic acid, and then alcohol. Three such runs were combined, and the solvents removed *in vacuo*, along with the toluene formed in the reaction. The remaining liquid was distilled through a 30-cm. Vigreux column, the main fraction being distilled at 167–171° at 2.7 mm.[2] and a middle fraction for analysis cut at 169°/2.7 mm. (Wood's metal-bath at 206°). The yield was 164.6 g. (97.5%) of clear colorless liquid; n_D^{25} 1.5032, d_4^{25} 1.0306, MR 73.2 (calc'd 72.4).

Anal. Calc'd for $C_{15}H_{24}O_3$: C, 71.4; H, 9.6.
Found: C, 71.5; H, 9.5.

3-(7'-Bromoheptyl)veratrole (VI). The above alcohol (V) was converted to the bromide with dry hydrogen bromide. One hundred fourteen grams of the alcohol (V) was placed in a 200-cc. 3-neck flask, and dry hydrogen bromide was bubbled through the liquid for a period of nine hours, while the temperature was maintained at 140–150° with an oil-bath. A water layer formed after thirty minutes. The flask was cooled, and the contents poured into a separatory funnel containing water. It was extracted with benzene, and washed again with water. The benzene and water were distilled off, and the red residue was placed in a 500-cc. 3-neck flask, equipped with stirrer, dropping-funnel, and bulb condenser, in

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[1] *o*-Veratraldehyde was prepared from Monsanto *o*-vanillin according to Organic Syntheses (16) in 83% yield.

[2] *1,12-Dihydroxydodecane.* The small forerun in the distillation coming over at 162–167°/2.7 mm., solidified. The white solid was insoluble in ether, water, and cold benzene, but on recrystallization from hot benzene melted at 82–82.5° and gave correct values for 1,12-dihydroxydodecane.

Anal. Calc'd for $C_{12}H_{26}O_2$: C, 71.3; H, 12.9.
Found: C, 71.3; H, 13.1.

This compound has not previously been reported and apparently arose from coupling in the Grignard reaction, step III, yielding 1,12-dibenzoxydodecane. During the reduction this yielded the glycol.

order to remethylate the phenolic hydroxyl groups liberated during the esterification (see below). Fifty-six grams of dimethyl sulfate and 50 cc. of methyl alcohol were added to the flask. A solution of 33 g. of potassium hydroxide in 78 cc. of water was added rapidly through the dropping-funnel with constant stirring and cooling. After the reaction subsided, 28 g. of dimethyl sulfate, and 16.7 g. of potassium hydroxide in 39 cc. of water were added as above. This was repeated until there was no color change of the mixture on addition of the alkali. After the last addition, the reaction mixture was diluted with water, and poured into a separatory funnel for extraction with benzene. The benzene extract was washed with water, 10% sodium carbonate, and 5% sodium chloride to prevent the formation of an emulsion. After distilling off the benzene and water, the residue was fractionated. The fraction boiling between 170–180°/1 mm. (Wood's metal-bath at 240–280°), yielded 104 g. (73%) of clear colorless VI with a faint bluish fluorescence. A middle fraction cut at 174°/1 mm. was analyzed; n_D^{25} 1.5118.

Anal. Calc'd for $C_{15}H_{23}BrO_2$: C, 57.1; H, 7.4; Br, 25.4.
Found: C, 57.1; H, 7.6; Br, 25.3.

The red residue formed in the reaction of V with hydrogen bromide exhibited vesicant activity. Apparently some of the dimethyl ether was split in this reaction, for the red residue exhibited the typical catechol reactions with ferric chloride (green to black), and lead acetate (white precipitate), and gave a rash similar to that of poison ivy. The remethylated compound (VI) was completely inactive, and gave negative tests with the above reagents.

3-(Nonynyl-8')veratrole (VII). Sodium acetylide 0.084 mole in 210 cc. of liquid ammonia was prepared according to the method of Hennion (11), and transferred into a previously dried steel autoclave of 1.82 liters capacity, immersed in a solid carbon dioxide and alcohol-bath, taking precautions to keep out moisture. A solution of 20 g. of the above bromide (VI) (0.064 mole) in 40 cc. of sodium-dried petroleum ether was slowly added, and then the autoclave head equipped with an ammonia valve and asbestos gasket[3] was clamped into place. The ammonia valve was closed, and the autoclave removed from the dry ice-bath. It was shaken by hand every five minutes, as it came to room temperature. After standing overnight it was cooled in solid carbon dioxide, and the ammonia pressure was released. The dry ice-bath was removed, and the ammonia slowly evaporated. Before all the liquid ammonia was gone, 7 g. of ammonium chloride was added to neutralize the excess sodium acetylide. To dissolve the salts, and facilitate the extraction of the product with ether, 50 cc. of water was slowly added. The rest of the ammonia was evaporated, and the mixture was extracted with ether. The ether extracts were washed with 9% hydrochloric acid, 5% sodium carbonate, and with some faintly acidulated water. After removal of ether the oil was dried by the addition and distillation of benzene. The residue was fractionated at 2 mm. to yield 8.5 g. (51.5%) of clear colorless liquid (VII) boiling at 141–143°. Repeating the reaction with a larger amount of (VI) gave a slightly lower percentage yield. The combined products were redistilled, and boiled at 145–146°/2.1 mm. (Wood's metal-bath at 176–179°), yielding a total of 34 g. of (VII). A middle fraction was taken at 146°/2 mm. (Wood's metal-bath at 178°), for analysis; n_D^{25} 1.5094.

Anal. Calc'd for $C_{17}H_{24}O_2$: C, 78.5; H, 9.5.
Found: C, 78.6; H, 9.4.

3-(Pentadecynyl-8')veratrole (VIII). This new disubstituted acetylene was prepared in a manner similar to that employed by Vaughn, Hennion, *et al.* (17), for the preparation of dialkyl acetylenes.

Sodamide (0.138 mole) made from 3.8 g. of sodium in 200 cc. of liquid ammonia, using ferric nitrate as catalyst, according to the method of Vaughn, Vogt, and Nieuwland (18), was transferred to an autoclave (see preparation of VII), with swirling to keep the sodamide in suspension. Twenty-four grams of the monosubstituted acetylene (VII) (0.092 mole) in

[3] A Johns-Manville graphited asbestos gasket coated with Lubriseal was found to work satisfactorily up to a tested pressure of 300 lbs. per square inch.

an equal volume of petroleum ether, and then 22.8 g. (0.138 mole) of hexyl bromide were added with swirling. The autoclave was closed, and agitated as it was allowed to come to room temperature. After standing at room temperature overnight, the autoclave was cooled and opened. Fourteen grams of ammonium chloride was added, and then 100 cc. of water. The liquid ammonia was evaporated, and the product extracted and worked up as in the preparation of VII. Distillation at 190–200°/2 mm. (Wood's metal-bath at 240–290°) yielded 18.5 g. (0.054 mole) of a clear colorless liquid (VIII), a yield of 85% on the basis of reacted starting material, since 7.5 g. of VII (0.028 mole) was recovered in the forerun. This product, combined with that from a smaller pilot run, was redistilled at 192–192.8°/1.2–1.4 mm. (bath at 248–251°), yielding a total of 19.4 g. of pure VIII. A middle fraction distilling at 192°/1.4 mm. was analyzed; n_D^{25} 1.4993, d_4^{25} 0.9414, MR 107.4 (calc'd 106.3).

Anal. Calc'd for $C_{25}H_{36}O_2$: C, 80.2; H, 10.5.
Found: C, 80.4; H, 10.5.

cis-*3-(Pentadecenyl-8')veratrole (IX).* Conversion of the disubstituted acetylene (VIII) to the *cis* olefin was accomplished by a quantitative hydrogenation in the presence of Raney nickel, according to the method of Campbell and O'Connor (12).

Four and ninety-four hundredths grams (0.0143 mole) of VIII, was hydrogenated in the presence of one-half cc. of wet Raney nickel (19), in 25 cc. of 95% ethyl alcohol, at 31° and a pressure of 763 mm. The theoretical amount of hydrogen required to convert 0.0143 mole of the acetylene to the olefin under these conditions is 373 cc. The hydrogenation was stopped after an uptake of 367 cc. (six minutes). The last 20 cc. was absorbed at an appreciably lower rate. The catalyst was filtered off, the alcohol distilled, and the residue fractionated. The product distilled at 196–198°/2 mm. (Wood's metal-bath at 238–251°) to give 4.4 g. of a clear colorless liquid (89% yield). A middle fraction cut at 198°/2 mm. (bath at 238°) was analyzed; n_D^{25} 1.4940, d_4^{25} 0.9359, MR 108.9 (calc'd 107.7).

Anal. Calc'd for $C_{23}H_{38}O_2$: C, 79.7; H, 11.1; OCH_3, 17.9.
Found: C, 79.7; H, 11.1; OCH_3, 17.7.

trans-*3-(Pentadecenyl-8')veratrole (X).* Two and thirty-one hundredths grams (0.10 mole) of sodium was dissolved in 200 cc. of liquid ammonia and transferred to the autoclave. Five and seven-tenths grams of the disubstituted acetylene (VIII) was added, the autoclave was closed and was shaken intermittently for two hours in an ice-water-bath. After cooling thoroughly in a solid carbon dioxide-bath, the autoclave was opened, and 3.0 g. of ammonium chloride was added, and then 45 cc. of water. After the liquid ammonia had evaporated, the reduced compound was extracted with ether, and the ether extracts washed with 9% hydrochloric acid, and twice with water. The ether was distilled off, and the water removed by adding benzene and distilling. The residue was fractionated at 211–212°/3.2 mm. (Wood's metal-bath at 242–254°) and yielded 5.3 g. (89%) of clear colorless liquid (X). A middle fraction boiling at 212/3.2 mm. (bath at 248°) was analyzed; n_D^{25} 1.4968, d_4^{25} 0.9323, MR 108.7 (calc'd 107.7).

Anal. Calc'd for $C_{23}H_{38}O_2$: C, 79.7; H, 11.1.
Found: C, 80.0; H, 11.1.

3-Pentadecylveratrole (XI). (Tetrahydrourushiol dimethyl ether). Complete reduction of the acetylenic linkage of (VIII) was accomplished by catalytic hydrogenation at a pressure of 754 mm. using Raney nickel catalyst. The shaking vessel contained 16 drops of wet catalyst and 0.968 g. (0.00282 mole) of VIII dissolved in 20 cc. of 95% ethyl alcohol. A marked drop in the rate of absorption of hydrogen was observed after an uptake of 71.0 cc. (0.00282 mole), indicating the preferential reduction of the acetylenic linkage by the nickel catalyst. The reduction continued, and was stopped after an uptake of 135.2 cc. of hydrogen (0.00564 mole at 26° and 745 mm. occupies 141.5 cc.). After filtering off the catalyst, the filtrate was concentrated and the residue was recrystallized twice from alcohol yielding white hair-like needles, melting at 36.8–37.0° in good yield.

Anal. Calc'd for $C_{23}H_{40}O_2$: C, 79.3; H, 11.6.
Found: C, 79.1; H, 11.7.

Oxidative degradation of (X). Three grams of the *trans* olefin (X) dissolved in 150 cc. of acetone was oxidized by 9 g. of powdered potassium permanganate added portionwise according to Armstrong and Hilditch (13). After refluxing for sixteen hours, most of the acetone was distilled off, and water was added. The manganese dioxide was dissolved by acidifying with dilute sulfuric acid, and adding sodium bisulfite. Then the solution was extracted with ether. The carboxylic acid degradation products were recovered from the ether by thoroughly washing with 10% sodium carbonate solution, and freed from unoxidized material by washing the aqueous layer several times with ether. The aqueous layer was acidified and steam distilled to separate the aliphatic acids from the less volatile aromatic acids. The distillate was saturated with salt, and extracted with ether. After evaporating the ether, the residue was dried by the addition and distillation of benzene, and then distilled at 12 mm. A middle fraction boiling at 110° was analyzed and identified as *n*-heptylic acid, thereby indicating the presence of a double bond in the 8′ position.

Anal. Calc'd for $C_7H_{14}O_2$: C, 64.5; H, 10.8.
Found: C, 64.7; H, 10.6.

The boiling point at 760 mm. (micro) was 222–223° (corr.). *n*-Heptylic acid at 760 mm. boils at 223.5° (Beilstein). The neutral equivalent calculated for *n*-heptylic acid is 130; found, 129.

The resin-like material in the steam distillation flask was extracted with ether, the ether evaporated, and the residue dried by the addition and distillation of benzene. On distillation at 2 mm. in a micro still (Wood's metal-bath at 95–100°) a white solid was obtained which on recrystallization from benzene yielded white needle-like crystals melting at 122°. The compound was identified as *o*-veratric acid, by a mixed melting point with a specimen of *o*-veratric acid made from Monsanto *o*-veratraldehyde by oxidation with alkaline permanganate according to Perkin and Robinson (20). Mixed melting point 122°.

Urushiol dimethyl ether (XII). The bark from poison ivy vine, collected in Westchester County, New York,[4] was extracted with alcohol, according to the procedure of Hill (2). Precautions were taken to minimize oxidation of the urushiol by keeping the bark and extracts under carbon dioxide at all times. Attempts to distill the urushiol directly from the concentrate were not very successful, due to oxidative polymerization and severe frothing. To minimize these effects the brown oil was methylated according to the method of Perkin and Weizman (10). The methylated oil was then distilled without serious frothing, at 172–205°/0.03 mm. Two batches of bark (about 40 lbs.) were carried to this point. The distillates were combined, remethylated, and redistilled. The main fraction boiled at 182–189°/0.04 mm., and amounted to 7.6 g. of a yellow oily liquid. The middle fraction boiling at 189°/0.045 mm. (Wood's metal-bath at 234–245°) was analyzed; n_D^{25} 1.5030, d_4^{25} 0.9407, MR 108.3 (calc'd 107.3).

Anal. Calc'd for $C_{23}H_{36}O_2$: C, 80.2; H, 10.5; OCH_3, 18.00.
Found: C, 80.6; H, 10.4; OCH_3, 15.4.

Quantititive hydrogenation with palladium black indicated 105% unsaturation. The hydrogenation data and low methoxyl value indicate the presence of an unsaturated impurity having approximately the same carbon and hydrogen values as urushiol dimethyl ether. The low methoxyl value cannot be attributed to possible steric hindrance of the methoxyl in position 2 since the synthetic compound IX gave correct values.

Tetrahydrourushiol dimethyl ether (XIII). The above urushiol dimethyl ether (XII) (0.591 g., 0.00171 mole) was catalytically reduced with 16 drops of wet Raney nickel catalyst in 25 cc. of 95% ethyl alcohol. The reduction was stopped after an uptake of 0.00342 mole of hydrogen, (88.0 cc. at 26° and 756 mm.). The absence of a sharp break in the rate of absorption of hydrogen after an uptake of 0.00171 mole as in the reduction of VIII under the same conditions, showed that the unsaturation in XII was due to olefinic linkages, and not to an acetylenic bond. After filtering off the catalyst, the filtrate was concentrated and cooled in the refrigerator. The precipitated white solid was recrystallized from ethyl

[4] On the property of Dr. B. Brown, Armonk, New York.

alcohol, yielding white needles melting at 36.2–37.0°. A mixed melting point with the synthetic tetrahydrourushiol dimethyl ether (XI) was at 36.6–37.0°.

Anal. Calc'd for $C_{23}H_{40}O_2$: C, 79.3; H, 11.6.
Found: C, 79.2; H, 11.7.

o-Dimethoxytoluene. *o*-Veratraldehyde was reduced by the Clemensen method as modified in Organic Syntheses (21), yielding 24 g. (56%) of the *o*-dimethoxytoluene boiling at 104°/24.5 mm. (oil-bath at 148°). It was redistilled and a middle fraction at 103° and 22.5 mm. (oil-bath at 142°) was analyzed; n_D^{25} 1.5121, d_4^{25} 1.0335, MR 44.2 (calc'd 43.4).

Anal. Calc'd for $C_9H_{12}O_2$: C, 71.0; H, 8.0.
Found: C, 71.2; H, 8.0.

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SUMMARY

A method of synthesis for 3-alkenyl veratroles has been developed that could be applied for the introduction of one or more double bonds in any desired position in the side chain.

Cis and *trans* 3-(pentadecenyl-8′)veratrole have been synthesized by this method. The reduced compound, 3-pentadecylveratrole was found to be identical with tetrahydrourushiol dimethyl ether obtained by the methylation and catalytic hydrogenation of urushiol extracted from poison ivy.

All of the 3-alkyl veratroles studied were found to exhibit an exaltation of the molecular refractivity of about 0.8–1.2 units.

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[CONTRIBUTION FROM THE GEORGE S. COX MEDICAL RESEARCH INSTITUTE, UNIVERSITY OF PENNSYLVANIA]

INVESTIGATIONS ON STEROIDS. VII. COMPOUNDS RELATED TO 6-METHYL-11-DESOXYCORTICOSTERONE[1]

MAXIMILIAN EHRENSTEIN

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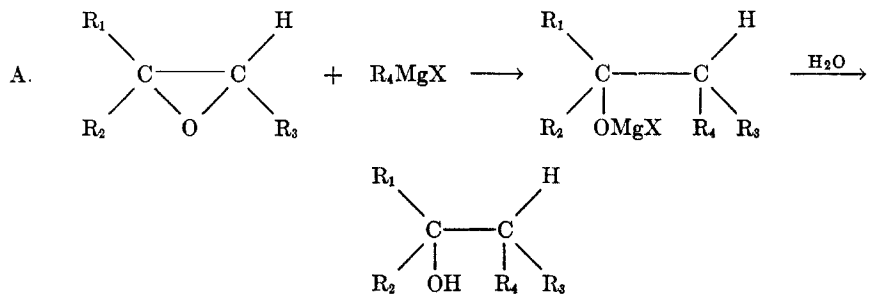
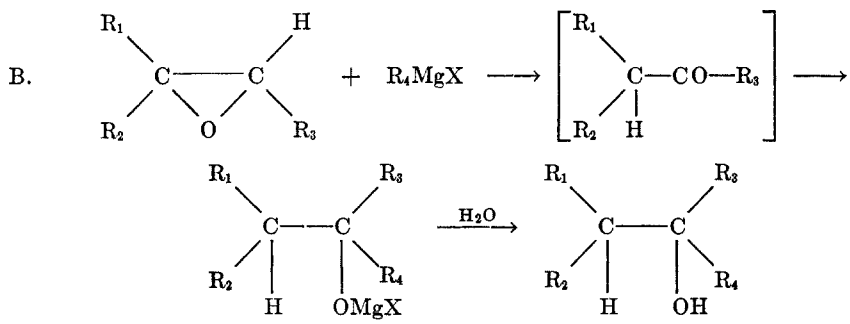
In connection with research on substances related to adrenal-cortical hormones the question arose whether it is possible to introduce certain aliphatic or hydroaromatic radicals in position 6 of the molecule of desoxycorticosterone. Before trying the radicals which we have ultimately in mind, a model experiment was planned with the purpose of synthesizing 6-methyl-11-desoxycorticosterone. So far only side chain homologs of desoxycorticosterone have been described in the literature (1).

As is known (2) Grignard reagents may react with certain substituted ethylene oxides in two different fashions:

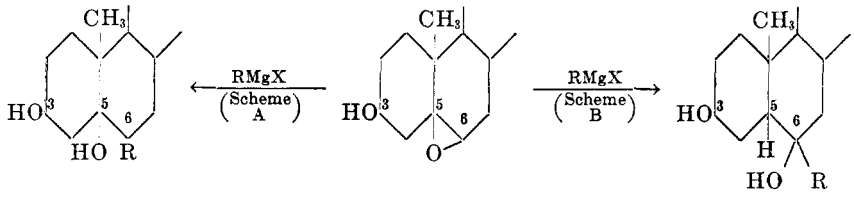




According to Scheme A the new radical becomes attached to the secondary carbon atom. If the reaction proceeds according to Scheme B, the reactant first rearranges to a ketone. The latter reacts in a normal fashion with the Grignard reagent and thereby furnishes a compound in which the hydroxyl group and the new radical appear at the same, originally secondary, carbon atom.

[1] Aided by a grant from the Smith, Kline and French Laboratories in Philadelphia.

The 5,6-oxides of the steroid series represent compounds to which the above described reactions should be applicable. In either case the new radical (R) would become attached to carbon atom 6.



A compound obtained according to scheme A should be easily transformable into an α,β-unsaturated ketone, namely by oxidation of the secondary hydroxyl group at C_3 and subsequent dehydration.

A reaction proceeding according to Scheme A was described by Madaeva, Ushakov, and Kosheleva (3). These authors succeeded in transforming the oxide of 5-androstene-3(β),17-diol into 6-methyl-3(β),5,17-triol by means of the Grignard reagent CH_3MgI. Essentially this reaction was carried out in a solution of benzene which was boiled for three hours. The yield of the crude 6-methyl compound was only about 30%. No yield of the purified substance is given. It can be concluded from the manipulations involved that it must have been small. The authors claim that by oxidation of the 6-methyl compound and by subsequent dehydration they were able to prepare 6-methyl-4-androstene-3,17-dione. No yields of the intermediary and of the end product are given. The final product possesses about the same androgenic activity as 4-androstene-3,17-dione.

A Grignard reaction in which essentially scheme B is involved was described by Chinaeva and Ushakov (4). The α-oxide of cholesterol was isomerized to cholestane-6-one-3(β)-ol by boiling it with a solution of C_6H_5MgBr in benzene. Subsequent treatment of the 6-keto compound with the Grignard reagent furnished 6-phenylcholestane-3(β), 6-diol, the 3-monoacetate of which could be dehydrated to 6-phenylcholesteryl acetate.

A suitable starting material for experiments in the series of cortin compounds appeared to be 21-acetoxypregnenonol (I) which is an intermediate in the synthesis of desoxycorticosterone. Provision had to be made to prevent the participation in the Grignard reaction of the C_{20}-keto group. This was achieved by reducing 21-acetoxypregnenonol (II) according to the method of Meerwein and of Ponndorf (5). The 5-pregnene-3(β),20,21-triol (II) thus obtained had been described previously by Steiger and Reichstein (6) as well as by Miescher, Hunziker, and Wettstein (7). The purification of the triol was carried out by way of the acetone compound (III), as was first described by Reichstein (6). This compound was subjected to numerous recrystallizations with the purpose of obtaining a substance representing mainly one of the two stereoisomeric forms which may be expected due to the epimerism at carbon atom 20. It is believed that the acetone compound ($[\alpha]_D^{29.5}$ — 46.5°

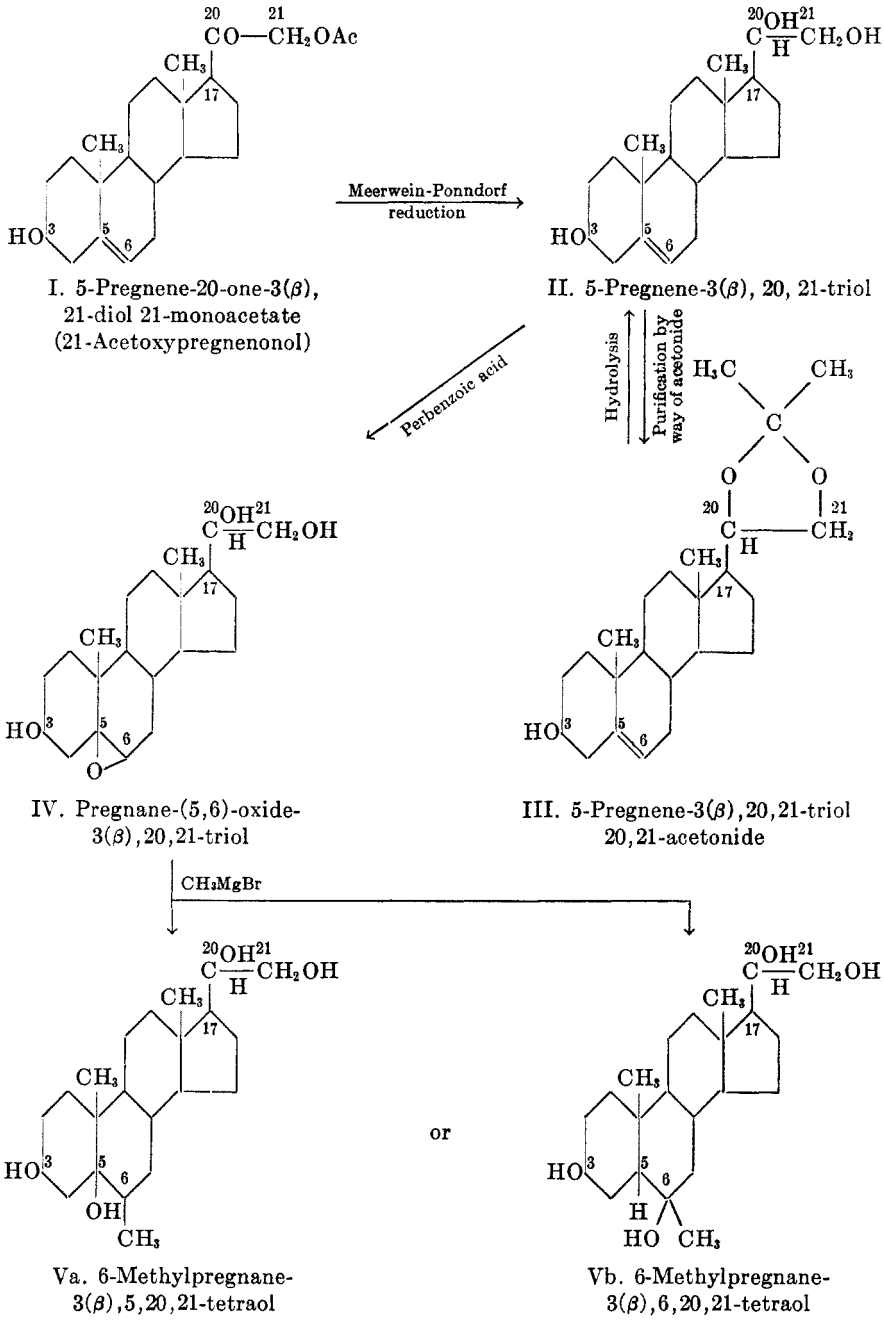
whereas Reichstein (6) recorded $[\alpha]_D^{21} - 50.8°$) is stereochemically rather pure because, on hydrolyzing it, several crops of 5-pregnene-3(β), 20,21-triol (II) with almost identical melting points were obtained. No special configuration regarding carbon atom 20 is assigned to this compound.

The triol (II) was treated with perbenzoic acid as described in several earlier publications (8, 9). The pregnane-(5,6)-oxide-3(β),20,21-triol (IV) thus obtained was subjected to purification by chromatographic adsorption. This was followed by numerous recrystallizations. It is almost certain that the purified material is stereochemically pure and it is probable that the oxide ring of this substance possesses the α-configuration. Because the configuration is not definitely proved, no assignment regarding it is given.

The oxide (IV) is not sufficiently soluble in those solvents which are most frequently used for Grignard reactions. The reaction was performed in a solution of anisole. By the action of methylmagnesium bromide upon the oxide, a methylated compound was obtained to which structure Va or Vb may be assigned, depending on whether the reaction proceeded according to the general scheme A or B. Repeated crystallizations of the reaction product furnished a fair yield of constant-melting material. There was, initially, every indication that the substance was uniform and it was tentatively assigned the structure of 6-methylpregnane-3(β),5,20,21-tetraol (Va). It must be borne in mind that both structures (Va and Vb) embody the possibility of stereoisomerism at carbon atoms 5 and 6.

As a subsequent step, the attempt was made to transform the tetraol (Va or Vb) into its 21-monoacetate by partial acetylation. It was realized that such a reaction had to be performed under mild conditions with only a slight excess of one equivalent of acetylating agent. Since the secondary hydroxyl group at carbon atom 3 is also easily esterified (*e.g.* 8, 9, 10) the formation of a certain amount of 3,21-diacetate was expected. The crude acetylation product was subjected to a separation of the components by means of chromatographic adsorption. It is known (11) that esters are less strongly adsorbed and hence more easily eluted than the corresponding alcohols. In the series of steroid compounds, for instance, mixtures of acetates of polyalcohols separate in such a way that the more acetylated material appears earlier and the less acetylated material later in the eluate (*e.g.* 8, 9, 10).

In the present instance about 20% of the employed acetate came out in two of the earlier fractions of the eluate. Part of this material crystallized. The analysis was in agreement with a diacetate. The compound was tentatively assigned the structure of 6-methylpregnane-3(β),5,20,21-tetraol 3,21-diacetate (VI), though an analogous structure derived from formula Vb is possible. It is rather probable that the acetoxyl groups are attached to carbon atoms 3 and 21, because oxidation of these crystals with chromic acid yielded material which strongly reduced an alkaline solution of silver diammine. The oxidation product was not isolated in a crystalline form, its structure can only be that of a 6-methylpregnane-20-one-3(β),5,21-triol 3,21-diacetate (VII) or of a compound of analogous structure derived from formula Vb.



I. 5-Pregnene-20-one-3(β), 21-diol 21-monoacetate (21-Acetoxypregnenonol)

II. 5-Pregnene-3(β), 20, 21-triol

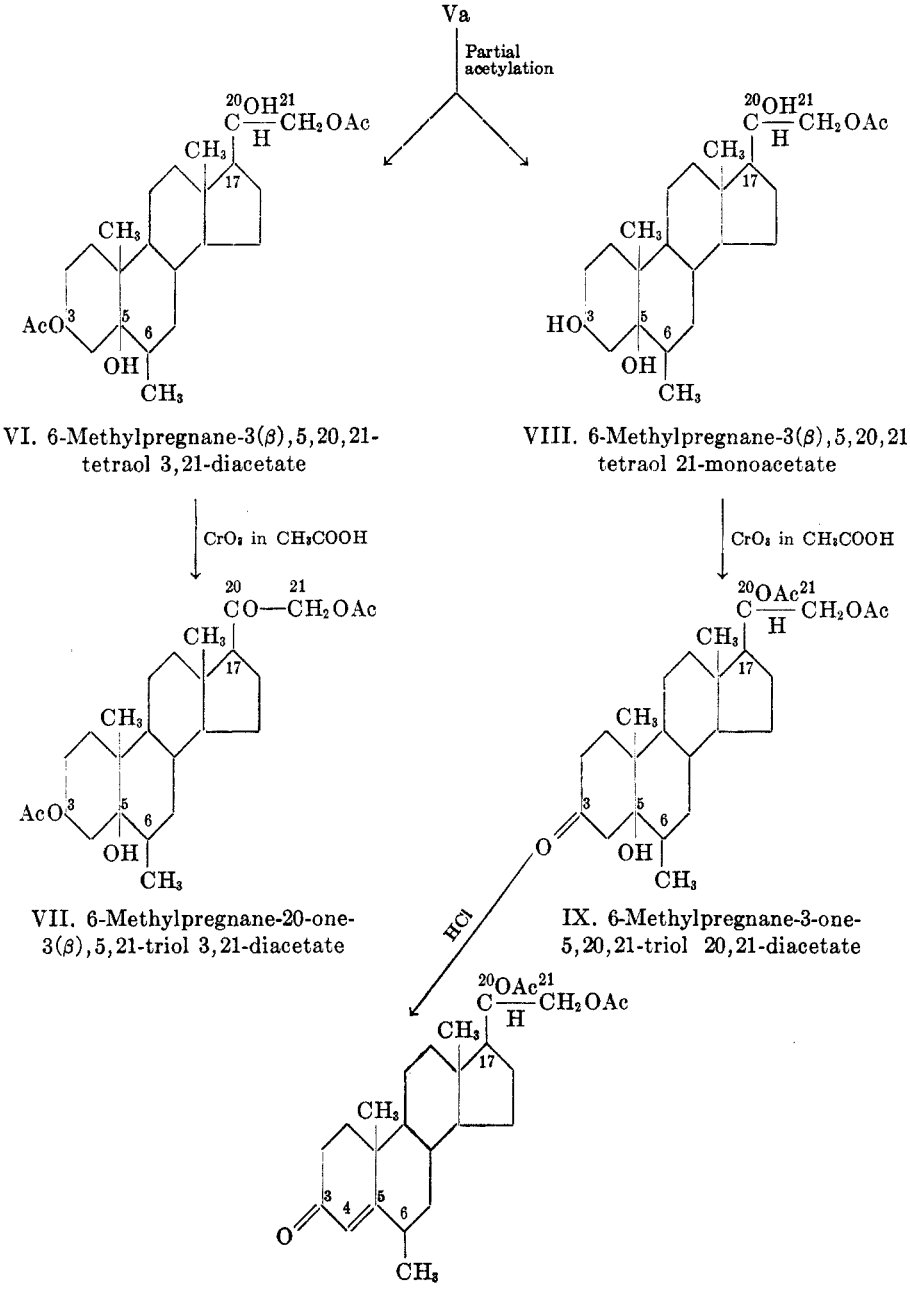
IV. Pregnane-(5,6)-oxide-3(β),20,21-triol

III. 5-Pregnene-3(β),20,21-triol 20,21-acetonide

Va. 6-Methylpregnane-3(β),5,20,21-tetraol

Vb. 6-Methylpregnane-3(β),6,20,21-tetraol

In the chromatographic procedure the major part of the acetate employed appeared in several of the later fractions of the eluate. Part of this material crystallized; the analysis was in agreement with a monoacetate. Also the



amorphous part of the major fraction yielded analytical results which are in conformity with a monoacetate. The crystalline substance was assigned the structure of a 6-methylpregnane-3(β),5,20,21-tetraol 21-monoacetate (VIII).

The behavior of this substance in the following reactions indicates that it is probably derived from structure Va rather than structure Vb. No specific structure was assigned to the amorphous part of the monoacetate fraction because the reactions which were carried out with it (oxidation and subsequent dehydration) yielded inconclusive results. One of the last fractions of the eluate was identified as unchanged tetraol.

It was intended to oxidize the 21-monoacetate (VIII) to the corresponding 3,20-diketo compound and to dehydrate the latter to the acetate of 6-methyl-desoxycorticosterone. For some unexplainable reason the reaction took a different course. When the crystalline 21-monoacetate (VIII) was treated with chromic acid, in acetic acid solution, slightly in excess of the equivalent of two oxygen atoms, a substance was obtained to which has to be assigned the

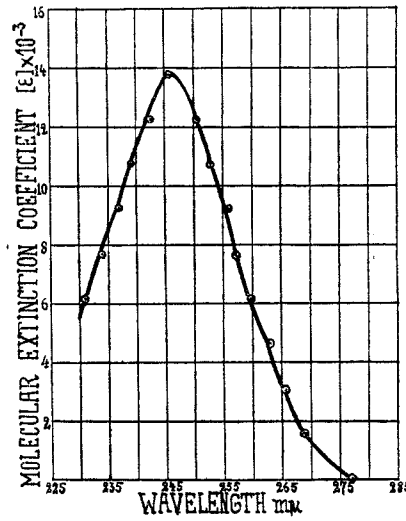


FIG. 1. ABSORPTION CURVE OF CRYSTALLINE 6-METHYL-4-PREGNENE-3-ONE-20,21-DIOL DIACETATE (IN ABSOLUTE ALCOHOL)[2]

structure of 6-methylpregnane-3-one-5,20,21-triol 20,21-diacetate (IX). Dehydration of the latter compound with dry hydrogen chloride in a solution of chloroform yielded 6-methyl-4-pregnene-3-one-20,21-diol diacetate (X). Neither compound IX nor X reduces complex silver-ammonium salts. Hence the presence of ketol side chains is out of the question. The end product (X) gave the characteristic ultra-violet absorption spectrum[2] of α,β-unsaturated ketones, with the maximum absorption at 245.5mμ and the molecular extinction coefficient 13.83×10^{-3}. The substance appears to be the diacetate of a homolog of one of the two epimeric forms of 4-pregnene-3-one-20,21-diol (6).

No reason can be advanced why the oxidation of the crystalline monoacetate

[2] We are indebted to Professor George R. Harrison of the Department of Physics of the Massachusetts Institute of Technology for the determination of the ultra-violet absorption spectra.

(VIII) did not involve the secondary alcohol group at carbon atom 20 and why, instead, the latter was acetylated. The simplest explanation would be the assumption that the structure which was assumed for compound VIII is wrong and that the structure is really that of the corresponding 20,21-diacetate. This argument may be supported by the fact that the substance (VIII) was only analyzed once. Unfortunately there was not sufficient material left for a repetition of the analysis. It is believed, however, that the location of this substance in the chromatogram makes it rather certain that it was really a monoacetate. Another explanation might be the formation during the oxidation of an enol diacetate, the enol grouping involving carbon atom 20. Because of a number of reasons it is considered certain that such a possibility can be ruled out.

As was mentioned, the non-crystalline monoacetate referred to above was subjected to oxidation and subsequent dehydration. Both reaction products were non-crystalline. The dehydration product moderately reduced a complex silver salt solution. Its ultra-violet absorption spectrum[2] and the result of the analysis were in disagreement with the structure of the acetate of 6-methyl-desoxycorticosterone. It is believed that the two reaction products represent mixtures and therefore these experiments are not included in the experimental part.

EXPERIMENTAL

All melting points were determined with the Fisher-Johns melting point apparatus of the Fisher Scientific Company (Pittsburgh, Pa.). The microanalyses were carried out by Mr. William Saschek, Columbia University, New York. The 21-acetoxypregnenonol was furnished by Dr. Erwin Schwenk of the Schering Corporation in Bloomfield, N. J.

5-Pregnene-3(β),20,21-triol 20,21-acetonide (III). To a solution of 6.2 g. of 21-acetoxypregnenonol (I) in 62 cc. of absolute isopropanol (distilled over sodium) was added 6.2 g. of freshly distilled aluminum isopropoxide. A distillation of the originally completely clear solution (oil-bath; temperature about 95°) was performed in such a fashion that about three to six drops went over per minute. Fresh isopropanol was added at the same rate. After about six hours the reaction with sodium nitroprusside had become practically negative. The distillation was continued under the same conditions for two more hours. A precipitate had formed gradually during the course of the reaction.

The reaction mixture was worked up as stated in the literature (6). The combined ethyl acetate extracts were eventually dried with sodium sulfate. On concentrating this solution several crops of crystalline material were obtained, the total amounting to 4.71 g. This material was dissolved in 37 cc. of a solution of 5% methanolic potassium hydroxide. The mixture was heated for a while on the water-bath. After the addition of 125 cc. of water, the methanol was removed *in vacuo*. The residue was extracted with ethyl acetate and the latter solution washed with water and dried with sodium sulfate. On concentrating the ethyl acetate solution *in vacuo*, several crops of crystalline material were obtained; the total was 4.49 g.

The combined crystalline material was dissolved in 2.4 liters of acetone (freshly distilled over calcium chloride). After the addition of 48 g. of anhydrous cupric sulfate the mixture was shaken on a machine for about four days. Subsequent filtering of the cupric sulfate, brief shaking with some potassium carbonate and renewed filtering yielded a solution which was gradually concentrated to a smaller volume. This furnished a main crop of crystalline material (wt. 3.03 g.; m.p. 167–169.5°), several smaller crops of crystalline

appearance (total wt. 1.51 g.; m.p. 135° and below) and a resinous residue (wt. 0.34 g.). The first crop was subjected to very numerous recrystallizations from acetone; the melting point could not be raised above 175°. The many fractions melting at 172–173°, 173–174°, and 174–175° were eventually combined; total: 2.68 g. The lower-melting, though crystalline, material of the whole experiment added up to 1.81 g. It was repeatedly observed that the pure substance crystallized from acetone first in fine long needles which on standing overnight changed to stout, long plates; $[\alpha]_D^{29.5}$ − 46.5° (20.0 mg. in 2.0 cc. of acetone).

5-Pregnene-3(β),20,21-triol (II). To a solution of 2.55 g. of the pure acetonide (III) in 88 cc. of absolute alcohol was added a mixture of 27.5 cc. of glacial acetic acid and 110 cc. of water. The ensuing precipitate went into solution on heating. The solution was refluxed by gentle heating for almost three hours. By subsequent concentrating *in vacuo* two crops of crystalline material, totalling 2.27 g. were obtained. Repeated recrystallizations from methanol furnished 1.69 g. of the pure substance; scales, m.p. 222–229°. Several other crystalline crops, totalling 0.48 g. had melting points only slightly lower than that recorded for the pure substance. $[\alpha]_D^{31}$ − 54.0° (15.0 mg. in 2.0 cc. of methanol).

Pregnane-(5,6)-oxide-3(β),20,21-triol (IV). To a solution of 1.69 g. of purest available triol (II) in 500 cc. of chloroform was added at room temperature 14.6 cc. of a chloroform solution containing approximately 20% excess of perbenzoic acid (870 mg.). The mixture was allowed to stand at room temperature (20°) for almost four days. It was then washed with *N* sodium carbonate solution and with water. After drying with sodium sulfate it was brought to dryness; the residue was a colorless brittle foam; wt. 1.75 g. This material was subjected to chromatographic adsorption, for which purpose it was dissolved in a mixture of 120 cc. of chloroform and 75 cc. of ether. This solution was filtered through a suitably prepared column of 36 g. of aluminum oxide (aluminum oxide anhydrous, standardized for chromatographic adsorption according to Brockmann, E. Merck, Darmstadt).

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE (MG.)	APPEARANCE OF RESIDUE
1.	120 cc. chloroform + 75 cc. ether	81.8	Mainly oily, some crystals
2.	60 cc. chloroform + 30 cc. ether	115.2	Soft resin
3.	60 cc. chloroform + 30 cc. ether	23.8	Glassy
4.	75 cc. chloroform + 15 cc. ether	32.2	Glassy
5.	75 cc. chloroform + 15 cc. ether	110.6	Brittle foam
6.	90 cc. chloroform	108.8	Brittle foam
7.	90 cc. chloroform	100.4	Brittle foam
8.	89.5 cc. chloroform + 0.5 cc. methanol	130.9	Crystalline
9.	89 cc. chloroform + 1 cc. methanol	323.4	Crystalline
10.	89 cc. chloroform + 1 cc. methanol	267.0	Crystalline
11.	89 cc. chloroform + 1 cc. methanol	140.0	Crystalline
12.	85 cc. chloroform + 5 cc. methanol	100.4	Partly crystalline
13.	80 cc. chloroform + 10 cc. methanol	58.2	Glassy
14.	75 cc. chloroform + 15 cc. methanol	15.1	Glassy
15.	90 cc. methanol	33.3	White mass
Total		1641.0	

The original solution was passed through the adsorbing column in about 3 hours, fractions 2-12 in about 30 minutes each. The remaining fractions were filtered somewhat more quickly. The residues of fractions 5, 6, and 7 crystallized when they were treated with some methanol. The crystalline fractions were separately treated with sufficient amounts

of methanol to bring them into solution. After the addition of some ether, crystallization occurred, either at once or after standing. The crystalline crops were filtered and the filtrates brought to dryness. The residues thus obtained were again treated with methanol and ether. This yielded further crops of crystalline material. A number of crystalline crops obtained from fractions 8, 9, 10, and 11 showed melting points between 180° and 200°. They were singled out for separate and repeated recrystallizations from acetone. The purest material thus obtained crystallized in polygonal plates, melting at 221–223°. It should be mentioned, however, that the molten substance did not appear quite homogeneous as a few oily droplets appeared suspended in it. Many crystalline fractions showed melting points between 218° and 222°; they were eventually combined, the total was 500 mg. A number of crystalline fractions with lower melting points added up to 270 mg. $[\alpha]_D^{20}$ − 63.5° (20.0 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{21}H_{34}O_4$: C, 71.95; H, 9.78.
Found: C, 71.66, 71.95; H, 9.66, 9.71.

6-Methyl-pregnane-3,(β),5,20,21-tetraol (*Va.*). The reaction was carried out in a solution of anisole because the oxide was practically insoluble in benzene, common ether, and several other aliphatic ethers. To 845 mg. of activated magnesium turnings (about 40 moles) was added 13 cc. of absolute ether and a trace of an iodine crystal. A dry stream of methyl bromide (washed with conc'd sulfuric acid) was passed through until the magnesium was practically dissolved. Three hundred milligrams of oxide (IV) melting between 218° and 222°, was dissolved in 80 cc. of anisole (distilled over sodium) by heating and the solution subsequently cooled to room temperature. To the Grignard solution was added 15 cc. of anisole and thereafter the solution of the oxide in anisole. The ether was removed from this mixture by gentle heating with the reflux condenser turned off. Thereupon the mixture was heated in a metal-bath at a temperature of about 130° for three and one-quarter hours. The next day a solution of saturated ammonium chloride and ice was added. After the addition of some ethyl acetate, the anisole-ethyl acetate phase was separated from the aqueous layer. Thereafter the aqueous phase was agitated three times with ample quantities of ethyl acetate. The various extracts were subsequently washed with cold dil. hydrochloric acid, dil. sodium carbonate, and twice with water. The anisole-ethyl acetate and the combined ethyl acetate phases were dried separately with sodium sulfate. They were brought to dryness *in vacuo* at a temperature not exceeding 65°. The residues were treated with some ethyl acetate, which was followed by filtering and bringing to dryness of the filtrate. The same treatment was repeated with the residues obtained as long as more crystalline crops could be secured. The main crop (137 mg.) had the melting point 207–211°, and two crops (totalling 86 mg.) melted between 193° and 203°; a few more crystalline crops (totalling 7 mg.) melted considerably lower and were consequently disregarded. Repeated recrystallizations of the crystalline material above described from acetone furnished a number of fractions (totalling 168 mg.), most of them melting with gas evolution between 221° and 227°. One especially pure fraction crystallized in rosettes of beautiful prisms; m.p. 229–230° (gas evolution). There was a depression of the melting point of about 20° when any of the above mentioned samples was mixed with the oxide (IV) of m.p. 221–223°; $[\alpha]_D^{20.5}$ − 24.0° (10.0 mg. in 2.0 cc. of methanol).

Anal. Calc'd for $C_{22}H_{38}O_4$: C, 72.07; H, 10.45.
Found: C, 72.37, 72.31; H, 10.61, 10.82.

Partial acetylation of 6-methylpregnane-3(β),5,20,21-tetraol (*Va.*). Various fractions of the above described tetraol with melting points ranging between 218° and 227° did not give melting point depressions when mixed in all combinations. A total of 191 mg. of such material was thoroughly mixed. This combined material, melting at 220–221° (gas evolution), was dissolved in 0.9 cc. of pure pyridine. To this solution was added in the cold room 0.2 cc. of a solution in pyridine of 65 mg. of acetic anhydride (about 25% excess of one mole). The mixture was allowed to remain in the cold room for 16.5 hours. After standing for 4.5 more hours at room temperature it was brought to a sirupy consistency

by concentrating it *in vacuo* (45°). Thereafter water was added and the material extracted with ether (approx. 100 cc.). The ether phase was subsequently washed with dil. hydrochloric acid, dil. sodium carbonate, and twice with water. A small sample of ether was used for re-extracting all wash solutions. The combined ether solutions were dried with sodium sulfate. After removal of the ether and drying *in vacuo* a brittle foam was obtained; wt. 228 mg. This material was subjected to chromatographic adsorption for which purpose it was dissolved in a mixture of 25 cc. of benzene and 6 cc. of petroleum ether. The solution was passed through a column of 7 g. of aluminum oxide (Brockmann).

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE (MG.)	APPEARANCE OF RESIDUE
1.	25 cc. benzene + 6 cc. petroleum ether	0.9	Greasy
2.	30 cc. benzene	3.4	Resin
3.	30 cc. benzene	8.4	Resin
4.	25 cc. benzene + 5 cc. ether	27.4	Sticky glass, trace of crystals
5.	20 cc. benzene + 10 cc. ether	25.5	Sticky glass
6.	10 cc. benzene + 20 cc. ether	6.3	Resin
7.	30 cc. ether	2.3	Resin
8.	30 cc. ether	1.9	Resin
9.	20 cc. ether + 10 cc. chloroform	4.3	Resin
10.	10 cc. ether + 20 cc. chloroform	14.7	Sticky glass
11.	30 cc. chloroform	31.2	Amorphous white mass
12.	29.8 cc. chloroform + 0.2 cc. methanol	64.6	Brittle foam
13.	29.5 cc. chloroform + 0.5 cc. methanol	27.3	Brittle foam
14.	25 cc. chloroform + 5 cc. methanol	20.4	Apparently partly crystalline
15.	30 cc. methanol	5.8	White mass
Total..... (Some residues were obviously not quite dry)		244.4	

The original solution was passed through the adsorbing column in about one hour, the following solvent combinations at the rate of approximately twenty minutes each. Crystalline material could ultimately be obtained from fractions 4, 5, 11, 12, and 13.

6-Methylpregnane-3(β),5,20,21-tetraol 3,21-diacetate (VI). When fractions 4 and 5 of the above chromatogram were treated with ether, two crops of crystalline material were obtained from each. Total yield from fraction 4: 5.2 mg.; total yield from fraction 5: 6.4 mg. The melting points of the four crops (between 178° and 186°) indicated identical material. Hence the total (11.6 mg.) was combined, dissolved in ether, and concentrated to a smaller volume. Crystallization began spontaneously. Several crops of long, flat needles were obtained. First crop: wt. 6.9 mg.; m.p. 185–187°. Second crop: wt. 1.9 mg.; m.p. 183–185.5°. The filtrate yielded 2.3 mg. of a crystalline residue. The analysis refers to the first crop.

Anal. Calc'd for $C_{26}H_{42}O_6$: C, 69.28; H, 9.40.
Found: C, 68.95; H, 9.66.

6-Methylpregnane-3(β),5,20,21-tetraol 21-monoacetate (VIII). Fractions 11, 12, and 13 of the chromatogram were separately dissolved in the required amounts of ether. On standing at room temperature for several days, one crop of crystals separated from each solution, the weights were 2.8 mg., 11.8 mg., and 7.2 mg. respectively. The melting points indicated identical material and hence these three crops (total 21.8 mg.) were combined

Recrystallization was performed by dissolving in a rather large amount of ether and then concentrating to a smaller volume. Separation of rosettes of very small crystals began spontaneously; first crop: wt. 15.4 mg.; m.p. 177.5–180°; second crop: wt. 2.5 mg.; m.p. 177.5–180°. The filtrate, on being brought to dryness, furnished a mainly resinous residue. The analytical data refer to the first crop; $[\alpha]_D^{30}$ + 15.0° (10.0 mg. in 2.0 cc. of methanol).

Anal. Calc'd for $C_{24}H_{40}O_5$: C, 70.53; H, 9.87.
Found: C, 70.17; H, 10.30.

An analysis was also performed with the amorphous part of fraction 12 of the chromatogram. It was obtained as a brittle foam after the removal of the crystalline material.

Anal. Calc'd for $C_{24}H_{40}O_5$: C, 70.53; H, 9.87.
Found: C, 70.58; H, 10.37.

It should be mentioned that the examination of fraction 14 of the above chromatogram furnished a fair amount (10.4 mg.) of material melting at 226–228°. It was identified by mixture melting point as unchanged tetraol.

6-Methylpregnane-20-one-3(β),5,21-triol 3,21-diacetate (VII). To a solution of 4.2 mg. of crystalline 6-methylpregnane-3(β), 5,20,21-tetraol 3,21-diacetate (VI) in 0.3 cc. of glacial acetic acid was added 0.54 cc. (the equivalent of 1.15 atoms of O) of a solution of 333 mg. of chromium trioxide in 100 cc. of 90% acetic acid. The mixture was allowed to stand at room temperature (26°) for 21 hours. It was then worked up in the usual fashion. The crude reaction product was resinous; no attempt was made to crystallize it. A solution of this oxidation product in methanol strongly reduced an alkaline solution of silver diammine.

6-Methylpregnane-3-one-5,20,21-triol 20,21-diacetate (IX). Ten milligrams of the crystalline modification of the 21-monoacetate of the tetraol (VIII) was dissolved in 0.5 cc. of glacial acetic acid. To this was added 1.13 cc. (the equivalent of 2.3 atoms of O) of a solution of 333 mg. of chromium trioxide in 100 cc. of 90% acetic acid. The mixture was allowed to stand at room temperature (29°) for 19 hours. After the addition of 1.0 cc. of alcohol it was brought almost to dryness *in vacuo*. A little water was added to the resinous residue; this caused a white precipitate to appear which was taken up in ether. The ether extract was washed with a solution of *N* sodium carbonate, three times with water, and was finally dried with sodium sulfate. The ethereal solution was brought to dryness and the residue treated with ether to which some petroleum ether was added. Some crystalline material separated; yield: 2.2 mg.; m.p. about 205–210°. It cannot be considered absolutely pure. The filtrate yielded 5.1 mg. of a crystalline residue. The analysis refers to the former material. A solution of the substance in methanol did not reduce an alkaline solution of silver diammine.

Anal. Calc'd for $C_{26}H_{40}O_6$: C, 69.59; H, 8.99.
Found: C, 69.38; H, 9.17.

On repetition of this experiment identical results were obtained.

6-Methyl-4-pregnene-3-one-20,21-diol diacetate (X). Six and four-tenths milligrams of crystalline 6-methylpregnane-3-one-5,20,21-triol 20,21-diacetate (IX) (combined samples of various melting points) was dissolved in 2 cc. of dry redistilled chloroform. A moderate stream of dry hydrogen chloride was passed through this solution for two and one-half hours; cooling with ice, temperature not above +2°. The solution was poured into ice-cold *N* sodium carbonate, shaken in a separatory funnel, washed three times with water, and dried with sodium sulfate. After the removal of the solvent and drying of the residue in a vacuum desiccator, 6.0 mg. of a colorless resin was obtained. This product was dissolved in ether and then some petroleum ether was added. On standing at room temperature for several days, the separation of about 2 mg. of crystalline warts, m.p. 165–170°, occurred. A part of this material was used for the determination of the ultra-violet absorption spectrum (Fig. 1). The rest of it was added to the filtrate and the latter subsequently brought to dryness. The residue was a resin which was subjected to microanalysis. A solution of this substance in methanol did not reduce an alkaline solution of silver diammine.

Anal. Calc'd for $C_{26}H_{38}O_5$: C, 72.51; H, 8.90.
Found: C, 72.20; H, 9.04.

SUMMARY

By treatment with perbenzoic acid 5-pregnene-3(β),20,21-triol (II) was transformed into a pure pregnane-(5,6)-oxide-3(β),20,21-triol (IV). The oxide ring possesses probably the α-configuration. By proper treatment of the oxide (IV) with methylmagnesium bromide a reaction product was obtained which consisted, at least partly, of a 6-methylpregnane-3(β),5,20,21-tetraol (IV). By acetylation of the tetraol with one equivalent of acetic anhydride, a monoacetate fraction was obtained from which the crystalline 6-methylpregnane-3(β),5,20,21-tetraol 21-monoacetate (VIII) was isolated. A comparatively small yield of a crystalline diacetate was secured which was tentatively assigned the structure of 6-methylpregnane-3(β),5,20,21-tetraol 3,21-diacetate (VI).

By oxidation of the crystalline monoacetate (VIII) with chromic acid in glacial acetic acid a compound was obtained which can only be interpreted as 6-methylpregnane-3-one-5,20,21-triol 20,21-diacetate (IX). No conclusive explanation for this unexpected reaction is offered. Dehydration of the before mentioned substance (IX) furnished 6-methyl-4-pregnene-3-one-20,21-diol diacetate.

By oxidation of the crystalline diacetate (VI) with chromic acid a substance was obtained which probably possesses the structure of 6-methylpregnane-20-one-3(β),5,21-triol 3,21-diacetate (VII).

PHILADELPHIA, PA.

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[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

DIACETONE XYLITOL

R. STUART TIPSON AND LEONARD H. CRETCHER

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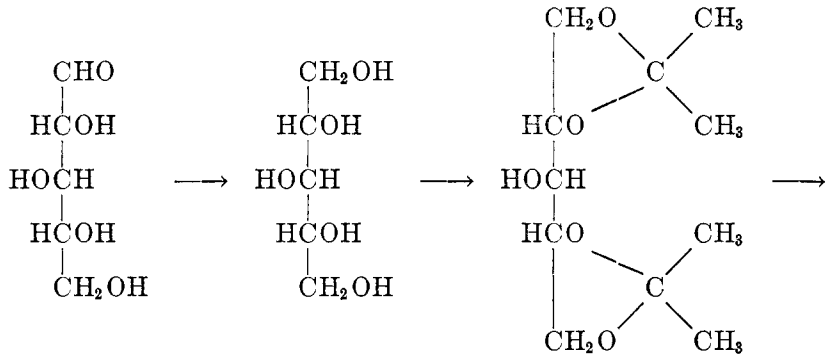
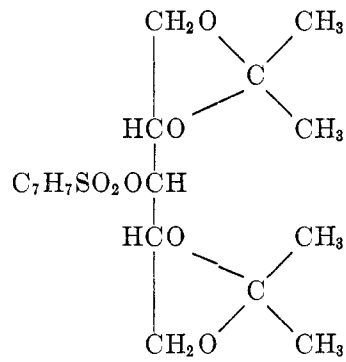
In the course of other work, it recently became desirable to prepare 3-tosyl xylitol and certain of its derivatives. It appeared probable that this could be accomplished by performing the following series of reactions.



D-xylose xylitol di-isopropylidene xylitol



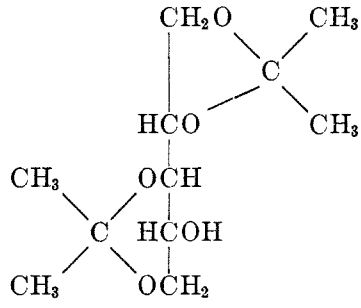
3-tosyl di-isopropylidene xylitol

I

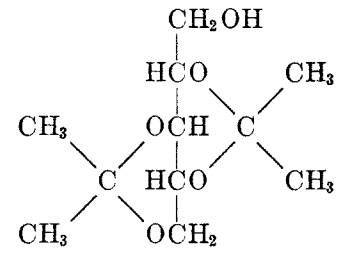
Accordingly, xylitol was condensed with acetone, giving a crystalline, optically inactive di-isopropylidene xylitol which was then esterified with *p*-toluenesulfonyl chloride in pyridine, yielding a crystalline, optically inactive monotosyl di-isopropylidene xylitol.

It was realized, however, that formulas II and III (although less probable than formula I for a diacetone xylitol) could not be excluded without proof. Despite the fact that compound I is *meso*, whereas compounds II and III should be capable of existence in optically active forms, the observed absence of optical

activity affords no evidence as to structure. Even if either (or both) of the unsymmetrical forms should result, the present type of reaction would yield a racemic mixture.



II



III

Now in the sugar series it has been established (1) that, on treatment (under standard conditions) with sodium iodide dissolved in acetone, a tosyl group attached to the primary alcoholic group in aldohexoses is readily substituted by iodine, whereas tosyl groups attached at other positions are unaffected. The applicability of the reaction has since been extended (2) to the aldopentofuranoses, but it has been shown (3) not to proceed with 1-tosyl-ketopentose or -ketohexose derivatives. If this rule also applies to the sugar alcohols, the tosyl ester of III would react with sodium iodide in acetone, but that of I or II would not.

On performing the reaction with tosyl diacetone xylitol, it was found that sodium iodide effects practically quantitative replacement of the tosyl group, which might be accepted as an indication that III is the correct formula. However, it was suspected that the rule might not apply to tosyl esters of sugar alcohols since it was recalled that Levene and Mehltretter (4) found that sodium iodide reacts with all three of the tosyl groups in tritosyl glycerol.

Consequently, we decided to investigate the action of sodium iodide on the polytosyl ester of some other sugar alcohol. Tetratosyl erythritol was therefore prepared; all four of its tosyl groups reacted with sodium iodide, giving a practically quantitative yield of sodium *p*-toluenesulfonate.

Hence, it may be concluded that Oldham and Rutherford's rule cannot be extended to the tosyl esters of sugar alcohols, and some doubt is cast on such work as that of Müller (5), who employed the reaction to indicate the position of tosyl groups in certain tosyl esters of sugar alcohols.

Incidentally, the method might prove of use in the preparation of certain unsaturated hydrocarbons from the corresponding sugars, through the sugar alcohols. It has been shown (6) that diiodo compounds having the iodine atoms attached at adjacent carbon atoms cannot be prepared by the action of sodium iodide in acetone on the corresponding dichloro or dibromo derivatives, since the diiodo compounds readily lose iodine to form unsaturated substances. In the present work, tetratosyl erythritol was found to give rise to butadiene and free iodine.

EXPERIMENTAL

Xylitol. Xylitol was prepared by the catalytic hydrogenation (7) of D-xylose (20 g.) in 45 cc. of water, in the presence of Raney's nickel catalyst, giving a quantitative yield of xylitol.

Diacetone xylitol. Xylitol (20 g.) was condensed with acetone (200 cc.) in the presence of 20 g. of anhydrous copper sulfate and 0.2 cc. of concentrated sulfuric acid as described (8) for the condensation of pentoses with acetone. The product (28 g.) was purified by distillation under a high vacuum. It had b.p. 80° at 0.1 mm. (bath temp., 94°) and n_D^{25} 1.4510. It crystallized spontaneously on cooling, and the colorless crystals were readily recrystallized from 2 volumes of pentane. It had m.p. 34–34.5° and $[\alpha]_D^{25}$ 0° (c = 5, in acetone).

Anal. Calc'd for $C_{11}H_{20}O_5$: C, 56.86; H, 8.7.
Found: C, 56.64; H, 8.8.

Tosyl diacetone xylitol. Diacetone xylitol (10 g.) was dissolved in 50 cc. of dry pyridine, and 9 g. of *p*-toluenesulfonyl chloride was added in one portion, with cooling. After standing overnight at room temperature, the product was isolated as described (3) for ditosyl monoacetone xylulose, giving a practically quantitative yield of colorless syrup which crystallized solid on standing overnight in the refrigerator. After recrystallization from absolute ethanol (2 volumes) it had m.p. 70–71° and $[\alpha]_D^{25}$ 0° (c = 5, in absolute ethanol).

Anal. Calc'd for $C_{18}H_{26}O_7S$: C, 55.92; H, 6.8; S, 8.30.
Found: C, 55.33; H, 6.8; S, 8.55.

Action of sodium iodide on tosyl diacetone xylitol. A mixture of 0.5 g. of dry, recrystallized tosyl diacetone xylitol with 0.4 g. of dry sodium iodide was dissolved in 5 cc. of acetone and the colorless solution heated in a sealed tube at 100° during 2 hours. The solution turned very pale yellow in color, and colorless, flaky crystals separated out. After cooling, the crystals were filtered off, washed with acetone and dried at 60°; wt. 0.236 g. (94% yield). The crystals had the following composition.

Anal. Calc'd for $C_7H_7NaO_3S$: S, 16.52. Found: S, 16.62.

It was also found that, by heating a solution of the same composition *under reflux* during 2 hours, some 18% of the theoretical yield of sodium *p*-toluenesulfonate crystallized out.

Tetratosyl erythritol. Erythritol (10 g.) was suspended in 200 cc. of dry pyridine, cooled to 0°, and 69 g. of *p*-toluenesulfonyl chloride was added in one portion. After standing in the refrigerator during 2 days, the product was isolated in the usual manner, giving 56.5 g. of crude, crystalline material. Ten grams was recrystallized by dissolving in 175 cc. of boiling acetone under reflux and cooling. The first crop (5.5 g.) had m.p. 165–166° and $[\alpha]_D^{22}$ 0° (c = 1, in chloroform).

Anal. Calc'd for $C_{32}H_{34}O_{12}S_4$: C, 52.00; H, 4.64; S, 17.37.
Found: C, 51.99; H, 4.62; S, 17.35.

Action of sodium iodide on tetratosyl erythritol. Dry, recrystallized tetratosyl erythritol (0.5 g.) was treated with 0.8 g. of sodium iodide in 10 cc. of acetone in a sealed tube at 100° during 2 hours. The yield of sodium *p*-toluenesulfonate (completely soluble in water) was 0.4773 g. (91% of the theoretical for removal of 4 tosyl groups). Much free iodine was liberated.

It was also found that by boiling a solution of the same composition *under a reflux condenser* (closed by a Drierite tube) for various intervals of time the yields of sodium *p*-toluenesulfonate were as follows: 41% (2 hrs.); 50.5% (4 hrs.); 74.5% (12 hrs.). Owing to the low solubility of tetratosyl erythritol in acetone, it was necessary to introduce the following slight modification. At the elapse of the specified time, the suspension was cooled, filtered, and the acetone-insoluble material washed with acetone, dried, and weighed. It was then thoroughly washed with water, and any water-insoluble material was dried at 110°, weighed, and its weight subtracted from the total weight, giving the yield of sodium *p*-toluenesulfonate.

After treatment of 10 g. of tetratosyl erythritol during 12 hours under reflux, and isola-

tion of the sodium *p*-toluenesulfonate as above, the acetone-insoluble material contained no water-insoluble material. The acetone filtrate and washings were combined and evaporated to dryness. The dark brown crystalline mass was dissolved in a mixture of chloroform and water, and sodium thiosulfate solution was added until, on shaking, the color of the free iodine disappeared. The chloroform solution was washed with water, dried with anhydrous sodium sulfate, filtered, and the clear, very pale yellow filtrate evaporated to dryness, giving 2.5 g. of crystalline product consisting mainly of unchanged tetratosyl erythritol, but containing a little iodinated material.

Anal. Calc'd for $C_{32}H_{34}O_{12}S_4$: S, 17.37; I, 0.0.
Calc'd for $C_4H_6I_4$: S, 0.0; I, 90.38.
Found: S, 15.2; I, 16.2.

It therefore appeared that the major portion of the organic reaction product had been lost at some stage in the above procedure.

Accordingly, 10 g. of tetratosyl erythritol was mixed with 16.3 g. of sodium iodide, and 175 cc. of acetone was added. The suspension was boiled during 3 hours (in a water-bath at 75°) under a reflux condenser to the top o which were connected, in series, two traps cooled in solid carbon dioxide-chloroform. A colorless liquid collected in the first trap and was found[1] to contain material possessing conjugated double bonds, presumably butadiene.

To make sure that the above results were not occasioned by some impurity in the sodium iodide or acetone employed (or in both), a sample (0.5 g.) of dry, recrystallized 3-tosyl diacetone D-glucose (m.p. 120–121°; $[\alpha]_D^{28}$ −70.5° (c = 1, in chloroform)) was treated with 0.4 g. of sodium iodide in 5 cc. of acetone in a sealed tube at 100° during 2 hours, but no reaction took place.

SUMMARY

The preparation and properties of di-isopropylidene xylitol, tosyl di-isopropylidene xylitol, and tetratosyl erythritol are described. All four of the *p*-toluenesulfonyl groups in the latter react with sodium iodide under standard conditions.

Oldham and Rutherford's rule apparently does not apply to tosyl esters of sugar alcohols.

PITTSBURGH, PA.

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[1] We are indebted to Dr. J. A. Hinckley and Mr. L. J. Lohr for this determination.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

THE REACTION OF GRIGNARD REAGENTS WITH OXIMES. II. THE ACTION OF ARYL GRIGNARD REAGENTS WITH MIXED KETOXIMES

KENNETH N. CAMPBELL, BARBARA KNAPP CAMPBELL, AND ELMER PAUL CHAPUT

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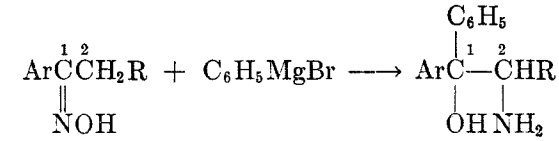
In an earlier paper from this Laboratory (1), it was shown that phenylmagnesium bromide reacts at elevated temperatures (no reaction takes place at ordinary temperatures) with mixed ketoximes to yield, not the hydroxylamines which would be formed by the addition of the Grignard reagent to the carbon-nitrogen double bond, but rather beta-amino alcohols. In this reaction a rearrangement of nitrogen from carbon atom 1 to carbon atom 2 has occurred.



In the earlier paper the reaction of phenylmagnesium bromide with the oximes of acetophenone, propiophenone, methyl *p*-tolyl ketone, and *p*-chloroacetophenone was described. It seemed of interest to extend this reaction to other mixed ketoximes, and especially to other aryl Grignard reagents; the results of this study are recorded in the present paper.

When acetophenone oxime was treated with *p*-tolylmagnesium bromide, α-naphthylmagnesium bromide, and *p*-anisylmagnesium bromide by the technique used previously, the corresponding amino alcohols were obtained. Amino alcohols were also obtained from propiophenone oxime and *p*-tolylmagnesium bromide, from *p*-phenylacetophenone oxime and phenylmagnesium bromide, and from butyrophenone oxime and phenylmagnesium bromide; the structures of these amino alcohols were established by comparison with authentic samples made by different methods; the data are recorded in Table I. Several attempts were made to prepare 1-phenyl-1-*p*-anisyl-2-aminoethanol from phenylmagnesium bromide and the oxime of *p*-methoxyacetophenone, but only tars were obtained.

In the case of the 1-phenyl-1-*p*-tolyl-2-amino propanol (from *p*-tolylmagnesium bromide and propiophenone oxime) two diastereoisomers are possible; only one of these was obtained, and it corresponded to the isomer prepared by Tiffeneau (2), from isonitrosopropiophenone and *p*-tolylmagnesium bromide.

EXPERIMENTAL

Preparation of materials. Most of the chemicals were obtained from the Eastman Kodak Co. and were purified by distillation. *p*-Phenylacetophenone (3), and *p*-methoxyacetophenone (4), were made by the Friedel-Crafts reaction; *p*-bromotoluene was prepared from *p*-toluidine (5), and *p*-bromoanisole was made by the bromination of anisole (6).

The ketoximes were prepared as follows. To 0.5 mole of ketone in 300 cc. of 95% alcohol was added a solution of 56 g. of hydroxylamine hydrochloride in 80 cc. of water; 157 g. of 50% aqueous potassium hydroxide solution was then added, and the mixture was refluxed for two hours. The cooled solution was poured into several volumes of ice and water, and then acidified with hydrochloric acid. The precipitated oxime was washed well with water, and was then dried *in vacuo* over calcium chloride and then over phosphorus pentoxide. The yields varied from 80–90%; the oximes had the following melting points; acetophenone, 59°; propiophenone, 53–55°; *p*-phenylacetophenone, 184–186°; butyrophenone, 50°.

Reaction of aryl Grignard reagents with ketoximes. Since these reactions were all carried out in the same general way, only a typical run will be described in detail.

The Grignard reagent was prepared from 6 g. of magnesium turnings, 125 cc. of dry ether, and a slight excess of aryl halide.[1] When all the magnesium had dissolved, ether was distilled off by heating the reaction flask in an oil-bath. When the bath temperature reached 150–155° the characteristic color change described previously (1), occurred, and the distillation was stopped. Usually about 60 cc. of ether was recovered in the distillation. Thirty cubic centimeters of dry toluene was added to the concentrated Grignard reagent, and a solution of 0.05 mole of oxime in about 30 cc. of dry toluene was added dropwise while the oil-bath temperature was kept at 150°. Usually a vigorous reaction occurred, and the addition required 30–40 minutes. When all the oxime solution had been added, the mixture was heated and stirred for 15–30 minutes more, and was then allowed to cool. It was hydrolyzed by pouring onto ice and hydrochloric acid. Usually the acid mixture was extracted three times with ether to remove non-basic impurities, and these extracts were discarded. Sometimes, especially with the naphthyl and diphenylamino alcohols, the sparingly soluble hydrochloride separated at the ether-water interface, and was removed by filtration. The acid aqueous layer was then made strongly basic with ammonium hydroxide, and was again extracted three times with ether. The ether solution was dried over anhydrous magnesium sulfate and the solvent removed. The solid residue was purified by recrystallization from alcohol or an alcohol-water mixture. The yields of amino alcohols so obtained varied from 40–75%.

The amino alcohols were converted to their hydrochlorides by adding a solution of dry hydrogen chloride in anhydrous ether to a solution of the amino alcohol in anhydrous ether, care being taken to avoid an excess of hydrogen chloride. The solid so formed was recrystallized from absolute alcohol and ether.

The amino alcohol benzamides were made from 1-g. quantities of the amino alcohols by the Schotten-Baumann procedure.

Comparisons of the amino alcohols and their derivatives with authentic samples are shown in Table I.

Synthesis of amino alcohols for comparison. 1-Phenyl-1-*p*-tolyl-2-aminoethanol (8), 1-phenyl-1-α-naphthyl-2-aminoethanol (9), and 1-phenyl-1-*p*-anisyl-2-aminoethanol (10) were prepared by the action of the appropriate Grignard reagent on phenacylamine hydrochloride (11). 1-Phenyl-1-*p*-tolyl-2-aminopropanol was made from *p*-tolylmagnesium bromide and alpha-aminopropiophenone hydrochloride (2). The amino alcohol so obtained melted higher (m.p. 74–75°) than the product reported by Tiffeneau (2), (m.p. 69–70°).

1-Phenyl-1-*p*-biphenyl-2-aminoethanol, which has not been reported before, was prepared as follows: α-Bromo-*p*-phenylacetophenone, prepared by the method of Drake and Bronitsky (3), was converted to alpha-amino-*p*-phenylacetophenone hydrochloride in the following way. A solution of 52 g. of the bromo ketone in 200 cc. of chloroform was treated with a solution of 33.3 g. of hexamethylenetetramine in 150 cc. of hot chloroform. The reaction mixture was allowed to stand for 24 hours, and the solid product was then collected. It was suspended in a mixture of 55 cc. of concentrated hydrochloric acid and 450 cc. of

[1] For the preparation of α-naphthylmagnesium bromide the procedure of Gilman and co-workers (7) was used.

95% alcohol, and this mixture was allowed to stand for several days. The precipitated solid was collected and recrystallized from hot water acidulated with hydrochloric acid. The amino ketone so obtained charred on heating, but showed no definite melting point. Nine and one-half grams of this amino ketone hydrochloride was added gradually to a solution of phenylmagnesium bromide prepared from 5 g. of magnesium, 33 g. of bromobenzene and 94 cc. of dry ether. After addition was complete, the reaction mixture was refluxed for four hours and then was hydrolyzed with ice and ammonium chloride, and extracted with ether. The solid remaining on evaporation of the ether was recrystallized from an alcohol-water mixture.

TABLE I

COMPARISON OF AMINO ALCOHOLS FROM OXIMES WITH AUTHENTIC SAMPLES

AMINO ALCOHOL	SOURCE	M.P. °C FREE BASE	M.P. °C HYDRO-CHLORIDE	M.P. °C BENZAMIDE
1-Phenyl-1-*p*-tolyl-2-aminoethanol	Acetophenone oxime and C_7H_7MgBr	103–104	183–184	142–143
	Phenacylamine and C_7H_7MgBr	104–105	183–184	142–143
	Mixture	104	183–184	142–143
1-Phenyl-1-naphthyl-2-aminoethanol	Acetophenone oxime and $C_{10}H_7MgBr$	159–160	232–234	193–194
	Phenacylamine and $C_{10}H_7MgBr$	158	236–238	192–193
	Mixture	159	236–237	193
1-Phenyl-1-*p*-anisyl-2-aminoethanol	Acetophenone oxime and $MeOC_6H_4MgBr$	132.5–133	162–163	
	Phenacylamine and $MeOC_6H_4MgBr$	134	164–165	
	Mixture	133–134	163–164	
1-Phenyl-1-biphenyl-2-aminoethanol	*p*-Phenylacetophenone oxime and C_6H_5MgBr	86–88	220–222	193–195
	Amino-*p*-phenylacetophenone and C_6H_5MgBr	85–87	222–224	192–194
	Mixture	86–88	220–223	192–194
1-Phenyl-1-*p*-tolyl-2-aminopropanol	Propiophenone oxime and C_7H_7MgBr	72–73	237–238	195–196
	Aminopropiophenone and C_7H_7MgBr	74–75	239	195–195.5
	Mixture	73–74	239	195
1,1-Diphenyl-2-aminobutanol	Butyrophenone oxime and C_6H_5MgBr	77–78	259	209–211
	Aminobutyric ester and C_6H_5MgBr	76.5–77	258	208–210
	Mixture	77–78	258	208–210

Anal. Calc'd for $C_{20}H_{19}NO$: C, 83.05; H, 6.62; N, 4.84.
Found: C, 83.12; H, 6.74; N, 4.69.

The benzamide of the amino alcohol was prepared; it was obtained as a white crystalline powder after recrystallization; it melted at 193–195°.

Anal. Calc'd for $C_{27}H_{23}NO_2$: N, 3.57. Found: N, 3.32.

1,1-Diphenyl-2-aminobutanol was prepared from ethyl α-aminobutyrate and phenylmagnesium bromide. Alpha-aminobutyric acid was obtained in 63% yield from alpha-bromobutyric acid (12), and was converted to the ester hydrochloride in the usual way.

Thirty-three grams of the ester hydrochloride (m.p. 141°) was added during the course of one hour to 1.25 moles of phenylmagnesium bromide, and the mixture was refluxed for one hour. It was hydrolyzed with ice, the basic solution was extracted several times with ether, and the extracts were dried over anhydrous magnesium sulfate. The solid obtained on evaporation of the ether was recrystallized from an alcohol-water mixture. The yield of recrystallized material was 33 g. or 62%.

Anal. Calc'd for $C_{16}H_{19}NO$: C, 79.65; H, 7.89; N, 5.81.
Found: C, 79.50; H, 8.05; N, 5.88.

The benzamide, prepared in the usual way, melted at 209–210° after recrystallization from alcohol.

Anal. Calc'd for $C_{24}H_{23}NO_2$: N, 3.92. Found: N, 3.89.

SUMMARY

Several aryl Grignard reagents have been shown to react with the oximes of aryl alkyl ketones to yield β-amino alcohols. Two new amino alcohols, 1-phenyl-1-*p*-biphenyl-2-aminoethanol, and 1,1-diphenyl-2-aminobutanol have been described.

NOTRE DAME, IND.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

THE ACTION OF GRIGNARD REAGENTS ON OXIMES. III. THE MECHANISM OF THE ACTION OF ARYLMAGNESIUM HALIDES ON MIXED KETOXIMES. A NEW SYNTHESIS OF ETHYLENEIMINES

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Ethyleneimines, unlike their analogs, the ethylene oxides, have not been studied extensively. This is due, in part at least, to the fact that there is no general method for the synthesis of ethyleneimines, and but few compounds of this class are known. Ethyleneimine itself, and a few of its derivatives can be prepared from the sulfate of the corresponding amino alcohol (1, 2).

$$CH_2OHCH_2NH_2 \longrightarrow CH_2OHCH_2NH_2 \cdot H_2SO_4 \longrightarrow \begin{matrix} CH_2CH_2NH_2 \\ | \quad\quad | \\ O{-}SO_2{-}O \end{matrix} \xrightarrow{NaOH} \begin{matrix} CH_2{-}{-}CH_2 \\ \diagdown \quad \diagup \\ \quad N \\ \quad H \end{matrix}$$

This method is not applicable to aryl-substituted amino alcohols, for with these dehydration by sulfuric acid leads to vinyl amines and other compounds (3). 2-Phenyl- and 2,3-diphenyl-ethyleneimine have been prepared from the amino alcohols *via* the corresponding chloroamines (4, 5).

$$C_6H_5CHOHCH_2NH_2 \longrightarrow C_6H_5CHClCH_2NH_2 \longrightarrow \begin{matrix} C_6H_5CH{-}{-}{-}{-}CH_2 \\ \quad\quad\quad\quad \diagdown \quad \diagup \\ \quad\quad\quad\quad\quad NH \end{matrix}$$

This method fails with tertiary amino alcohols, because it is extremely difficult to prepare the necessary chloroamines (6, 7).

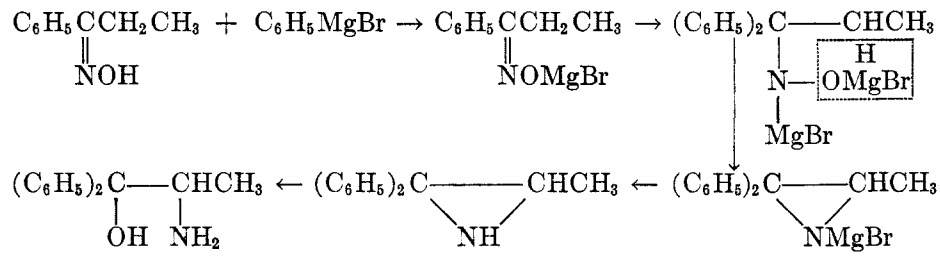
Previous work in this Laboratory (8, 9) has shown that arylmagnesium halides react with mixed aryl-alkyl ketoximes to give beta-amino alcohols by rearrangement, rather than the expected hydroxylamines. This rearrangement is a fairly general one, and amino alcohols have been obtained from a wide variety of aryl Grignard reagents and substituted acetophenone oximes:

$$ArMgBr + \begin{matrix} Ar'C{-}CH_2R \\ \| \\ NOH \end{matrix} \longrightarrow \begin{matrix} \quad\quad Ar \\ \quad\quad | \\ Ar'C{-}{-}CHR \\ | \quad\quad | \\ OH \quad NH_2 \end{matrix}$$

In every case the structure of the amino alcohol was established by comparison with an authentic sample. The reaction has shown itself to be a useful one for the synthesis of aryl-substituted beta-amino alcohols, and in many cases the preparation of the amino alcohol is simpler by this method than by older ones.

Although in the earlier work no attempt was made to determine the mechanism

of this rearrangement, it seemed probable than an ethyleneimine was formed as intermediate, and that this subsequently cleaved to the amino alcohol.

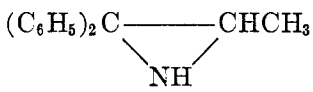


Hoch (10) reported that he obtained an ethyleneimine from the action of phenylmagnesium bromide on propiophenone oxime, but he did not give any experimental details or proof of structure of his product. Since the reaction might lead to a general method of preparation of ethyleneimines, and since it was of interest to determine the mechanism of the reaction between Grignard reagents and ketoximes, a detailed study was made of the action of phenylmagnesium bromide on propiophenone and butyrophenone oximes.

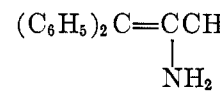
When propiophenone oxime was treated with phenylmagnesium bromide, it was found that the conditions of the experiment markedly affected not only the yields but also the nature of the product isolated. When the reaction was carried out as previously described (8), namely, using a concentrated Grignard reagent and hydrolyzing the reaction complex with acid and ice, the amino alcohol, 1,1-diphenyl-2-aminopropanol, m.p. 103–104°, was obtained in 30–40% yield. If no acid was used in the hydrolysis, or if the complex was hydrolyzed with acid at 0°, immediately made basic with ammonium hydroxide, and extracted, a product melting at 72–73° was obtained. This same material was isolated, in better yield and in a purer state, when the Grignard reaction was carried out in toluene solution at 135–145° and the complex hydrolyzed without the use of acid, or the acid solution kept very cold and worked up at once. If the acid hydrolysis mixture was allowed to stand for any length of time, or to get warm, both the substance melting at 72–73° and the amino alcohol were obtained. When the Grignard reaction was carried out in diethyl ether, and the mixture hydrolyzed without the use of acid, a large amount of propiophenone oxime was recovered, and some of the compound melting at 72–73° was isolated.

Analysis of the compound melting at 72–73° gave values agreeing with those calculated for a substance of the formula $C_{15}H_{15}N$. It seemed likely, therefore, that the substance was the ethyleneimine of structure I. This was then definitely shown to be the case by chemical evidence which ruled out the other possibilities, IIa, IIb, and III, and by synthesis.

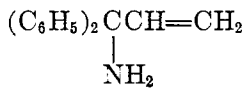
The compound, m.p. 72–73°, readily forms a stable, non-hygroscopic hydrochloride, from which the free base can be regenerated by treatment with aqueous alkali. It reduces an aqueous or acetone solution of potassium permanganate in the cold very slowly. When it is warmed for a short while with 2 *N* sulfuric acid or 6 *N* hydrochloric acid, it is converted quantitatively into 1,1-diphenyl-2-



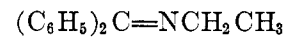
I



IIa

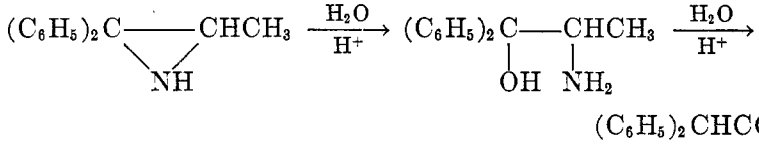


IIb



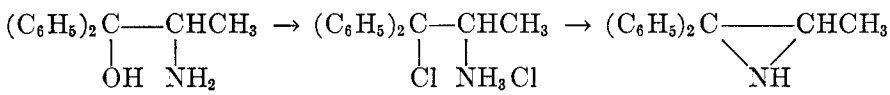
III

aminopropanol; on longer warming, a mixture of diphenylacetone, ammonia, and the amino alcohol is obtained. The amino alcohol itself undergoes decomposition on treatment with acid, to diphenylacetone and ammonia (11).



These data conclusively eliminate structures IIa, IIb, and III from consideration. Benzophenone ethylimide, III, melts at 62° (12), and is very easily hydrolyzed by aqueous acid, cold, to benzophenone and ethylamine; furthermore, it does not form a stable hydrochloride. A vinyl amine, such as IIa, would be hydrolyzed by dilute acid to ammonia and diphenylacetone, and would not give the amino alcohol under these conditions. An unsaturated amine such as IIb should be readily oxidized by potassium permanganate, whereas ethyleneimines are known to be stable to this reagent (13).

It seems certain, therefore, that the primary product from the reaction of phenylmagnesium bromide on propiophenone oxime is 2,2-diphenyl-3-methylethleneimine (I), and that the amino alcohol obtained previously resulted from acid cleavage of the ring. An attempt was made to synthesize the ethyleneimine from the amino alcohol by the following series of reactions, which are similar to those which have been used successfully for the synthesis of 2,3-diphenylethyleneimine (5):



Although the hydroxyl group in the amino alcohol is tertiary, and hence should be easily replaceable by halogen, we were unable to find conditions which would give a good yield of the chloro amine. Others (6, 7) have had similar difficulties with related amino alcohols. A small amount of a product was obtained, however, when the amino alcohol was treated with thionyl chloride. Treatment of this material with alcoholic potassium hydroxide yielded an amine, m.p. 72–73°, which did not depress the melting point of the ethyleneimine obtained from propiophenone oxime.

2,2-Diphenyl-3-ethylethyleneimine was made by the action of phenylmagnesium bromide on butyrophenone oxime in toluene solution. Like its lower

homolog, this compound forms a stable hydrochloride from which the free base can be regenerated. It does not readily reduce an acetone solution of potassium permanganate, and is hydrolyzed by dilute acids to 1,1-diphenyl-2-aminobutanol.

The hydrochlorides of the two ethyleneimines have the formula:

$$(C_6H_5)_2C\text{——}CHR\cdot HCl,$$
$$\quad\quad\diagdown\ \diagup$$
$$\quad\quad NH$$

as shown by analysis for ionizable and total chlorine. In this respect these ethyleneimines differ from some of the previously known compounds of this class, for 2,3-diphenylethyleneimine (5) and 2-phenylethyleneimine (4) react with anhydrous hydrogen chloride to give ring-opening, with the formation of the corresponding chloro amine hydrochlorides.

Both the ethyleneimines reported react with isocyanates and isothiocyanates to give characteristic derivatives, but all attempts to prepare benzoyl derivatives were fruitless.

EXPERIMENTAL

Reaction of phenylmagnesium bromide with propiophenone oxime. (A). *In concentrated solution.* This reaction was carried out substantially as described earlier (8), using one mole of phenylmagnesium bromide and 25 g. of propiophenone oxime. The reaction mixture was hydrolyzed with ice and ammonium chloride; the aqueous layer was extracted several times with ether, and the ether extracts, dried over potassium carbonate, were treated with an ether solution of hydrogen chloride. The white solid so obtained weighed 12 g., and melted at 141–142°. When it was dissolved in cold water and treated with dilute sodium hydroxide, a free base was obtained which melted at 72–73° after recrystallization from aqueous alcohol.

The reaction was repeated, except that the Girgnard complex was hydrolyzed with ice acidified with 150 ml. of concentrated hydrochloric acid. The acid solution was immediately extracted with ether to remove non-basic impurities, and the aqueous layer was at once made basic with ammonium hydroxide and again extracted with ether. From this ether extract was isolated 15 g. of a hydrochloride, m.p. 140–142°, whose free base melted at 72–73°. Other runs were made, following the same procedure, except that the reaction mixture was hydrolyzed with ice and hydrochloric acid, the mixture extracted with ether, and the acid solution allowed to stand for several hours before it was made basic and again extracted. In this case 10–12 g. of 1,1-diphenyl-2-aminopropanol, m.p. 103–104°, was obtained.

(B). *In toluene solution.* The Grignard reagent prepared from 24 g. of magnesium turnings, 160 g. of bromobenzene, and 315 ml. of dry ether was concentrated until the color change occurred (8). The hot mixture was diluted with 120 ml. of dry toluene, and a solution of 25 g. of propiophenone oxime in 100 ml. of dry toluene was added over a period of 15 minutes, while the temperature of the oil-bath was kept at 135–145°. Stirring and heating were continued for an additional 20–30 minutes. The reaction mixture was allowed to cool to room temperature, and was then hydrolyzed with ice and ammonium chloride. From this reaction was isolated 18.5 g. of a hydrochloride, m.p. 146°, whose free base melted at 72–73°. Less tar was formed in this reaction than when no toluene was used. The free base could be isolated directly, instead of *via* the hydrochloride, by evaporating the ether and toluene and distilling the residue under reduced pressure. In a typical experiment 15 g. of material, b.p. 130–132°/1 mm., m.p. 72°, was obtained.

When the Grignard complex was hydrolyzed with ice and acid, and worked up immediately, 11–15 g. of free base, m.p. 72–73° was obtained. If the acid hydrolysis mixture was allowed to stand for a few hours, the main product was the amino alcohol, of which 6–10 g. was obtained.

(C). *In dilute ether solution.* In this run the Grignard reagent was not concentrated. The oxime was added over a period of 15 minutes, at room temperature, with no visible reaction; the mixture was then refluxed for two hours. Hydrolysis was accomplished with ice and ammonium chloride. By repeated freezing of the oil obtained on evaporation of the ether extracts, various crops of unreacted oxime were recovered, amounting altogether to 10.2 g. From the residual oil a small amount of a hydrochloride was isolated, from which the free base, m.p. 72–73° was obtained.

2,2-Diphenyl-3-methylethyleneimine is best purified by distillation at 1 mm. or less, followed by recrystallization from aqueous alcohol. When so purified it is obtained as white or very light cream colored prisms, m.p. 74.5–75°. When pure, it reduces potassium permanganate in acetone only very slowly.

Anal. Calc'd for $C_{15}H_{15}N$: C, 86.15; H, 7.18; N, 6.70; Mol. wt. 209.
Found: C, 85.98; H, 7.09; N, 6.70; Mol. wt. (cryoscopic), 217.

Treatment of the amine in dry ether with an ether solution of hydrogen chloride yields a white, stable, non-hygroscopic hydrochloride which melts at 139–140° after recrystallization from an alcohol-ether mixture.

Anal. Calc'd for $C_{15}H_{16}ClN$: N, 5.70; Cl, 14.45.
Found: N, 5.75; Cl, 14.40.

The amine forms a picrate which was obtained as yellow crystals, m.p. 199–200°. It also forms a phenylthiourea, m.p. 126.5–127° after recrystallization from alcohol. On treatment with 3-nitrophthalic anhydride (14) the amine forms a derivative melting at 190–192°.

Anal. Neutralization equivalent calculated for $(C_{22}H_{17}N_2O_3)CO_2H$, 402. Found, 405.

Hydrolysis of 2,2-diphenyl-3-methylethyleneimine. (A). *With dilute sulfuric acid.* One gram of the ring hydrochloride was refluxed for one hour with 50 ml. of 2 *N* sulfuric acid. The reaction mixture was cooled, extracted with ether, and the aqueous layer made basic with ammonium hydroxide and then extracted with benzene. Evaporation of the ether extract yielded nothing. Evaporation of the benzene extract yielded 0.7 g. of 1,1-diphenyl-2-aminopropanol, m.p. 103–104° (8). A mixture of this material with an authentic sample showed no depression of the melting point. The hydrolysis product formed a hydrochloride, m.p. 246°, which did not depress the melting point of 1,1-diphenyl-2-aminopropanol hydrochloride (246–247°).

(B). *With dilute hydrochloric acid.* When the amine was dissolved in 5% hydrochloric acid and the solution at once made basic and extracted with ether, the original substance was recovered quantitatively. If the hydrochloric acid solution was allowed to stand overnight at room temperature, or was refluxed for 20 minutes, the amino alcohol was obtained.

One gram of the amine was dissolved in 35–40 ml. of 6 *N* hydrochloric acid and the solution was refluxed for 30 minutes. A purple oil which floated on top of the aqueous layer was taken up in ether. From this ether layer a solid was isolated which melted at 44–45°. This compound formed a semicarbazone, m.p. 166.5–167°, and a 2,4-dinitrophenylhydrazone, m.p. 142.5–143°. No depression of the melting point occurred when these substances were mixed with unsymmetrical diphenylacetone (m.p. 46°), its semicarbazone (m.p. 168°), and its 2,4-dinitrophenylhydrazone (m.p. 143–144°), respectively.

The aqueous acid layer from the hydrolysis was evaporated to dryness under reduced pressure, and the resulting white solid was extracted with absolute alcohol. The alcohol-insoluble portion was shown to be ammonium chloride by the fact that it did not melt, was not hygroscopic, and on treatment with 10% sodium hydroxide solution it yielded a volatile, non-inflammable base. The alcohol-soluble portion melted at 244° and when mixed with the amino alcohol hydrochloride there was no depression of the melting point.

Synthesis of 2,2-diphenyl-3-methylethyleneimine from 1,1-diphenyl-2-aminopropanol.

A suspension of 10 g. of the amino alcohol hydrochloride in 200 ml. of dry chloroform was treated with 20 ml. of redistilled thionyl chloride, and the mixture was refluxed for five hours. Filtration of the mixture yielded 5.7 g. of recovered amino alcohol hydrochloride. The filtrate was concentrated under reduced pressure to a volume of about 50 ml. The addition of ligroin caused the precipitation of 0.4 g. of a dark yellow solid, which melted at 139°. A mixture of this with the ethyleneimine hydrochloride melted at 130°. The solid was dissolved in 30 ml. of 95% alcohol and a solution of 1 g. of potassium hydroxide in 10 ml. of alcohol was added. The solution was allowed to stand at room temperature for several hours, and was then poured into a large volume of cold water and extracted with ether. Evaporation of the dried ether solution yielded an oil which would not crystallize. The oil was treated with hydrogen chloride in ether solution to give a white solid, m.p. 139–140° which did not depress the melting point of the ethyleneimine hydrochloride (142°). On treatment of an aqueous solution of this hydrochloride with 10% potassium hydroxide a white solid formed, which melted at 73° after recrystallization from aqueous alcohol, and did not depress the melting point of the ethyleneimine (m.p. 73°).

Reaction of phenylmagnesium bromide with butyrophenone oxime. The Grignard reagent from 24 g. of magnesium, 160 g. of bromobenzene and 325 ml. of dry ether was concentrated until the color change occurred, and then 125 ml. of dry toluene was added. A solution of 28 g. (0.19 mole) of dry butyrophenone oxime in 100 ml. of dry toluene was added dropwise with stirring while the oil-bath was maintained at 150°. Stirring and heating were continued for thirty minutes, and the reaction mixture was then allowed to cool. It was hydrolyzed by pouring onto ice and ammonium chloride, and the mixture was extracted with ether. The combined ether-toluene solutions were dried over anhydrous potassium carbonate. The product could be isolated by direct distillation under reduced pressure (b.p. 124°/0.5 mm.), or by forming the hydrochloride. In the latter case 15–18 g. of a white hydrochloride was obtained, m.p. 144.5–145° after recrystallization from chloroform-ligroin and alcohol-ether mixtures.

Anal. Calc'd for $C_{16}H_{18}ClN$: N, 5.4; Cl, 13.68.
Found: N, 5.3; Cl, 13.86.

The free base was obtained as white crystals, m.p. 44.5–45° after recrystallization from aqueous alcohol.

Anal. Calc'd for $C_{16}H_{17}N$: C, 86.10; H, 7.62; N, 6.28.
Found: C, 85.90; H, 7.79; N, 6.35.

The free base reduced an acetone solution of potassium permanganate very slowly. It formed an alpha-naphthylurea, m.p. 184–185° after recrystallization from carbon tetrachloride; the phenylthiourea was an oil.

When the compound was warmed with 3 *N* sulfuric acid for an hour, and the solution made basic, a white solid was obtained which melted at 77–78° after recrystallization from dilute alcohol. Comparison of this material with the 1,1-diphenyl-2-aminobutanol (9) showed them to be identical.

SUMMARY

1. The primary product of the action of phenylmagnesium bromide on propiophenone oxime has been found to be 2,2-diphenyl-3-ethylethyleneimine. The structure of this compound has been established by analysis, by hydrolysis to 1,1-diphenyl-2-amino-1-propanol, and by synthesis from this amino alcohol.

2. If the Grignard reaction product is allowed to stand for a short while with aqueous acid the amino alcohol, previously isolated from this reaction, is obtained.

3. Phenylmagnesium bromide reacts with butyrophenone oxime at 150° to form 2,2-diphenyl-3-ethylethyleneimine.

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THE PROBLEM OF CARBOHYDRATE FORMATION IN NATURE

THOMAS S. GARDNER[1]

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I. *In Vitro* SYNTHESES OF MONOSES

Some monosaccharides occur in nature in the free state either as polysaccharides or as units of larger, complex molecules. It might be supposed that all of the possible configurations of the sugars would exist in various natural products but, on the contrary, only a limited number have so far been detected; for example, dihydroxyacetone, D-glyceraldehyde, D-xylose, D- and L-arabinose, D-ribose, D- and L-galactose, D-glucose, (L-glucose has been reported once), D- and L-fructose, D-mannose, a few other hexose units and only two heptoses. Of almost a hundred possible monosaccharide units containing from two to seven carbon atoms inclusive, less than a score have been found in plant and animal cells to date. The reason for this phenomenon has not been satisfactorily explained. The specific role of enzymes in the asymmetric synthesis of carbohydrates in cells is, doubtless, the true explanation, but the mechanisms and conditions are not very well known. Therefore a consideration of the mechanisms responsible for carbohydrate formation in nature from a chemical viewpoint is desirable. Enzymes have been used to explain the formation of natural products without proper emphasis on the chemical reactions and mechanisms involved, due to a lack of knowledge of the steps in the reaction.

In 1870 Baeyer (1) suggested that carbohydrates in nature arise by the reduction of carbon dioxide to formaldehyde in the presence of water and sunlight. Subsequent aldol condensations[2] would then yield carbohydrates. Formaldehyde has been reported in the plant cells of *Elodea canadensis*, a water weed (2), but later work (3) has shown that the formaldehyde detected resulted from the presence of the dimedon reagent which had been used for its identification.

Random aldol condensation of formaldehyde should produce all of the possible carbohydrates but only a few of them are actually found in nature. This may result from any one or all of the following causes: 1. It is possible that directive influences are present to limit the configuration of the sugars synthesized; 2. mechanisms operate that do not result in the synthesis of many types and yield only the few that are known and probably a few others that may be isolated by future work; 3. all are formed and some of them are then destroyed and thus

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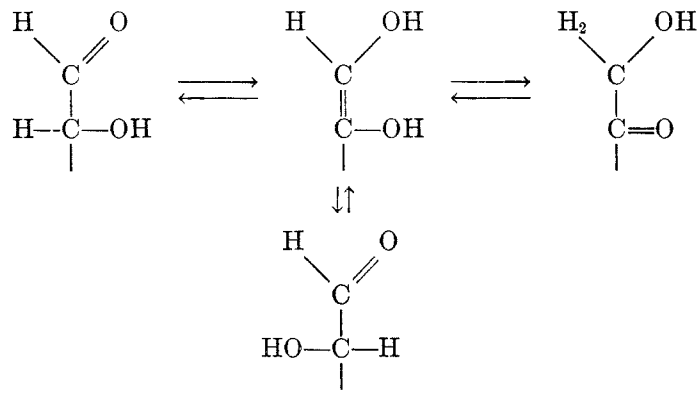
[2] The terminology used for the condensation of aldehydes to sugars is not precise, and is inadequate to describe the reaction. Karrer, "Organic Chemistry," 1938, p. 312, uses aldol condensation to describe the polymerization of formaldehyde, glycolaldehyde and glyceraldehyde to sugars. Micheel, "Chemie der Zucker und Polysaccharide," 1939, p. 188, prefers acyloin condensation for the formaldehyde polymerization and aldol condensation for the polymerization of other aldehydes to sugars.

cannot easily be detected. At the present time insufficient evidence prevents selection of the correct explanation.

In 1861 Butlerow (4) treated a formaldehyde solution with lime water, an aldol condensation catalyst, and obtained a sirupy sugar which he called formose. Fischer (5) prepared formose from formaldehyde, and also from a mixture of glyceraldehyde and dihydroxyacetone, and separated formose into two fractions, α- and β-acrose. α-Acrose was shown to be DL-fructose (5) and β-acrose was demonstrated to be DL-sorbose (6). Experiments on DL-glyceraldehyde indicated that condensation took place at the triose stage to produce α- and β-acrose (7). Glycolaldehyde (8) as well as formaldehyde, glyceraldehyde, and dihydroxyacetone have thus been used to synthesize *in vitro* the keto sugars, DL-fructose and DL-sorbose.

Ultra-violet light condenses formaldehyde to sugars (9, 10) and the presence of inorganic catalysts markedly influences the conversion (10, 11). It has been reported (12) that in the presence of calcium carbonate, formaldehyde is condensed by ultra-violet light to a mixture of aldose sugars, polyhydroxy phenols, lactones, etc. Neutral or only slightly alkaline condensing conditions should yield primarily the aldose sugars by an aldol condensation because the Lobry de Bruyn-van Ekenstein (13) rearrangement is negligible in such cases and the ketose form would not be the major product. The Lobry de Bruyn-van Ekenstein rearrangement takes place primarily in alkaline solution, although some rearrangement occurs in the presence of salts and slightly acid conditions. Under such conditions sugars rearrange to form an active 1,2-ene-diol, which may then further rearrange to yield a ketose sugar or both configurational forms about C_2 of the aldose series. Thus, for example, on treatment with alkali, either glucose, mannose, or fructose rearranges to give the other two forms as well as the starting material. By-products consist of other ketose sugars and saccharinic acids, depending upon the conditions and length of time of the alkali treatment. A definite equilibrium in an alkaline solution is set up as follows:



Evidently, if ultra-violet light polymerizes formaldehyde to aldose sugars, the triose formed polymerizes at once without rearranging to the ketose form (12).

Glyceraldehyde is found in nature as the phosphate ester in the breakdown

products of carbohydrate metabolism. Dihydroxyacetone has been similarly identified. It is highly probable that glyceraldehyde is the fundamental building unit in the synthesis of carbohydrates and since members of the D- family are especially abundant, D-glyceraldehyde is probably the isomer synthesized.

II. PHOTOSYNTHETIC INVESTIGATIONS ON THE ORIGIN OF CARBOHYDRATES

Recent work on the utilization of carbon dioxide by the plant has thrown doubt on the hypothesis that sugars arise from the condensation of formaldehyde. It has been demonstrated by the use of tagged carbon atoms in carbon dioxide that the carbon utilized in the synthesis of carbohydrates in nature first appears in the form of a carboxyl group of an organic acid during the photosynthetic process (14).

Woods (15) has shown that the reaction $H_2 + CO_2 \rightarrow HCOOH$ takes place using molecular hydrogen or organic hydrogen donors. If acetic acid and formic acid can be demonstrated to yield pyruvic acid, a chemical mechanism for the formation of glyceraldehyde, and hence of the carbohydrates, can be developed (16).

It has been shown that the reduction of carbon dioxide to the carboxyl group takes place on a large molecule (14) which may then react further as follows:

$$RH + CO_2 \longrightarrow RCOOH$$

$$RCOOH + H_2O + nh\nu \xrightarrow[\text{Chlorophyll}]{} RCH_2OH + O_2 \xrightarrow[\text{Chlorophyll}]{CO_2} RCHOHCOOH, \text{ etc.}$$

Then, $RCHOHCHOHCH_2OH \rightarrow RCHOHCHOHCHO \rightarrow RH + CH_2OHCHO$-$HCHO$

Therefore, it is probable that the reaction yields D-glyceraldehyde, which may dismutate to fatty acids or polymerize to sugars. In no case is the reaction as simple as indicated, but the over-all reaction may be assumed to be:

$$3CO_2 + 3H_2O \xrightarrow[\text{Chlorophyll}]{nh\nu} 3O_2 + CH_2OHCHOHCHO$$

In which the oxygen comes from the water taking part in the reaction (17), as demonstrated by the use of O^{18} as a tracer.

III. THE OCCURRENCE OF TETROSE TYPES IN NATURE

The tetroses have not been found in natural products, but a reduced form, a tetrahydroxy alcohol, erythritol, exists. It has been assumed that the non-existence of tetroses is due to their extreme reactivity. It is more probable that the tetroses are not synthesized directly but that the alcohol found is the decarboxylation product of a five carbon sugar acid. The decarboxylation of D-arabonic acid would yield *i*-erythritol, which is found in some lichens. D-Arabonic acid is not found anywhere and rarely is D-arabinose found. However, D-arabitol does occur in lichens. Ketose tetroses may be eventually detected in nature as a by-

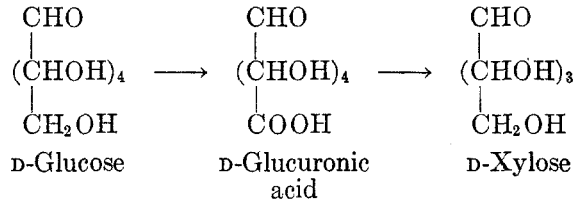
product analogous to L-sorbose. The same bacterium (*B. xylinium*) that oxidizes D-sorbitol to L-sorbose in the mountain ash berry (*vide infra*) also converts the naturally occurring erythritol to D-erythulose (18).

The presence of carbohydrate alcohols in nature may be accounted for by a direct reduction of the reducing sugar or through decarboxylation of the corresponding higher aldonic acid. However there is no evidence for either mechanism in nature.

IV. THE FORMATION OF THE PENTOSES

The problem of the occurrence of the pentose sugars has not been satisfactorily solved. Two probable mechanisms may be considered. The first is a direct aldolization of two lower sugars, such as glycolaldehyde with a triose. Such a reaction has been accomplished *in vitro* using an enzyme (zymohexase), muscle extract, or an alkali as a catalyst for the condensation of dihydroxyacetone phosphate with glyceraldehyde or glycolaldehyde (19). In such a condensation, reaction of glyceraldehyde 3-phosphate with glycolaldehyde would result in an aldose pentose. However only one ketopentose has been found in nature, L-xyloketose, which occurs in the urine of animals after injection or heavy feeding of sugar acids or certain sugars (20). It could easily arise by the aldol condensation of dihydroxyacetone phosphate and glycolaldehyde. This is the probable mechanism for its formation, as muscle extract catalyzes the reaction (19) and both intermediates are products of metabolism. Unless one assumes that glyceraldehyde phosphate undergoes an aldol condensation with glycolaldehyde, or that the ketopentose is first formed from dihydroxyacetone phosphate and glycolaldehyde to undergo an immediate ene-diol rearrangement to the aldose sugar, another mechanism must be used for the formation of the aldopentoses.

The second mechanism is the much discussed decarboxylation hypothesis. In this mechanism the pentose arises from the decarboxylation of the hexose uronic acid as follows:



Xylose is found associated with glucose polymers in the form of xylan in straw, hay, oat hulls, cottonseed hulls, etc. L-Arabinose, obtained from the hydrolysis of the arabans of cherry gum, is also found associated with galactans which on hydrolysis yield D-galactose. The decarboxylation of D-galacturonic acid would yield L-arabinose.

Enzymes capable of decarboxylating uronic acids have not been isolated from plants. Bacteria which are capable of decarboxylating glucuronic acid to D-xylose have been isolated from putrifying flesh (21). According to the decarboxylation hypothesis, D-arabinose should result from the loss of carbon dioxide from the uronic acids of the sugars D-altrose, which is unknown in nature,

or L-galactose which is rare, but known. Also D-arabinose would result from the decarboxylation of D-gluconic acid followed by oxidation of the D-arabitol formed. It has been shown that yeast cells bring about the following reaction (22); glucose 6-phosphate → gluconic acid 6-phosphate → arabonic acid 5-phosphate. Stopping the oxidation at the proper point would yield D-arabinose.

D-Ribose, which is found in plant nucleic acid and other cell constituents, offers a problem for the decarboxylation hypothesis unless we assume the existence of D-allose, which is not known to occur naturally at the present time. This difficulty is at once explained on the basis of an ene-diol rearrangement of D-arabinose, or by a Walden inversion around C_3 by saponification of xylose 3-phosphoric acid (28).

Decarboxylation may be wholly an enzyme reaction, but sunlight also catalyzes the loss of carbon dioxide from *alpha*-hydroxy acids.

The fact that the terminal group in some xylans consists of L-arabofuranose units casts doubt on the hypothesis that pentosans are formed by the decarboxylation of uronic acids in a polyuronide without previous hydrolysis (23). Investigations of the origins of pectins and plant gums (24) indicate that it is highly improbable that pentosan formation occurs from the uronic acids while polymerized, but that hydrolysis precedes decarboxylation, and then resynthesis to the polysaccharide takes place. If sunlight or enzymes brought about the loss of carbon dioxide from uronic acids, the reactions involved would be facilitated by a preliminary hydrolysis, since they would take place in solution rather than between two phases.

If decarboxylation of hexose uronic acids gives rise to the pentoses, one might also expect to find D-lyxose from D-mannuronic acid and L-xylose from L-glucuronic acid, as the corresponding hexose sugars occur in nature, but they have not been isolated at the present time.

IV. THE FORMATION OF THE HEXOSES

If carbohydrate formation in nature takes place through aldol condensations of formaldehyde, then one would expect many more types of monose units than are actually found. The tetroses should then be represented far more than they are, either as the sugar or as its reduction or oxidation product. Also, the pentoses would be expected to be even more prevalent than they are, and the hexoses less frequent in occurrence than the pentoses. Actually, the bulk of carbohydrates exists in the form of D-glucose units, a hexose. The frequency of occurrence of D-glucose may indicate a possible mechanism in which D-glyceraldehyde becomes the basal unit for carbohydrate synthesis. This supports the evidence that D-glyceraldehyde may arise from a carboxylic acid as previously described (14) and would thus be the first carbohydrate to be synthesized. In such a case glycolaldehyde would be present only as a degradation product of carbohydrate metabolism. It is evident that the sheer bulk in nature and the importance of D-glucose units in metabolism overshadows all the rest of the naturally occurring carbohydrates.

It is possible that D-glucose may be the only D-hexose synthesized in nature and all the rest of the D-hexoses arise through transformations of D-glucose.

Three mechanisms can account for the transformations between the various hexoses:

1. The Lobry de Bruyn-van Ekenstein rearrangement (13). This conversion usually requires an alkaline medium and it has been shown that cell sap, both animal and plant, is slightly alkaline in many cases. Thus, from either D- or L-glucose, D- or L-fructose and D- or L-mannose may arise. L-Mannose has not yet been demonstrated to appear in natural sources. If it be assumed that D-fructose is synthesized directly, then it is also necessary to assume a separate synthesis of dihydroxyacetone from D-glyceraldehyde by a Lobry de Bruyn-van Ekenstein rearrangement, to be followed by the synthesis of fructose through the phosphate (*vide infra*). For the L-series, that is probably the mechanism, because the conditions that would allow the formation of dihydroxyacetone from D-glyceraldehyde would also give rise to L-glyceraldehyde and then immediate condensation would take place to L-fructose. Although no evidence has been collected regarding the rates of condensation of various aldose and ketose units in sugar synthesis, indications are that the most rapid rates are for the trioses. This is supported by the alkaline condensations of formaldehyde and the trioses. In the former case, neither tetroses nor pentoses are found, but a slow build-up to the triose, and an immediate reaction to the hexose, with the same result as starting with the triose alone. Therefore, conditions that would allow the formation of dihydroxyacetone and L-glyceraldehyde from D-glyceraldehyde would have a competing rate of reaction between two moles of D- or L-glyceraldehyde to form D- or L-glucose, and D- and L-glyceraldehyde with dihydroxyacetone to yield D- or L-fructose. Under the same conditions L-fructose or L-glucose may yield the other form by rearrangement. Thus, if D-fructose is synthesized by condensation of dihydroxyacetone and D-glyceraldehyde, L-glucose may be associated with it, as the same conditions that would give rise to dihydroxyacetone would also necessarily produce the L-glyceraldehyde. L-Glucose has not been found associated with D-fructose in any case so far examined. The absence of L-glucose renders it probable that D-fructose arises from D-glucose, and that L-fructose is synthesized directly from the appropriate trioses. L-Glucose would then be synthesized directly from two moles of L-glyceraldehyde or by a Lobry de Bruyn-van Ekenstein rearrangement of L-fructose.

2. There are two probable mechanisms for the synthesis of D-galactose from D-glucose. Examination of the formula for galactose shows that the only difference between glucose and galactose is in the configuration around C_4, *i.e.*, a Walden inversion around C_4 converts glucose to galactose.

In one mechanism, conversion occurs on the hexose. This can be accomplished *in vitro* by the introduction of an appropriate ester group, such as the sulfate (26) or tosyl (27) on C_3 or C_4, and on removal of the ester group by an alkaline reagent an ethylene oxide ring forms, which undergoes a Walden inversion on opening that involves the carbon atoms in the ring. Asymmetric conditions may direct the configuration attained, and, as sulfates exist in nature as esters, such a reaction is not too improbable. The role of phosphates in such a conversion is not known, and although the phosphate esters have not been observed to give ring closure on removal or Walden inversion, such a mechanism

has been suggested (28). An examination of the stereochemical formula for glucose has led to the suggestion that under asymmetric conditions an abnormal opening of the furanoid lactal ring would allow a Walden inversion on C_4 by splitting between oxygen and C_4, *i.e.*, the furanoid ring would open and inversion take place, followed by ring closure on the other side to yield galactofuranose. This line of reasoning results from the known Walden inversion on the opening of anhydro rings in carbohydrates (29). This mechanism is supported by investigations on the synthesis of D-galactose from D-glucose in the animal body. It has been shown that slices of mammary gland from a lactating guinea pig convert glucose to galactose in order to form lactose, but lactose is not synthesized from maltose, fructose, or galactose (25). The fact that galactose is not converted to glucose indicates that direct conversion of the hexose takes place, rather than splitting to the triose stage by the mammary gland extracts (25), for if galactose were to be split to the triose stage, then some glucose should be formed, and consequently lactose.

If D-galactose arises from D-glucose without previous splitting to the triose stage, *i.e.*, a Walden inversion around C_4, then it is possible that L-glucose is the precursor of L-galactose. There is some evidence that L-glucose is associated with L-galactose in collagen (30).

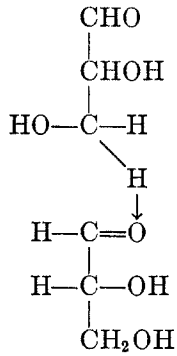
The other mechanism involves the breakdown of glucose to glyceraldehyde and resynthesis to the appropriate hexose, as galactose, mannose, or fructose. This breakdown undoubtedly occurs in the metabolism of galactose and it is possible that galactose is synthesized from the breakdown products under the right conditions.

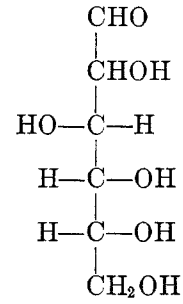
3. A recent mechanism has been advanced to account for the occurrence of L-galactose in agar (31). In this mechanism it is postulated that an internal oxidation-reduction takes place in which D-galactose 1-sulfate substituted at C_3 in a galactan breaks the lactal ring by the addition of water, transfers a hydrogen atom from C_1 to C_6, eliminates a molecule of water from C_6 and yields L-galactose 6-sulfate substituted at C_4. If true for this example, the mechanism breaks down for the synthesis of other members of the L-series; for example, the most common of the D-series, glucose, would yield L-gulose, which is not known in nature. An interesting *in vitro* transformation of D-galactose to L-galactose was performed by Micheel and his co-workers (32). 6-Iodo-2,3,4,5-tetra-acetyl-*aldehydo*-D-galactose (I) was treated with $ZnCl_2$ in acetic anhydride to yield *aldehydo*-DL-galactose heptaacetate (II). A mechanism was postulated in which (I) cyclizes through an aldol condensation to yield a substituted inositol, loss of HI then gives an ethylene oxide bridge, which on scission results in equal quantities of (II).

L-Sorbose is a special case. This ketose sugar arises from oxidation of D-sorbitol by a bacterium (*B. xylinium*) introduced into the mountain ash by the vinegar fly (33). However, L-sorbose may also appear elsewhere in nature. *In vitro* it has been prepared by the aldol condensation of formaldehyde with alkali (4, 5, 6), and by the condensation of L-glyceraldehyde with dihydroxyacetone phosphate (19).

V. A GENERAL MECHANISM FOR CARBOHYDRATES

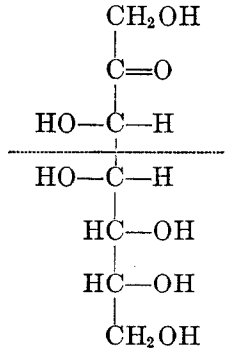
It is probable that in the D-series only D-glyceraldehyde and D-glucose are actually synthesized in nature, in the L-series, L-glyceraldehyde and either L-fructose or L-glucose or both. Therefore, if the pentoses are degradation products of the hexoses and the reduced tetrose arises from a pentose, D-glyceraldehyde is the first and primary carbohydrate synthesized and all the carbohydrates through the hexoses arise from the reaction of D-glyceraldehyde on itself and on its rearrangement products. If this is true, then in nature condensation occurs by one main route in which a hydrogen of the primary alcoholic group of a triose reacts with the carbonyl of another molecule. The formerly primary hydroxyl now is *trans* to the hydroxyl formed from the carbonyl group; and the latter hydroxyl is usually formed on the same side of the chain, or *cis*, to the adjacent secondary hydroxyl, if one is present. For example:



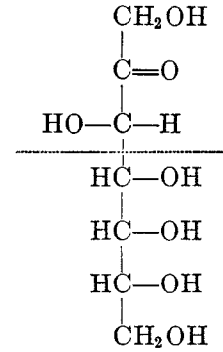


In vitro this mechanism, as well as a strict across-the-chain type for each hydroxyl in the case of DL-sorbose (19), is known. An exception in nature would be the synthesis of D-galactose from D-glucose by splitting to the trioses and condensing the hydroxyls across the chain, as written in the conventional manner, up the top half of the molecule, if that is the mechanism that operates.

On application of this principle to the heptoses the following may be deduced in regard to the two naturally occurring forms:



D-Mannoketoheptose
(avocado)



D-Altroketoheptose
(*Sedum spectabile*)

The dotted lines indicate a synthesis from the two very labile and active intermediates, dihydroxyacetone and D-erythrose. As no tetrose exists in nature, but the reduced erythrose only, the required erythrose intermediate for the heptoses could easily appear from the oxidation of erythritol, as it was assumed above that erythritol was formed directly from arabonic acid by decarboxylation.

The mechanisms outlined above can be used to account for the appearance of the desoxy and branched chain "carbohydrates" such as rhamnose, fucose, apiose, etc., as the required aldehydes and ketones appear as metabolism by-products and as fermentation intermediates. For example, the condensation of L-lactaldehyde and D-glyceraldehyde yields L-rhamnose. Lactaldehyde is the partial reduction product of pyruvic aldehyde which is found in animal and plant tissues.

SUMMARY

The formation of monosaccharide units in nature is not satisfactorily explained on the basis of formaldehyde condensations. The presence of formaldehyde in cells is doubtful. If it appears at all it is probably the by-product of metabolism. The utilization of carbon dioxide by the plant goes through a carboxylic acid to the carbohydrate. D-Glyceraldehyde is probably the first and only carbohydrate synthesized as such by the plant; the remainder arise through rearrangements and condensations of D-glyceraldehyde. Pentoses may arise by condensation of glycolaldehyde and a triose or by the decarboxylation of hexuronic acids. Both mechanisms probably operate in nature, the decarboxylation mechanism being responsible for the majority of the pentoses.

The hexoses arise *via* condensation of trioses. It is probable that D-glucose is the only D-hexose to be synthesized and the remainder arise through a Lobry de Bruyn-van Ekenstein rearrangement and Walden inversions around C_4. The L-hexoses are explainable on a similar basis.

Exceptions occur in which the carbohydrate is of secondary origin; for example, L-sorbose in nature arises by oxidation of D-sorbitol. The heptoses may arise by aldolization of a triose and the postulated D-erythrose.

Appropriate mechanisms are suggested for the direction of condensations for the carbohydrates.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CINCINNATI]

SULFONIUM COMPOUNDS. II (1). DERIVATIVES OF NITRIC AND OF ORGANIC ACIDS[1]

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The sulfonium halides and sulfates can be prepared in many cases by direct combination of divalent sulfur compounds with alkyl halides and sulfates. For this reason they have been studied extensively. Other sulfonium salts can be prepared by treating the iodides with the desired silver compound. By this method Kruger (2) prepared methyldiethylsulfonium hydroxide, which he converted to the nitrate by treatment with nitric acid. He states that the nitrate is hygroscopic, but gives no further properties.

Renshaw and Searle (3) prepared four crystalline sulfonium nitrates by treating the mercuric iodide double salt with silver nitrate, followed by the precipitation of the mercury with hydrogen sulfide. Compounds of the following formulas were obtained as solids and characterized: $(C_6H_5CH_2)_2S(NO_3)CH_3$, $(C_6H_5CH_2)_2S(NO_3)CH_2COOC_2H_5$, $(C_6H_5)_2S(NO_3)CH_3$, and $(CH_3)_2S(NO_3)CH_2CH_2OC_6H_5$. The last compound was somewhat hygroscopic and an attempt to prepare $(C_2H_5)_2S(NO_3)CH_2CH_2OC_6H_5$ resulted in "only a gummy semi-solid."

A somewhat similar method had been used by Kehrmann and Sava (4) in 1912 to prepare sulfonium bases. Courtot and Tung (5) prepared tri (hydroxyphenyl) sulfonium nitrate from the hydroxide.

Addy and Macbeth (6) prepared trimethyl- and triethyl-sulfonium nitrites by treating the iodides with aqueous silver nitrite. They report that these compounds are very deliquescent and have a bad odor. In the light of our work we believe that the odor they observed was due to impurities, chiefly sulfide or mercaptan, formed by the following decompositions:

$$(CH_3)_3SNO_2 \rightleftarrows CH_3SCH_3 + CH_3ONO$$

$$(CH_3)_3SNO_2 + H_2O \longrightarrow CH_3SH + CH_3OH + CH_3ONO$$

Of the organic acids, only picric acid has been used extensively to prepare and characterize sulfonium compounds. Two carbonates, however, were prepared by Kehrmann and Sava (4); *o*-anisyldimethylsulfonium carbonate and *o*-phenetyldimethylsulfonium carbonate.

A number of organic thiuronium salts have been prepared by the direct combination of ester and thiourea (7) but these may be regarded as special cases.

Libermann (8) reported the preparation of benzoates of the following compositions: $(C_6H_5COOC_6H_4)_3SOCOC_6H_5$, $[CH_3(C_6H_5COO)C_6H_3]_3SOCOC_6H_5$, and $[Cl(C_6H_5COO)C_6H_3]_3SOCOC_6H_5$. These were prepared by heating the corresponding arylchlorosulfites in equimolar quantities of pyridine, followed by the benzoylation of the resulting bases. They were, considering their high molecular weight and salt-like properties, extremely low-melting compounds

[1] Presented before Section C, A. A. A. S., Columbus, Ohio, Dec. 29, 1939.

(35°, 53°, and 57°). They were also soluble in ether. From the physiological standpoint these properties are extremely important.

Ferrer (9) prepared sulfonium xanthates by reacting carbon disulfide with the sulfonium bases.

We undertook to determine if organic sulfides would react *directly* with alkyl nitrates. When dimethyl sulfide was allowed to stand with methyl nitrate in a sealed tube at room temperature, white crystals could be observed after two days. After two months about ten per cent of the material had reacted. The solid, on separation from the mother liquor, proved to be very hygroscopic. Drying over phosphorus pentoxide removed the water, but resulted also in a gradual decrease in the melting point from 96–98° to 84–86°. The percentage of sulfur was too high for trimethylsulfonium nitrate. This may have been due to methylsulfoxide formation or to the presence of methyl sulfide of crystallization.

The explosive nature of methyl nitrate makes the use of sealed tubes inconvenient. Using pressure bottles with spring caps made tight with rubber washers, we obtained, at the end of eight months, thick, hard prisms (1 × 3 mm.) that melted at 129–131° without visible decomposition. On recrystallization from methanol the substance melted at 133° and was analytically pure trimethylsulfonium nitrate. The crystals from methanol were smaller, less hard, and somewhat hygroscopic. The compound was soluble in water, methyl and ethyl alcohols, but insoluble in benzene and acetone. In the presence of water or excess sulfide it was difficult to isolate the pure nitrate but the trimethylsulfonium ion was isolated as the picrate. Trimethylsulfonium sulfate was then treated with a solution of barium nitrate. On evaporation, only an oil was obtained but the trimethylsulfonium picrate mentioned above was obtained from this oil. It is obvious that anhydrous conditions are desirable and possibly necessary to the isolation of the lower sulfonium nitrates.

When methyl nitrate and methylethyl sulfide were heated together at 55° the liquid separated into two phases. In the water-soluble phase the trimethylsulfonium ion was identified as its picrate. The formation of the trimethylsulfonium ion is explained by the extension of the mechanism of Ray and Levine (1) to include sulfonium nitrates as well as halides.

$$\begin{aligned} CH_3NO_3 + CH_3SC_2H_5 &\rightleftarrows (CH_3)_2C_2H_5SNO_3 \\ &\quad \downarrow\uparrow \\ &\quad (CH_3)_2S + C_2H_5NO_3 \\ &+ CH_3NO_3 \quad \uparrow\downarrow \\ &\quad (CH_3)_3SNO_3 \end{aligned}$$

While the presence of the other possible sulfonium compounds was not demonstrated, there can be little doubt that it was their presence that caused the formation of a liquid product.

Ethyl nitrate and dimethyl sulfide gave only a trace of an oily reaction product soluble in water. No pure compound could be isolated.

Ethyl nitrate and diethyl sulfide gave a small amount of crystals, which were soluble in water and were identified as containing the triethylsulfonium ion by conversion to the picrate.

Hellstrom (10) has shown that the presence of acid inhibits the sulfonium reaction. Pyridine was added, therefore, to a mixture of ethyl nitrate and diethyl sulfide and the solution was heated on the water-bath. At first crystals formed, but these disappeared and a reddish oil separated. It was soluble in water, from which triethylsulfonium picrate was isolated on the addition of picric acid.

A mixture of methyl nitrate and methylphenyl sulfide slowly turned green, the color deepening with time. This color change is characteristic of the anhydrous higher molecular weight sulfonium compounds (1). The color disappeared on the addition of water, but no definite compound could be isolated from the small amount of gummy residue obtained. The ether extract on distillation gave a small amount of dimethyl sulfide, which also indicates that some sulfonium formation probably took place.

$$CH_3SC_6H_5 + CH_3NO_3 \rightleftarrows (CH_3)_2C_6H_5SNO_3 \rightleftarrows (CH_3)_2S + C_6H_5NO_3$$

No evidence was obtained for the direct reaction of methyl nitrate with diphenyl sulfide.

One might well question whether the direct sulfonium reaction which takes place with the esters of inorganic acids also takes place with the esters of organic acids. Methyl formate and dimethyl sulfide, therefore, were heated in a pressure-bottle and after a few hours fine white crystals were visible. They melted indefinitely at 90–100° and charred above 150°.

Methyl stearate and dimethyl sulfide also formed fine crystals which, however, could not be freed from the mother liquor. The aqueous extract gave a picrate which, while not pure, indicated that the trimethylsulfonium ion had been formed.

A neutral cottonseed oil was then heated with an excess of dimethyl sulfide. Although there was no visible change, the aqueous extract yielded a small amount of a picrate which melted at about 90° to the characteristic red liquid of a sulfonium picrate.

EXPERIMENTAL

Trimethylsulfonium nitrate. Fifteen cubic centimeters (0.25 mole) of methyl nitrate and 23 cc. (0.3 mole) of dimethyl sulfide were kept in a pear-shaped pressure-bottle for eight months. Crystals began to separate after two weeks and gradually increased in amount and size, a yield of 18% being obtained. Recrystallization from methanol resulted in a smaller, softer crystal which melted at 133° and was analytically pure. The compound was soluble in water, methyl and ethyl alcohols, but insoluble in benzene and acetone.

Anal. Calc'd for $C_3H_9NO_3S$: S, 23.0. Found: S, 23.1.

It gave tests for the nitrate ion with both brucine and diphenylamine. The monopicrate melts at 199° while the dipicrate melts at 70–75°.

Methyl nitrate and methylethyl sulfide (0.1 mole of each) on standing gave a trace of oil. On heating to 55° the amount of immiscible oil increased considerably. It could not be

crystallized. It was extracted with water and converted to its picrate which, when purified, proved to be identical with trimethylsulfonium picrate by a mixed melting point.

Ethyl nitrate and dimethyl sulfide failed to react at room temperature. When heated for 200 hours at 70° there seemed to be a trace of immiscible oil formed. We were unable to get any evidence that it was a sulfonium compound.

Triethylsulfonium nitrate. Forty-one and five-tenths cubic centimeters (0.5 mole) of ethyl nitrate and 53.5 cc. (0.5 mole) of diethyl sulfide were allowed to stand in a pressure-bottle at room temperature for eight months. Crystals were formed, but they could not be freed from the adhering oil. The mixture was treated with ether and extracted with water. From the yellow aqueous solution was obtained triethylsulfonium picrate melting at 115° (1).

Pyridine as a catalyst. To a mixture of 8.4 cc. (0.1 mole) of ethyl nitrate and 10.8 cc. (0.1 mole) of diethyl sulfide was added 0.8 cc. (0.01 mole) of pyridine. After two weeks a drop of heavy oil was visible. This increased slowly at room temperature. On heating on the water-bath the amount of oil rapidly increased until it formed about 30% of the total liquid. The main body of liquid was yellow, but the oil was dark red. This red oil was a mixture of triethylsulfonium nitrate and pyridine. It was soluble in water and although it could not be obtained crystalline, it yielded triethylsulfonium picrate. It is thus evident that organic bases have a strong catalytic effect on the sulfonium reaction. Whether the pyridine first forms an intermediate pyridinium compound or catalyzes the reaction by virtue of its alkalinity (10) remains to be determined.

Trimethylsulfonium formate. Twelve cubic centimeters (0.16 mole) of dimethyl sulfide and 10.1 cc. (0.16 mole) of methyl formate were heated on the water-bath. After two hours fine white crystals were observed. They could not be isolated in a pure form but melted indefinitely at 90–100°. The mixture was evaporated on the steam-bath and a dark oily residue was obtained.

Methyl stearate (0.5 mole) *and dimethyl sulfide* (0.15 mole) were heated for 200 hours at 70° in a pressure-bottle. Some fine solid was observed in the liquid. The material was treated with ether and extracted with dilute hydrochloric acid. From the aqueous acid solution the low-melting trimethylsulfonium dipicrate was obtained.

Cottonseed oil (0.01 mole) *and dimethyl sulfide* (0.06 mole) were heated on the water-bath for 200 hours in a pressure-bottle from which the air had been expelled. There was no visible change. The product was treated with ether and extracted with water. From the aqueous extract on treatment with picric acid there was obtained a picrate that melted at 90° to a red liquid.

In the case of the latter compounds higher temperatures and pressures would doubtless give good yields of the trimethylsulfonium salts of the long-chain fatty acids.

SUMMARY

It has been shown that a direct reaction occurs between organic sulfides and the esters of nitric acid. The equilibrium theory of Ray and Levine has been extended to cover this reaction.

A direct reaction occurs also between organic sulfides and esters of organic acids, such as methyl formate, methyl stearate, and glycerol esters of cottonseed oil. The catalytic effect of organic bases on the sulfonium reaction has been demonstrated.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

REARRANGEMENTS IN THE FRIEDEL-CRAFTS ALKYLATION OF BENZENE

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INTRODUCTION

Alkylation by the Friedel-Crafts reaction usually involves rearrangement of the alkyl group. The report that *n*-octadecyl bromide, with benzene and aluminum chloride, gave *n*-octadecylbenzene as the principal product (1), was in such contrast to the behavior of the lower alkyl halides, that a further investigation of the effect of chain length on isomerization seemed advisable.

HISTORICAL

Alkyl halides and aluminum halides. Shortly after Friedel and Crafts (2) had obtained amylbenzene from amyl chloride with benzene and aluminum chloride, Gustavson (3) found that either isopropyl bromide or *n*-propyl bromide with benzene and aluminum chloride gave isopropylbenzene. Silva (4) confirmed this, using the two propyl chlorides. Heise (5) was the first to offer a derivative as proof of the structure of the propylbenzene obtained. He observed that at $-2°$, *n*-propyl bromide with benzene and aluminum chloride gave *n*-propylbenzene, identified as its sulfonamide. Genvresse (6) obtained both *n*-propylbenzene and isopropylbenzene by conducting the reaction at reflux temperature. Konowalow (7) found that below 0° *n*-propyl chloride gave *n*-propylbenzene, while from 0° to reflux temperature it gave mixtures of *n*-propylbenzene and isopropylbenzene. More recently it has been shown that at $-6°$, 60% of the monopropylbenzene was *n*-propylbenzene, and 40% was isopropylbenzene. At 35° this ratio was reversed. The relative proportions of the two isomers were determined by fractional crystallization of the diacetamino derivatives (8).

Both isopropyl chloride and *n*-propyl chloride have been found to give 1,3-dimethyl-5-isopropylbenzene on reaction with *m*-xylene in the presence of aluminum chloride; the product was identified as its diacetamino derivative (9).

Gossin reported that isobutyl chloride with benzene and aluminum chloride gave a butylbenzene boiling at 166–167°, and a small amount of an alkylbenzene boiling at 152–155°. On the basis of physical properties he decided that the former was isobutylbenzene, while the latter was *t*-butylbenzene (10).[1] These conclusions were shown to be incorrect by Schramm (11), who found that isobutyl chloride and *t*-butyl chloride both gave *t*-butylbenzene. The product was identified as its bromo derivative. He also observed that *n*-butyl chloride gave *s*-butylbenzene, identical with the *s*-butylbenzene prepared from diethylzinc and α-bromoethylbenzene (12). Whereas Kekulé and Schrötter had found that *n*-propyl bromide when refluxed with aluminum bromide gave isopropyl bro-

[1] Kelbe and Pfeiffer, *Ber.*, **19**, 1723 (1886), likewise reported the preparation of isobutyltoluene from isobutyl bromide and toluene with aluminum bromide. They did not prove the structure of the side chain.

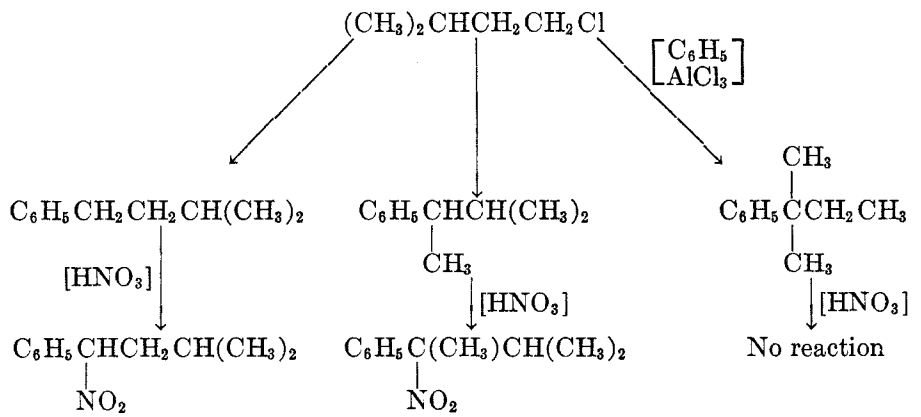
mide (13), and had explained Gustavson's results on this basis, Schramm found, that isobutyl chloride did not give *t*-butyl chloride with aluminum chloride. Moreover, since *t*-butyl chloride treated in this way gave butylene and hydrogen chloride, Schramm thought the olefin to be the intermediate in the Friedel-Crafts reaction. Others have reported that the isobutyl group is isomerized to *t*-butyl in reactions with aluminum chloride and benzene (7, 14) or toluene (15).

Estreicher discovered that at 0°, *n*-butyl chloride with benzene and aluminum chloride gave a mixture of *n*-butylbenzene and *s*-butylbenzene, while at reflux temperature *s*-butylbenzene appeared to be the only monobutylbenzene formed (16). Shoesmith and McGechen pointed out that Estreicher's identification of his butylbenzenes was not satisfactory. They obtained a mixture of *m*- and *p*-*s*-butyltoluenes from *n*-butyl chloride and toluene with aluminum chloride; the products were identified as their sulfonanilides (17). It has been reported that *n*-butyl chloride gave di-*n*-butylbenzene "as the first product" (18). On the other hand Calloway (19) found that *t*-butylbenzene was formed when *n*-butyl fluoride reacted with benzene and aluminum chloride, but he gave only the boiling point as evidence.

Friedel and Crafts (2) and later Austin (20) did not identify the amylbenzenes they obtained, nor is it clear which amyl chlorides they used. Essner (21) treated amylene hydrochloride and amylene with benzene and aluminum chloride, and in each case obtained a product boiling at 185–190°, which he believed to be the same as that obtained by Friedel and Crafts. He claimed to have evidence that the product was not the same as the known amylbenzene (22) or 3-phenylpentane (23); apparently the evidence was the difference in boiling points, for no other data were presented.

n-Amyl chloride with benzene and aluminum chloride "did not yield pure 2-phenylpentane." No experimental data were given (23 a).

Isoamyl chloride reacted with benzene and aluminum chloride to give a mixture of monoamylbenzenes. When this mixture was treated with nitric acid three products were obtained: one nitrated product soluble in alkali, one nitrated product not soluble in alkali, and one portion of the hydrocarbon not attacked by the acid (24). This was explained according to the following scheme.



Although this evidence is not entirely convincing, no better work has been published on this reaction.[2] Other interpretations could be given to the experimental results, though admittedly those advanced by the authors are most reasonable.

Neopentyl chloride has been shown to give 2-methyl-3-phenylbutane,

$$(CH_3)_3CCH_2Cl \xrightarrow[{[C_6H_6]}]{[AlCl_3]} (CH_3)_2CH\underset{\displaystyle CH_3}{\underset{|}{C}}HC_6H_5$$

which was identified as its diacetamino derivative. The yield was not large (24%), and the product was not pure (26).

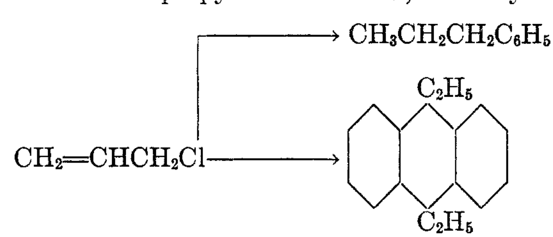
It has been reported that 1,1-dichloroheptane with benzene and aluminum chloride gave 1-phenylheptane as well as 1,1-diphenylheptane (27). The boiling point of the heptylbenzene did not agree with that of synthetic 1-phenylheptane, however, and it is not likely that this was the product obtained.

Schreiner (28) and Halse (29) prepared a number of tertiary alkylbenzenes from tertiary alkyl chlorides. The configurations of the products were assumed to be the same as those of the reactants.

Seidel and Engelfried (30 a) prepared octadecylbenzene from *n*-octadecyl bromide with benzene and aluminum chloride. They prepared the sulfonamide of their product, but did not try to establish its structure. Gilman and Turck (1) later showed that this was the sulfonamide of 1-phenyloctadecane.

Kursanoff (31) treated *o*-dichlorocyclohexane with benzene and aluminum chloride and claimed, without much evidence, to have obtained *o*-diphenylcyclohexane, with probably some *m*- isomer. More recently *o*-dibromocyclohexane has been found to give *p*-diphenylcyclohexane and *m*-diphenylcyclohexane (32). The structures were proved by dehydrogenation with selenium to the known diphenylbenzenes.

Allyl chloride has been reported to give isopropylbenzene (4) and *n*-propylbenzene (33). Recently it has been found that in the presence of anhydrous aluminum chloride 1,2-diphenylpropane was obtained, while with wet aluminum chloride the products were *n*-propylbenzene and 9,10-diethylanthracene (34).



Ferric chloride as a catalyst gave 1,2-diphenylpropane and 2-chloropropylbenzene.

It should be noted here that Gilman, Calloway, and Turck (30 b, c) found that a number of substituted furans reacted with *n*-alkyl halides of various chain lengths to give *t*-butyl substituted furans. For example, ethyl 5-bromo-2-furoate with *n*-octadecyl bromide and aluminum chloride (1.1 mole) gave a 46%

[2] Gleditsch (25) simply assumed that isoamyl chloride yielded *t*-amyl compounds.

yield of ethyl 4-*t*-butyl-5-bromo-2-furoate, as well as 32% of isobutane and 7% of butane. With benzene, *n*-octadecyl bromide and other *n*-alkyl halides have been shown not to undergo such extensive rearrangement using aluminum chloride.

Alkyl halides and other catalysts. *n*-Propyl bromide with benzene and hydrogen fluoride gave 88% of isopropylbenzene and 12% of *n*-propylbenzene in the monopropylbenzene fraction. The products were identified as their sulfonamides, and the ratio of the two isomers was estimated from the melting point of the crude mixture of sulfonamides (35).

Butyl chloride with magnesium and toluene at reflux temperature gave *n*-butyltoluene, which, however, was identified only by its physical constants. Similarly, isoamyl chloride was claimed to give *p*-isoamyltoluene (36). *n*-Butyl bromide with toluene and beryllium bromide gave a small yield of butyltoluene, which was not identified (37).

Phenylaluminum halides have been reported to give isopropylbenzene on reaction with *n*-propyl iodide (38); isoamyl iodide gave isoamylbenzene. Duplication of the experiment with *n*-propyl iodide in these laboratories has given a mixture of *n*-propylbenzene and isopropylbenzene, which were identified as their diacetamino derivatives (39).

Alcohols, esters, and other alkylating agents, with various catalysts. Isomerization is common in the reactions of aliphatic alcohols with aromatic hydrocarbons. Secondary and tertiary alcohols condensed with benzene in the presence of aluminum chloride, but primary alcohols did not react (40). Isopropyl alcohol gave isopropylbenzene, and *s*-butyl alcohol yielded *s*-butylbenzene. Pentanol-2 was reported to give 2-phenylpentane, while 2-methylbutanol-3 gave 2-methyl-3-phenylbutane. No evidence other than boiling point was given for any of these structures. Isopropyl alcohol and *s*-butyl alcohol reacted with benzene and toluene to give the unisomerized products. (41). A number of tertiary heptyl alcohols have been shown to react with phenol and aluminum chloride to give *t*-heptylphenols (42).

Price and Lund (43) alkylated benzene with *d*-*s*-butyl alcohol. In the presence of aluminum chloride the product was *dl*-*s*-butylbenzene, but when boron trifluoride was used as catalyst the product had optical activity.

Neopentyl alcohol with benzene and aluminum chloride gave a 9% yield of neopentylbenzene (26).

Cycloheptanol with benzene and aluminum chloride yielded largely cycloheptylbenzene, but was to some extent "converted to a six-membered ring" (44). 2,2,4-Trimethylpentanol-2 gave, in addition to the expected *t*-octylbenzene, about 17 to 42% of *t*-butylbenzene (45).

$$(CH_3)_3CCH_2C(CH_3)_2OH \xrightarrow[[AlCl_3]]{[C_6H_5]} \begin{cases} (CH_3)_3CC_6H_5 \\ + \\ (CH_3)_3CCH_2\overset{\displaystyle CH_3}{\overset{|}{C}}C_6H_5 \\ \qquad\quad \overset{|}{CH_3} \end{cases}$$

Toussaint and Hennion (46) alkylated benzene by a number of alcohols in the presence of zinc chloride, sulfuric acid, aluminum chloride, or boron fluoride. It was claimed that primary alcohols gave secondary alkylbenzenes; dodecyl alcohol gave *s*-dodecylbenzene. No details were given on the identification of the products.

Meyer and Bernhauer (47) alkylated benzene, toluene, phenol, and other aromatic compounds with alcohols in the presence of 80% sulfuric acid at 65°. Isopropyl alcohol and *n*-propyl alcohol (8) both gave isopropylbenzene. Isobutyl alcohol and *t*-butyl alcohol both yielded *t*-butylbenzene, identified as its bromo derivative. Both *s*-butyl alcohol and *n*-butyl alcohol gave *s*-butylbenzene. Cyclohexanol yielded cyclohexylbenzene. Other aromatic compounds gave similar results. Nightingale and Smith (48) obtained 1,3-dimethyl-4-*s*-butylbenzene from *m*-xylene and *s*-butyl or *n*-butyl alcohol with sulfuric acid; *n*-butyl alcohol gave only a 6% yield.

Neopentyl alcohol with benzene and sulfuric acid produced *t*-amylbenzene, identified as its diacetamino derivative (26).

$$(CH_3)_3CCH_2OH \xrightarrow[[H_2SO_4]]{[C_6H_6]} CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}C_6H_5$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \underset{\displaystyle CH_3}{|}$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad 65°$$

Isoamyl alcohol gave *t*-amylbenzene (8). *n*-Amyl alcohol yielded a monoamylbenzene fraction of which 60–65% was 2-phenylpentane and 35–40% was 3-phenylpentane, when treated with benzene and 80% sulfuric acid at 70° for six hours. Apparently 1-phenylpentane was absent.

In the presence of boron fluoride, both propyl alcohols gave isopropylbenzene; *n*-butyl alcohol and *s*-butyl alcohol yielded *s*-butylbenzene; and isobutyl alcohol and *t*-butyl alcohol gave *t*-butylbenzene. Cyclohexylbenzene was obtained from cyclohexyl alcohol. Allyl alcohol yielded allylbenzene. The dialkylbenzenes obtained were shown to be the para isomers. No derivatives of the alkylbenzenes were reported (49).

Esters other than halides have also been used. Triisobutyl borate with xylene and aluminum chloride gave a 90% yield of *t*-butylxylene (50). Dibutyl sulfate yielded unidentified isomeric butylbenzenes (51). McKenna and Sowa (52) reported that *n*-propyl formate and *n*-propyl sulfate, as well as several isopropyl esters, reacted with benzene in the presence of boron fluoride to give isopropylbenzene. *n*-Butyl phosphate and formate, and several *s*-butyl esters, yielded *s*-butylbenzene. Isobutyl formate gave *t*-butylbenzene. Vinyl acetate reacted violently and gave resinous products. A great many esters did not react. The identification of the propylbenzenes and butylbenzenes was not described.

Bowden (53) alkylated benzene by esters in the presence of aluminum chloride. He identified his alkylbenzenes by means of their diacetamino derivatives. At temperatures up to 60°, *n*-propyl sulfite and *n*-propyl formate gave *n*-propylbenzene, with at most only a small proportion of isopropylbenzene. *n*-Butyl oxalate, sulfite, formate, propionate, isobutyrate, valerate, 2-ethylvalerate, benzoate, and stearate, all gave *s*-butylbenzene. The report on the propyl esters

differs from the work of other investigators, but Bowden's proof appears to be conclusive. Nightingale and Carton (9) obtained 5-isopropyl-*m*-xylene from *m*-xylene with *n*-propyl formate and aluminum chloride. *n*-Butyl acetate has been reported to give *n*-butylbenzene and *n*-butylacetophenone, when treated with benzene and aluminum chloride (54).

Berman and Lowy (55) alkylated benzene with tri-*n*-butyl phosphate in the presence of aluminum chloride, and obtained *s*-butylbenzene. *s*-Butyl acetate gave *s*-butylbenzene. Methylamyl acetate was reported to yield 2-methyl-4-phenylpentane,

$$CH_3COOCH(CH_3)CH_2CH(CH_3)_2 \xrightarrow[[AlCl_3]]{[C_6H_5]} \underset{\displaystyle C_6H_5}{\overset{\displaystyle |}{CH_3CHCH_2CH(CH_3)_2}}$$

but it is doubtful that this was the only product. All of the alkylbenzenes were identified by their physical constants only.

With hydrogen fluoride and benzene, *n*-butyl acetate gave *s*-butylbenzene, identified as its diacetamino derivative, and some acetophenone (56).

Isoamyl ether with benzene and boron fluoride yielded *t*-amylbenzene; *n*-amyl ether gave *s*-amylbenzene. The former was identified as its diacetamino derivative, but no derivative of the secondary amylbenzene was prepared (57). Benzyl *n*-propyl ether gave about 10% of isopropylbenzene and 45% of benzylbenzene when treated with benzene and boron fluoride. Derivatives were not prepared (58).

Olefinic compounds with various catalysts. Compounds with an ethylenic linkage have been widely used as alkylating agents. The reliability of much of the data is questionable, from the point of view of the study of isomerization, but it is probable that in general addition takes place at the double bond, and possibly also at other points. If olefins are involved in the mechanism of the rearrangement of alkyl halides, the olefins should act in much the same way as the halides themselves. It cannot be definitely said that this is the case.

Propylene, as would be expected, gave isopropylbenzene when aluminum chloride (59), boron fluoride (60, 61), hydrogen fluoride (62) or ferric chloride (63) were used as catalysts. *n*-Propylbenzene was not formed.

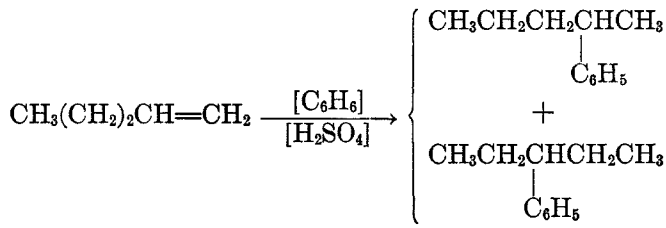
Isobutylene with xylene and aluminum chloride gave *t*-butylxylene (64). Ipatieff (65)[3] treated isobutylene with benzene in the presence of phosphoric acid, sulfuric acid, or aluminum chloride, and obtained butylbenzene. Hydrogen fluoride (62) and ferric chloride (63) yielded *t*-butylbenzene.

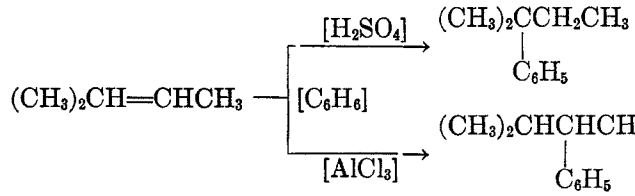
Pentene-2 has been condensed with benzene in the presence of hydrogen fluoride, but the product was only tentatively identified as a mixture of 2-phenylpentane and 3-phenylpentane. 2-Methylbutene-2 gave *t*-amylbenzene (62).

With benzene and sulfuric acid, pentene-1 gave a mixture of 2-phenylpentane and 3-phenylpentane; 2-methylbutene-2 yielded *t*-amylbenzene under these conditions, but gave 2-methyl-3-phenylbutane with aluminum chloride as catalyst.

[3] The product was called "isobutylbenzene" in the Zentralblatt reference (65), but it was probably *t*-butylbenzene.

The structures were established by preparation of the known diacetamino derivatives (8).

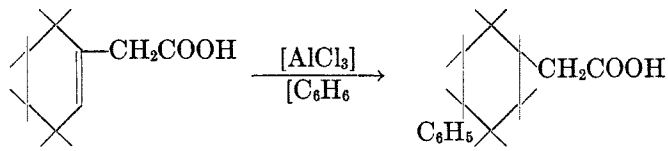




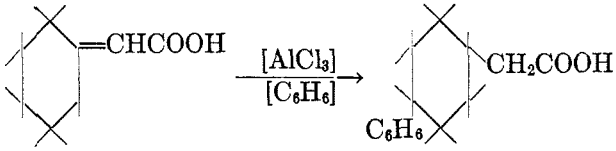
Hexene-2 has been reported to give 2-phenylhexane, with benzene and sulfuric acid, but there was no proof of this or of the presence or absence of other isomers (66). Likewise, hexene-3 has been claimed to give 3-phenylhexane when treated with benzene in the presence of hydrogen fluoride, $H_3BO_2F_2$, or sulfuric acid. No derivatives were prepared. The boiling point (209–212°) indicated 2-phenylhexane rather than 3-phenylhexane, but this is not wholly reliable evidence (67).

Treatment of fractions of cracked gasolines with benzene and aluminum chloride (68) or ferric chloride (69) gave a series of alkylbenzenes, from amyl to octyl, which were not identified except by physical constants. Tilicheev (70) believed these to be secondary alkylbenzenes, which, while it appears probable, lacks any proof. The "amylene" used was a product boiling at 30–40° and containing about 50% of amylene, obtained from paraffin by cracking; "heptylene" was a similar fraction, boiling at 95–98°, and containing 45% of heptylene. With no adequate evidence the products obtained by reaction of these fractions were called 2-phenylpentane, 2-phenylheptane, and so on, up to 2-phenylhexadecane.

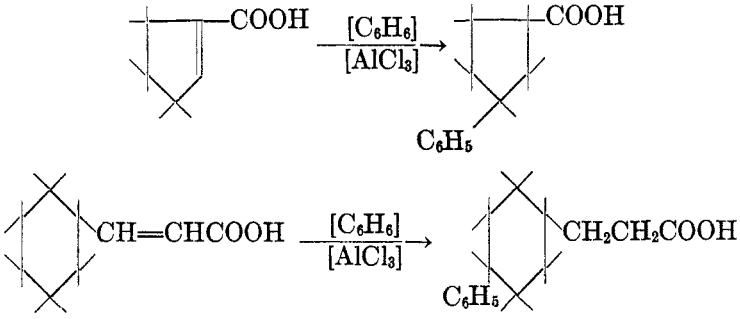
Cyclohexylbenzene is formed from cyclohexene with benzene and aluminum chloride (59) or hydrogen fluoride (62). The reaction of 2-cyclohexenylacetic acid with benzene in the presence of aluminum chloride at from 0° to 25° has been reported to give 2-phenylcyclohexylacetic acid (71), but Cook and Goulden (72) obtained a 7% yield of 4-phenylcyclohexylacetic acid in this reaction, and could find no evidence of 2-phenylcyclohexylacetic acid. The product was identified by decarboxylation and dehydrogenation to the known *p*-methylbiphenyl.



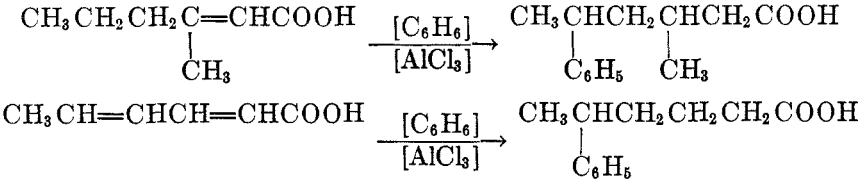
This result was confirmed by Nenitzescu and Gavăt (73), who also found that cyclohexylideneacetic acid gave the same product.



1-Cyclopentene-1-carboxylic acid yielded 3-phenylcylopentane-1-carboxylic acid (74), and 2-cyclohexylacrylic acid gave 2-(4-phenylcyclohexyl)propionic acid (73).



Open-chain unsaturated acids have been found by Nenitzescu (75) and his coworkers to show similar isomerizations in their reactions with benzene and aluminum chloride. The phenyl group entered the molecule at the methylene group farthest removed from the carboxyl group. Hexene-2-oic acid-1 was observed to show a shift in the position of the double bond, away from the carboxyl group, in the presence of aluminum chloride; this may explain the other isomerizations noted. The reduction of a double bond in the second example is reminiscent of that noted with allyl chloride (34).



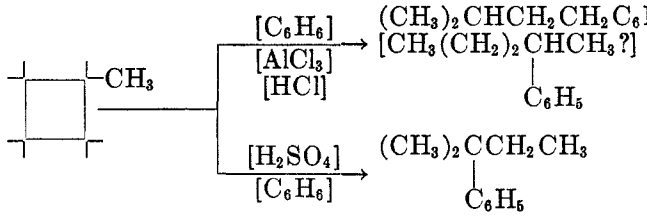
In all cases the structures were proved by independent synthesis and mixed melting point observations. The earlier work of Eijkman (76) on this type of reaction indicated that phenylation always took place at the site of the double bond, but in all cases in which his proof of structure was satisfactory, the only alternative would have involved phenylation of a terminal methyl group.[4]

Harmon and Marvel (78) compared the properties of "phenylstearic acid", prepared from oleic acid with benzene and aluminum chloride, with those of synthetic 9-phenylstearic acid and 10-phenylstearic acid. They concluded that phenylstearic acid is a mixture of these two acids. Other isomers may or may not be formed.

[4] Hopff (77) noted phenylation of the terminal methylene group in acrylic acid, with benzene and aluminum chloride.

Cyclopropane reacted with benzene in the presence of aluminum chloride and hydrogen chloride to give *n*-propylbenzene; isopropylbenzene was not detected by derivatization or by examination of the Raman spectra (79). With *m*-xylene and aluminum chloride (9) or ferric chloride (80), cyclopropane gave 1,3-dimethyl-4-*n*-propylbenzene. Hydrogen fluoride and benzene also gave *n*-propylbenzene and no isopropylbenzene (81). Sulfuric acid at 2 to 4° gave *n*-propylbenzene and *n*-propyl alcohol (82), but at 65° the hydrocarbon product was isopropylbenzene (8).

Methylcyclobutane with aluminum chloride and hydrogen chloride catalysts gave isoamylbenzene and an unidentified fraction which was probably 2-phenylpentane (79). With sulfuric acid the product was *t*-amylbenzene (82).



Cyclopentane did not react with benzene in the presence of sulfuric acid (82), but with aluminum chloride and hydrogen chloride it gave unidentified amylbenzenes, and cyclopentylbenzene (79).

Isoöctane reacted with benzene and aluminum chloride to give *t*-butylbenzene and isobutane, with small amounts of *n*-butane (83, 84). Toluene, biphenyl, and other aromatics reacted similarly. Phenol and aluminum chloride reacted with *t*-octylphenol to give *t*-butylphenol (85).

Alkylating catalysts may cause alkylbenzenes to rearrange. It has recently been reported that 1,3-dimethyl-4-*n*-propylbenzene with aluminum chloride at 55° for three hours gave the unchanged hydrocarbon, but at 85–90° for four hours yielded what appeared to be a mixture of 4-*n*-propylxylene and 5-isopropylxylene. When the reactants were held at 100° for four hours, a product definitely identified as 5-isopropylxylene was obtained (9). This is in contrast to the early work of Heise and Töhl (86), who found, that *n*-propylbenzene with aluminum chloride and hydrogen chloride at 100° for six hours gave benzene, *n*-propylbenzene, and *m*- and *p*-di-*n*-propylbenzenes. The products were identified as their sulfonamides. Baddeley and Kenner (87) likewise found no rearrangement of the *n*-propyl group in the treatment of *p*-di-*n*-propylbenzene with aluminum chloride at 100° for twenty-two hours. Identification was accomplished by means of the acetamino derivatives.

The reactions of butylxylenes with aluminum chloride and ferric chloride have given interesting rearrangements; 1,3-dimethyl-4-*n*-butylbenzene at 100° for four hours gave 1,3-dimethyl-5-*s*-butylbenzene, identified as its trinitro derivative. Surprisingly, 1,3-dimethyl-4-*s*-butylbenzene yielded 1,3-dimethyl-5-*t*-butylbenzene when warmed with aluminum chloride for 2½ hours. Isobutylxylene gave a complex mixture (48). In the presence of ferric chloride, 1,3-dimethyl-4-isobutylbenzene yielded the expected 1,3-dimethyl-5-*t*-butylbenzene, and the other butylxylenes reacted as described in the case of aluminum chloride (80).

Bodendorf (88) condensed propionaldehyde with benzene and aluminum chloride, and obtained *n*-propylbenzene, but gave no details concerning the identification of the product. Similarly he claimed that butyraldehyde gave *n*-butylbenzene, while isobutyraldehyde gave isobutylbenzene, but with no adequate proof.

Conclusion. This study of the isomerization accompanying alkylation shows that the subject requires further and more careful study, for many of the important orienting experiments may be at fault because the products were not properly identified. Boiling point, density, and refractive index are not always sufficient to differentiate between isomers. If, however, we examine the more decisive experiments we can draw a few general conclusions. Primary alkyl compounds give both primary and secondary alkylbenzenes, and higher temperatures favor the formation of the latter. Secondary alkyl compounds give secondary and never primary, alkylbenzenes. Isoalkyl compounds apparently have little tendency to form isoalkylbenzenes, and give largely tertiary alkylbenzenes instead. Tertiary alkyl compounds yield only tertiary alkylbenzenes.

To explain these results we might assume a series of eliminations and additions of hydrogen halide to the alkyl group (75), although in the absence of benzene (or other aromatic compound) this reaction may not take place readily under the mild conditions generally used for Friedel-Crafts reactions (11). Since pentene-1 did not yield any 1-phenylpentane (8) in reaction with benzene and sulfuric acid, and since primary alkyl halides do give some 1-phenylalkanes, it may be supposed that it is the alkyl halide that actually reacts, and not the olefin, although there is, unfortunately, a paucity of information on olefin reactions in which aluminum chloride is the catalyst.

With *n*-hexyl bromide, which has been shown to give 1-phenylhexane, 2-phenylhexane, and 3-phenylhexane (89), the reactions involved would be, according to this mechanism,

$$CH_3(CH_2)_4CH_2Br \xrightarrow[{[AlCl_3]}]{[C_6H_6]} CH_3(CH_2)_4CH_2C_6H_5$$

$$\downarrow -HBr$$

$$CH_3(CH_2)_3CH{=}CH_2$$

$$\downarrow +HBr$$

$$CH_3(CH_2)_3CHBrCH_3 \xrightarrow[{[AlCl_3]}]{[C_6H_6]} CH_3(CH_2)_3CH(C_6H_5)CH_3$$

$$\downarrow -HBr$$

$$CH_2(CH_2)_2CH{=}CHCH_2$$

$$\downarrow +HBr$$

$$CH_3(CH_2)_2CHBrCH_2CH_3 \xrightarrow[{[AlCl_3]}]{[C_6H_6]} CH_3(CH_2)_2CH(C_6H_5)CH_2CH_3$$

DISCUSSION OF EXPERIMENTAL RESULTS

Hexyl bromide and benzene. Hexyl bromide reacted readily with benzene and aluminum chloride at low to moderate temperatures to give good yields of hexylbenzene. Fractional crystallization of the diacetamino derivatives of the product showed that 1-phenylhexane and 3-phenylhexane were present, and indicated, not so satisfactorily, that 2-phenylhexane had also been formed. It was later shown by use of the sulfonamides that 2-phenylhexane was actually present. The three hexylbenzenes were synthesized for purposes of comparison; derivatives were prepared of each, and mixed melting point depressions were observed, in order to eliminate possibility of error, in so far as was practicable.[5] There remains the chance that the carbon skeleton of the hexyl group rearranged, but it is not probable that in the presence of considerable amounts of other isomers the derivatives of the three isomers found could have been obtained so readily, and with no indication of any other hexylbenzene.

For instance, if all seventeen possible hexylbenzenes and all 3,057 possible dodecylbenzenes were formed in this reaction and in the reaction with dodecyl bromide described below, the odds against isolating the five derivatives obtained are four million to one. On the other hand, if only one other hexylbenzene and one other dodecylbenzene formed, the odds against our experiments falling into the pattern obtained are 3.33 to one. The actual chances fall somewhere between these two figures.

Dodecyl bromide and benzene. A preliminary study of the reaction of *n*-dodecyl bromide with benzene and aluminum chloride indicated that this alkyl bromide behaved as did octadecyl bromide. When, however, the five normal secondary dodecylbenzenes were synthesized, and derivatives of these were compared with those of the reaction product, it was found that 1-phenyldodecane and 6-phenyldodecane were both present. Attempts to identify definitely any other isomers did not succeed. There is reason to believe, however, that all six normal dodecylbenzenes were in the product.

Other long-chain alkyl bromides. Tetradecyl bromide reacted with benzene and aluminum chloride to give a mixture of tetradecylbenzenes. As with dodecyl and octadecyl bromides, the product was shown to contain the normal primary alkylbenzene, 1-phenyltetradecane. Similarly, hexadecyl bromide yielded a product containing 1-phenylhexadecane. It is believed that in both cases, all of the possible normal secondary alkylbenzenes were also formed. The octadecylbenzene obtained by Gilman and Turck (1) from *n*-octadecyl bromide with benzene and aluminum chloride was likewise not pure 1-phenyloctadecane, as they supposed, but undoubtedly contained the eight secondary phenyloctadecanes as well. The cause of their error lay in their method of preparing the sulfonamide, and this aspect is discussed in the following section.

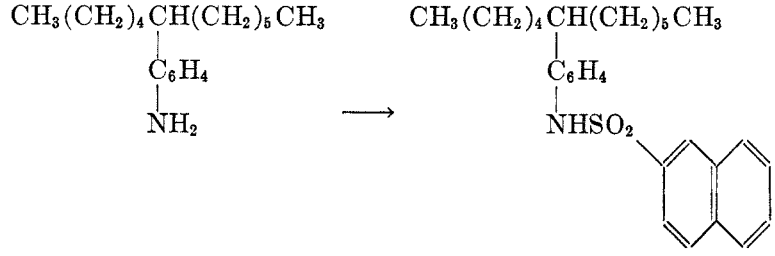
Derivatization of alkylbenzenes. Turck (91) used the procedure described by Seidel and Engelfried (30a) for the preparation of the sulfonamide of octadecylbenzene. In this procedure the alkylbenzenesulfonic acid in ether is shaken

[5] There are 14 other possible hexylbenzenes, few of which are known (*cf.* 90).

with saturated aqueous sodium chloride, and the sodium alkylbenzenesulfonate precipitates and is filtered off for use in preparation of the sulfonamide. We have found that while this is satisfactory for 1-phenylalkanes, the secondary alkylbenzenes in general do not give precipitates, for the sodium salts of the sulfonic acids prepared from them are quite soluble in ether. An exception to this rule is 2-phenyldodecane, which after standing for a short time gave the expected sodium salt. With hexylbenzene and heptylbenzene even the sodium sulfonate of the 1-phenylalkane was sufficiently soluble so that the reaction product containing the three normal alkylbenzenes did not give a precipitate of the sodium sulfonate in this procedure. Pure 1-phenylhexane or 1-phenylheptane did give precipitates, however.

It is probable that the reason that the sulfonamides of only the 1-phenylalkanes were found in the cases of dodecyl-, tetradecyl-, hexadecyl-, and octadecylbenzenes prepared by the Friedel-Crafts reaction, was that the secondary alkylbenzenes were lost at this point in the preparation of the derivative.

The diacetamino derivatives, whose method of preparation was described by Ipatieff and Schmerling (92), were found to be useful in the identification and separation of the hexylbenzenes. In the case of the dodecylbenzenes, however, crystalline derivatives could not be obtained with acetic anhydride and the amino derivative. When β-naphthalenesulfonyl chloride was substituted for the acetic anhydride, a very convenient series of derivatives was obtained, which complemented the series of sulfonamides and made possible the identification of 6-phenyldodecane in the mixture of dodecylbenzenes. The derivative was



probably a mixture of the ortho and para isomers.

No satisfactory way has been found of estimating the proportions of the isomers in the hexylbenzene or dodecylbenzene produced from the alkyl bromides with benzene and aluminum chloride. Even with hexylbenzene, our fractional distillation did not separate the isomers efficiently. The crude separation achieved did not indicate a great preponderance of any of the isomers.

A comparison of the yields of ether-insoluble sodium sulfonates obtained from 1-phenyldodecane and from Friedel-Crafts dodecylbenzene indicated that 1-phenyldodecane and 2-phenyldodecane together make up about 40% of the latter. Here again, no great preponderance of any one isomer was indicated.

EXPERIMENTAL

Alkylation of benzene. Benzene and aluminum chloride (B. and A. reagent) were mixed in a 3-necked flask equipped with a stirrer and a reflux condenser to which a drying-tube

and an outlet for hydrogen halides were attached. The alkyl bromide was added slowly through a dropping-funnel and the mixture was stirred. Table I gives the conditions of the reactions and the results obtained.

Identification of alkylbenzenes. The sulfonamide of the hexadecylbenzene obtained in experiment 1 melted at 97°, and did not depress the melting point of the sulfonamide of synthetic 1-phenylhexadecane. The sulfonamide of the tetradecylbenzene obtained in experiment 2 melted at 97.5°, and did not depress the melting point of the sulfonamide of synthetic 1-phenyltetradecane. The sulfonamide of the dodecylbenzene obtained in experiment 3 melted at 97.5°, and did not depress the melting point of the sulfonamide of synthetic 1-phenyldodecane.

The products of reaction in experiment 4 were fractionated by distillation. After removal of the solvent the lowest-boiling fraction distilled at 100° at 43 mm., or 205–208° at 1

TABLE I

FRIEDEL-CRAFTS ALKYLATIONS

EXPT. NO.	ALKYL BROMIDE	RBr		BENZENE		$AlCl_3$		TEMP. °C.	TIME HR.	B.P. °C.	ALKYLBENZENES			
		G.	MOLES	CC.	MOLES	G.	MOLES				PRESS. MM.	YIELD		
												G.	MOLES	%
1	*n*-Hexadecyl	30.5	0.10	77	0.85	2.0	0.015	Room	26.5	211–228	13	11.6	0.038	38.4
								50–53	4					
2	*n*-Tetradecyl	16.6	0.06	45	0.50	1.2	0.009	Room	34	170–179	6	10.3	0.038	62.6
								45–55	4					
3	*n*-Dodecyl	16.5	0.066	45	0.50	1.3	0.01	Room	34	144–151	5	6.8	0.027	41.7
								40–50	4					
4	*n*-Dodecyl	80.7	0.324	265	2.98	7.0	0.052	0–23	48	—	—	—	—	—
5	*n*-Dodecyl	16.6	0.066	45	0.50	1.3	0.01	Room	35	200–218	43	8.4	0.038	57
								40–60	4.5					
6	*n*-Heptyl	17.7	0.10	77	0.85	2.0	0.015	Room	34	129–133	37	8.0	0.046	46
								40–50	4					
7	*n*-Hexyl	16.5	0.10	77	0.85	2.0	0.015	Room	45	213–223	atm.	8.7	0.054	53.6
								50	4					
8	*n*-Hexyl	19.8	0.12	92	1.03	2.4	0.018	0	20	210–213	atm.	8.1	0.050	41.5
9	*n*-Hexyl	82.5	0.50	380	4.38	10	0.075	0–23	48	200–227	atm.	60.1	0.37	74
10	*n*-Hexyl	82.5	0.50	380	4.38	10	0.075	0	49	200–227	atm.	56.9	0.35	70
11	*n*-Hexyl	90.8	0.55	365	4.21	11	0.083	0	40	—	—	—	—	—
12	*n*-Octadecyl	16.6	0.05	38	0.43	1.0	0.008	Room	34	205–215	6	7.9	0.024	48.2
								40–60	4					

atm. The yield was 3.4 g; n_D^{20} 1.4233; d_{20}^{20} 0.752. This may be a mixture of dodecenes (93). The second portion boiled at 185–190° at 33 mm., or 194–203° at 46 mm.; n_D^{20} 1.4810; d_{20}^{20} 0.857. The yield was 4.8 g. (5.5%). This fraction was nitrated and reduced (92), and the monoamine was treated with β-naphthalenesulfonyl chloride. Fractional crystallization of the resulting derivative gave a product which melted at 127°. A mixed melting point with the β-naphthalene sulfonamide of 6-phenyldodecane was 127–128°. A third fraction boiled at 190–195° at 34 mm.; n_D^{20} 1.4821; d_{20}^{20} 0.858; yield 11.3 g. (11.9%). The sodium sulfonate obtained from this was soluble in ether. A fourth portion distilled at 195–201° at 35 mm.; yield 11.7 g. (12.4%). The undistilled residue weighed 5.9 g.

In the fifth experiment the product was sulfonated with fuming sulfuric acid in a carefully standardized procedure. The yield of sodium sulfonate insoluble in ether was 16.7%. The same procedure gave a 41% yield with pure 1-phenyldodecane. Since the only two *n*-dodecylbenzenes giving ether-insoluble sodium sulfonates were 1-phenyldodecane and

2-phenyldodecane, it was concluded that about 40% of the Friedel-Crafts product consisted of these two dodecylbenzenes.

The sodium sulfonates of the heptylbenzene obtained in experiment 6 and of the hexylbenzenes obtained in experiments 7 and 8 were soluble in ether.

The hexylbenzene from experiment 9 was fractionated in a small, jacketed column. The first portion distilled at 200–205° and weighed 2.8 g; n_D^{10} 1.4875; d_{21}^{21} 0.861. The diacetamino derivative after several recrystallizations melted at 201°, and did not depress the melting point of the diacetamino derivative of 3-phenylhexane. The third portion boiled at 207.5–210° and weighed 12.1 g; n_D^{10} 1.4886; d_{21}^{21} 0.860. From this was obtained a diacetamino derivative which melted at 172°. In mixture with the diacetamino derivative of 2-phenylhexane (m.p. 178°), it melted at 175–178°. The fourth fraction, boiling at 210–215°, and weighing 10.9 g. (n_D^{10} 1.4885; d_{21}^{21} 0.860), gave a diacetamino derivative similar to that obtained from the third fraction. The sixth fraction, which distilled above 220°, weighed 4.9 g.; n_D^{10} 1.4924; d_{20}^{21} 0.867. The diacetamino derivative of this melted at 201°, and did not depress the melting point of the diacetamino derivative of 1-phenylhexane.

TABLE II

PREPARATION OF KETONES

KETONE	B.P. °C.	PRESS. MM.	M.P. °C.	YIELD[a] %	SEMICARBAZONE M.P. °C.	ANALYSIS	
						N FOUND	N CALC'D
n-$C_{15}H_{31}COC_6H_5$	—	—	56	67	88	11.25	11.26
n-$C_{13}H_{27}COC_6H_5$	206	5	52	45	97[b]	12.41	12.16
n-$C_{11}H_{23}COC_6H_5$	187	5	42.5	64	94.5–95	13.60	13.24
n-$C_9H_{19}COC_6H_5$[c]	168	5	35–36	82.8	124	15.0	14.53
n-$C_8H_{13}COC_6H_5$[d]	173	34	—	—	—	—	—
n-$C_5H_{11}COC_6H_5$	160	33	—	73.8	131[e]	—	—
n-$C_4H_9COC_6H_5$	161	67	—	44	—	—	—
n-$C_3H_7COC_6H_5$	110	10	—	82.5[f]	—	—	—
n-$C_2H_5COC_6H_5$	212–215	atm.	—	32.3	—	—	—

[a] Yield is based on acid used.

[b] Sabatier and Maihle, *Compt. rend.*, **158,** 834 (1914) reported 75°.

[c] *Anal.* Calc'd for $C_{16}H_{24}O$: C, 82.70; H, 10.4. Found: C, 82.32; H, 10.70.

[d] Krafft, *Ber.*, **19,** 2987 (1886). Observed n_D^{20} 1.5068.

[e] Schroeter, *Ber.*, **40,** 1603 (1907).

[f] Based on butyryl chloride.

The hexylbenzene from experiment 11 was fractionated through a jacketed column (94) and divided into a number of (2-cc.) portions. The thirteenth fraction gave the diacetamino derivative of 1-phenylhexane mixed with what appeared to be that of 2-phenylhexane. Fraction 14 (b.p. 210°; n_D^{20} 1.4879) gave a sulfonamide which melted at 82°. The mixed melting point with the sulfonamide of 2-phenylhexane was 82–83°.

The octadecylbenzene from experiment 12 yielded a sulfonamide which melted at 99–100°, and which did not depress the melting point of the sulfonamide prepared by Turek from synthetic 1-phenyloctadecane (1).

Preparation of synthetic hydrocarbons. The synthetic hydrocarbons were prepared solely for the purpose of obtaining the melting points of their derivatives, and of obtaining samples for mixed melting point determinations. No particular efforts were made to remove small amounts of impurities which would not interfere with this purpose. The physical constants should for this reason not be taken as the constants of the pure hydrocarbons. The 1-phenylalkanes were each prepared in two ways: by the Clemmensen reduction of the appropriate alkyl phenyl ketone, and by the Wurtz-Fittig reactions. In each case the sulfon-

amides of both products were prepared, and were shown to be identical by the method of mixed melting points. The results are shown in Tables II, III, and IV. The ketones were prepared from the acid chlorides and benzene, with aluminum chloride. They were reduced by a modification of the Clemmensen method (95). The Wurtz-Fittig reactions were carried out in about 35 cc. of benzene, per 5 g. of sodium. Hexylbenzene and heptylbenzene prepared by this method were very impure, since the two symmetrical coupling products distilled at very nearly the same temperature as the alkylbenzene in each case.

The secondary alkylbenzenes were prepared in three steps: (a) the reaction of a ketone with a Grignard reagent to give a tertiary carbinol, (b) dehydration of the carbinol with

TABLE III

REDUCTION OF KETONES

KETONE	ALKYLBENZENE	TIME OF REDUCTION	YIELD %	B.P. °C.	PRESS. MM.	n_D^t	d_{20}^t	MOLECULAR REFRACTION	
								FOUND	CALC'D
n-$C_{15}H_{31}COC_6H_5$....	n-Hexadecyl	29 hr.	29.6	202–213	7	$1.4802^{27.5}$	$0.858^{27.3}$	100.2	100.2
n-$C_{13}H_{27}COC_6H_5$....	n-Tetradecyl	—	58	188–189	6	$1.4835^{24.8}$	$0.857^{23.6}$	91.53	90.96
n-$C_{11}H_{23}COC_6H_5$....	n-Dodecyl	—	31	164	4	1.4857^{20}	$0.859^{24.2}$	82.00	81.72
n-$C_6H_{13}COC_6H_5$.....	n-Heptyl	—	—	240–244	atm.	$1.4842^{31.5}$	0.959^{27}	58.8	58.63
n-$C_5H_{11}COC_6H_5$.....	n-Hexyl	12	51.8	220–222	atm.	1.4880^{20}	0.861^{20}	54.34	54.02

TABLE IV

WURTZ-FITTIG REACTIONS

NO.	ALKYLBENZENE	RBr		BROMOBENZENE		SODIUM		YIELD %	B.P. °C	PRESS. MM.	n_D^t	d_{20}^t	MOLECULAR REFRACTION	
		G.	MOLES	G.	MOLES	G.	ATOMS						FOUND	CALC'D
1	n-Hexadecyl	15.3	0.05	8.7	0.055	5	0.217	26.4	230–232	14	$1.4793^{27.5}$	$0.857^{25.4}$	100.0	100.2
2	n-Tetradecyl	13.6	0.05	8.7	0.055	5	0.217	33.6	193	7	1.4822^{26}	—	—	—
3	n-Dodecyl	16.2	0.065	11.5	0.073	6.35	0.276	38.1	164	5	1.4832^{20}	0.854^{24}	82.13	81.72

60% sulfuric acid to produce the olefin, and (c) reduction of the olefin with sodium and alcohol. The results are given in Tables V, VI, and VII. A description of the preparation of 2-phenyldodecane will be sufficient to show the methods used.

Decyl bromide was prepared from n-decyl alcohol by heating with 48% hydrobromic acid and concentrated sulfuric acid (96); boiling point 152–155° at 66 mm.; n_D^{20} 1.4551 (97). To the Grignard reagent prepared from 23.7 g. of decyl bromide (0.107 mole), 2.6 g. of magnesium, and 100 cc. of ether, 12.8 g. of acetophenone (0.106 mole) was added slowly at 0°. The product was hydrolyzed with ammonium chloride solution, separated, washed with dilute sodium carbonate solution, and finally with water. It was dried over sodium sulfate and distilled *in vacuo*. This yielded 14 g. (50%) of 2-phenyldodecanol-2.

Fourteen grams (0.053 mole) of 2-phenyldodecanol-2 and 20 g. of 60% sulfuric acid (98) were warmed on a water-bath until the upper layer became clear. The upper layer was then separated, washed with water, then with dilute sodium carbonate solution, and dried over calcium chloride. The yield was 10.7 g. (82.2%) of 2-phenyldodecene.

TABLE V

PREPARATION OF TERTIARY CARBINOLS

CARBINOL	KETONE	GRIGNARD REAGENT FROM	YIELD %	B.P. °C.	PRESS. MM.	n_D^{20}	d_{20}^{20}	M.R.[a] FOUND	ANALYSIS[b] C	ANALYSIS[b] H
2-Phenyldodecanol-2	Acetophenone	Decyl bromide	50	174–177	7	1.4914	0.911	83.52	82.78	11.94
3-Phenyldodecanol-3	*n*-Nonyl phenyl ketone	Ethyl bromide	82	168	5	1.4954	0.920	83.22	82.90	11.59
4-Phenyldodecanol-4	*n*-Propyl phenyl ketone	Octyl bromide	50.2	170	4	1.4940	0.917	83.39	82.42	11.77
5-Phenyldodecanol-5	*n*-Butyl phenyl ketone	Heptyl bromide	62	166–168	5	1.4961	0.922	83.10	82.32	11.39
6-Phenyldodecanol-6	*n*-Amyl phenyl ketone	Hexyl bromide	66	169–170	6	1.4947	0.921	83.12	82.84	11.51
2-Phenylhexanol-2[c]	Acetophenone	Butyl bromide	52.9	120	10	1.5084	0.963	55.46	80.72	10.41
3-Phenylhexanol-3[d]	Propiophenone	Propyl bromide	72.4	134	27	1.5100	0.966	55.1	—	—

[a] Molecular refraction calc'd for $C_{18}H_{30}O$ is 83.45; for $C_{12}H_{18}O$ it is 55.42.

[b] Calc'd for $C_{18}H_{30}O$: C, 82.39; H, 11.53. Calc'd for $C_{12}H_{18}O$: C, 80.87; H, 10.17.

[c] Conant and Carlson, *J. Am. Chem. Soc.*, **54,** 4084 (1932).

[d] Yéramian, *Compt. rend.*, **173,** 362 (1921).

TABLE VI

DEHYDRATION OF CARBINOLS

CARBINOL	OLEFIN[d]	YIELD %	B.P. °C.	PRESS. MM.	n_D^{20}	d_{20}^{20}	M.R.[a] FOUND	ANALYSES[b] C	ANALYSES[b] H
2-Phenyldodecanol-2	2-Phenyldodecene	82.2	160–162	5	1.5003	0.873	82.38	88.20	11.63
3-Phenyldodecanol-3	3-Phenyldodecene	89	165	7	1.5025	0.880	81.98	88.38	11.83
4-Phenyldodecanol-4	4-Phenyldodecene	84.5	153–154	5	1.5011	0.876	82.16	88.84	11.86
5-Phenyldodecanol-5	5-Phenyldodecene	85	156–157	6	1.5034	0.881	82.08	88.14	11.67
6-Phenyldodecanol-6	6-Phenyldodecene	77	161	9	1.5025	0.875	82.47	88.48	11.67
			192	33					
2-Phenylhexanol-2	2-Phenylhexene	87.8	125–130	42	1.5230	0.899	54.16	89.82	10.26
3-Phenylhexanol-3	3-Phenylhexene[c]	76	125–130	56	1.5236	0.895	54.68	—	—
			206–217	atm.					

[a] Molecular refraction; calc'd for $C_{18}H_{28}$ is 81.20; for $C_{12}H_{16}$ is 53.54.

[b] Calc'd for $C_{18}H_{28}$: C, 88.46; H, 11.54.
Calc'd for $C_{12}H_{16}$: C, 89.95; H, 10.05.

[c] Yéramian, *Compt. rend.*, **173,** 362 (1921).

[d] The position of the double bond was not ascertained.

Ten and seven-tenths grams of 2-phenyldodecene (0.043 mole) was dissolved in 80 cc. of absolute alcohol, and the solution was treated with 8.7 g. of sodium. The product was hydrolyzed, acidified, extracted with petroleum ether, separated, washed, and dried over calcium chloride. There was obtained 8.5 g. (78.8%) of 2-phenyldodecane.

Since it was thought possible that 60% sulfuric acid might cause rearrangement of the hydrocarbon during dehydration, 2-phenylhexanol-2 was reduced to 2-phenylhexane with hydrogen iodide, and the product was compared with the 2-phenylhexane obtained by the usual method.

Three and one-quarter grams of red phosphorus, 1.1 g. of iodine, and 54 cc. of glacial acetic acid were warmed for one-half hour. To this mixture was added 1.1 cc. of water, followed by 16.9 g. (0.095 mole) of 2-phenylhexanol-2. The mixture was refluxed gently for five hours. It was filtered, diluted with water, extracted with ether, washed with sodium bisulfite, then with dilute sodium carbonate, and finally with water. It was dried over calcium chloride, and distilled; boiling point 62–67° at 4 mm.; n_D^{25} 1.4960; d_{20}^{25} 0.866; M.R. 54.7 (calc'd 54.0). The acetamino derivative of this 2-phenylhexane melted at 76° and gave

TABLE VII

PREPARATION OF SECONDARY ALKYLBENZENES

ALKYLBENZENE	YIELD %	B.P. °C.	PRESS. MM.	n_D^{20}	d_{20}^{20}	M.R.[a] FOUND	ANALYSES[b]	
							C	H
2-Phenyldodecane.....	78.8	161	7	1.4800	0.854	81.98	88.18	12.37
3-Phenyldodecane.....	80.7	171	13	1.4845	0.861	81.94	87.30	12.26
		151	5					
4-Phenyldodecane.....	78	164	17	1.4855	0.861	82.1	88.20	12.26
5-Phenyldodecane.....	83	158	7.5	1.4880	0.863	82.24	87.25	11.77
6-Phenyldodecane.....	82	153	6	1.4885	0.860	82.62	87.70	11.97
		190	35					
2-Phenylhexane.....	86.2	208.7–210	741	1.4873	0.861	54.26	89.15	11.09
3-Phenylhexane[c].....	48	200–203.5	atm.	1.4894	0.863	54.36	88.67	11.04

[a] Calc'd for $C_{18}H_{30}$: M, 81.7. Calc'd for $C_{12}H_{18}$: M, 54.02.

[b] Calc'd for $C_{18}H_{30}$: C, 87.73; H, 12.27. Calc'd for $C_{12}H_{18}$: C, 88.84; H, 11.16.

[c] Levene and Marker, *J. Biol. Chem.*, **93**, 749 (1931).

no depression of the melting point when mixed with the acetamino derivative of the other 2-phenylhexane.

Preparation of derivatives. Sulfonamides. The sulfonamides of the 1-phenylalkanes and of 2-phenyldodecane were prepared according to the directions of Turck (91). The other sulfonamides could not be conveniently prepared in this way. It was found better to neutralize the acids with calcium oxide, extract the calcium alkylbenzenesulfonate with water, and decompose with sodium carbonate. The solution was evaporated and the sodium alkylbenzenesulfonate was extracted with alcohol. The alcohol was evaporated to give the dry salt. This was treated with phosphorus pentachloride and then with ammonia to give the sulfonamide. *Acetamino.* The procedure of Ipatieff and Schmerling (92) was used to prepare the acetamino and diacetamino derivatives of the hexylbenzenes. *β-Naphthalenesulfonamides.* The monoamino derivatives were prepared and isolated by the method of Ipatieff and Schmerling (92). The amine was dissolved in benzene, and treated with half its weight of β-naphthalenesulfonyl chloride. The benzene was removed by distillation, and the residue was dissolved in petroleum ether. The solution was shaken with 10% aqueous sodium hydroxide; methanol was added to break the emulsion. The petroleum ether layer was separated, dried over sodium sulfate, filtered, and heated in an open flask on the steam-bath until a thick gel formed. Acetone was added and the precipi-

TABLE VIII

DERIVATIVES OF ALKYLBENZENES

ALKYLBENZENE	DERIVATIVE	M.P. °C.	N FOUND	N CALC'D
Hexadecyl-(1)	Sulfonamide	97	3.67	3.67
Tetradecyl-(1)	"	97.5–98	4.29	3.96
Dodecyl-(1)	"	97.5	4.35	4.30
Dodecyl-(2)	"	99	4.25	4.30
Dodecyl-(3)	"	56	4.38	4.30
Dodecyl-(4)	"	60	4.26	4.30
Heptyl-(1)	"	90.5	5.52	5.49
Hexyl-(1)	"	86	5.75	5.81
Hexyl-(2)	"	83	6.01	5.81
Hexyl-(3)	"	63	5.95	5.81
Dodecyl-(3)	β-Naphthalene sulfonamide	103	3.12	3.10
Dodecyl-(4)	"	112–112.5	3.26	3.10
Dodecyl-(5)	"	107–107.5	3.34	3.10
Dodecyl-(6)	"	128	3.41	3.10
Hexyl-(1)	Acetamino	91	6.32	6.39
Hexyl-(2)	"	76	6.48	6.39
Hexyl-(3)	"	127	6.43	6.39
Hexyl-(1)	Diacetamino	200–202	10.08	10.13
Hexyl-(2)	"	178	10.43	10.13
Hexyl-(3)	"	199–201	10.47	10.13

TABLE IX

MIXED MELTING POINTS OF DERIVATIVES

A	M.P. °C.	B	M.P. °C.	A + B M.P. °C.
SULFONAMIDES				
1-Phenyloctadecane	99–100	1-Phenylhexadecane	97	96
1-Phenyltetradecane	97.5–98	1-Phenylhexadecane	97	94
1-Phenyltetradecane	97.5–98	1-Phenyldodecane	97.5	93
2-Phenyldodecane	99	1-Phenyldodecane	97.5	82–95
3-Phenyldodecane	56	4-Phenyldodecane	60	44–47
1-Phenylhexane	86	2-Phenylhexane	83	62–66
1-Phenylhexane	86	3-Phenylhexane	63	50
2-Phenylhexane	83	3-Phenylhexane	63	51
DIACETAMINO DERIVATIVES				
1-Phenylhexane	200–202	2-Phenylhexane	178	135–170
1-Phenylhexane	200–202	3-Phenylhexane	199–201	145–155
2-Phenylhexane	178	3-Phenylhexane	199–201	165–168
β-NAPHTHALENE SULFONAMIDES				
3-Phenyldodecane	103	4-Phenyldodecane	112–112.5	103–104
3-Phenyldodecane	103	5-Phenyldodecane	107–107.5	81–87
4-Phenyldodecane	112–112.5	5-Phenyldodecane	107–107.5	98–100
4-Phenyldodecane	112–112.5	6-Phenyldodecane	128	97–117

tate was filtered off. The sodium salt so obtained was decomposed by suspending it in ether and treating the suspension with dilute hydrochloric acid. The ether solution was washed, dried over sodium sulfate, filtered, and evaporated nearly to dryness. The residue was treated with petroleum ether and set aside to crystallize. The product was recrystallized from petroleum ether, alcohol, or aqueous alcohol. The yield was about 10%. Nitrogen analyses showed the products to be the β-naphthalene-sulfono-dodecylanilides, β-$C_{10}H_7SO_2NHC_6H_4C_{11}H_{25}$. The orientation of the amine was not determined. These are the derivatives referred to in Table VIII as the β-naphthalenesulfonamides.

Mixed melting points. Melting points were observed for mixtures of various pairs of the above derivatives. The results are shown in Table IX. The observations show clearly that the conclusions drawn concerning the identity of the alkylbenzenes were justified, for in only one instance did mixtures of isomers fail to give a distinct lowering of the melting point.

SUMMARY

Normal hexyl bromide has been shown to give 1-phenylhexane, 2-phenylhexane, and 3-phenylhexane, when treated with benzene in the presence of aluminum chloride. Under the same conditions, *n*-dodecyl bromide yielded a mixture of dodecylbenzenes, in which 1-phenyldodecane and 6-phenyldodecane have been identified.

Derivatives of synthetic primary and secondary *n*-hexyl- and *n*-dodecylbenzenes have been prepared, and the structures of the Friedel-Crafts alkylation products have been established by the method of mixed melting points. A study of the melting points of known mixtures showed that this method was reliable in the cases in which it was applied.

Among the products of the reaction of *n*-tetradecyl bromide with benzene and aluminum chloride, 1-phenyltetradecane has been identified. *n*-Hexadecyl bromide under these conditions gave some 1-phenylhexadecane, and *n*-octadecyl bromide gave some 1-phenyloctadecane.

It may be concluded from present findings, that under mild conditions benzene reacts with a normal primary alkyl bromide in the presence of aluminum chloride to give a mixture of alkylbenzenes, in which the phenyl group is very probably attached to each one of the carbon atoms in the alkyl residue. The evidence obtained does not indicate any appreciable amount of branching of the alkyl chain under the experimental conditions used.

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ON THE MECHANISM OF THE GATTERMANN REACTION. II.[1,2]

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Recently it was established that sodium cyanide, instead of the dangerous hydrogen cyanide, which requires great precautions, can be applied extensively in the preparation of alkylated aromatic aldehydes according to the Gattermann reaction (1). The convenience and ease with which this agent could be used in the study of this transformation gave rise to an investigation of the mechanism of this fundamental process.

The use of sodium cyanide instead of hydrogen cyanide in the Gattermann reaction involves a more complicated mechanism than that with the latter reagent. In the Gattermann reaction the catalyst traps the hydrogen cyanide, thereby itself being prevented from entering extensive side-reactions except with groups extremely labile in the presence of aluminum chloride.

With sodium cyanide, however, the mechanism involves first the formation of an intermediate, which is later condensed with the hydrocarbon. This process occurs through the action of the aluminum chloride-hydrocarbon complex on the sodium cyanide, thereby giving rise to alkylations and migrations as predominant phases in this modification.

Toluene yields, by using sodium cyanide, *m*- and *p*-tolualdehydes, the former predominating; whereas in the presence of a suitable solvent, such as chlorobenzene, the latter isomer is formed exclusively. The use of *o*-dichlorobenzene as solvent, however, decreases the yield of the aldehyde. Thus, aldehyde formation is influenced by the type of solvent employed. In the process of formation of the intermediate aldehyde precursor and its condensation with the hydrocarbon, migration of the alkyl group occurs, to yield the rearranged product.

Using *o*-xylene, the formation of 2,4-dimethylbenzaldehyde indicates, as in the case of toluene, that aluminum chloride causes migration, as observed by Heise and Tohl (2).

From *m*-xylene, 2,4-dimethylbenzaldehyde is formed in greater proportion than 2,4,5-trimethylbenzaldehyde; however, *p*-xylene yields the latter isomer in greater amounts. The production of the trimethylbenzaldehyde emphasizes the alkylating side-reaction of the aluminum chloride effect.

The anomalous results obtained with the xylenes can be accounted for as proceeding through two alternative courses. Phase I may account for the rearranging influence of the catalyst to produce the *m*-xylene which undergoes reaction with the aldehyde intermediate, hydrolysis yielding the 2,4-dimethyl-

[1] Abridged from a part of the dissertation of E. L. N. (at present Ensign, U. S. Naval Reserve) submitted in partial fulfillment of the requirements of Doctor of Philosophy to the Graduate School of Fordham University, January, 1943.

[2] Presented before the Fall meeting of the American Chemical Society, Buffalo, N. Y., September, 1942.

TABLE I

EXPERIMENT[a]	HYDROCARBON	AMOUNT CC.	$AlCl_3$ GMS.	NaCN GMS.	-BENZALDEHYDE	% YIELD BASED ON 2 MOLES CN^-	PHYSICAL CONSTANTS
	o-Xylene	100	66	25	2,4-Dimethyl-	74.6	
2	*m*-Xylene	150	99	38	a. 2,4-Dimethyl-	25.8	
					b. 2,4,5-Trimethyl-	12.6	
3	*p*-Xylene	150	99	38	a. 2,4-Dimethyl-	16.9	
					b. 2,4,5-Trimethyl-	20.7	
4	Ethylbenzene	350	300	100	a. Diethyl-	13.0	115–118° (9 mm.); n_D^{23} 1.5378; d_4 0.972
					b. Triethyl-	5.3	138–140° (9 mm.); n_D^{25} 1.5346; d_4^{23} .969
5	Cumene[b]	400	400	150	Diisopropyl-	12.3	126–134° (9 mm.); n_D^{22} 1.5180; d_4^{23} .965
6	*m*-Diisopropylbenzene	250	200	75	Diisopropyl-	38.9	126–130° (9 mm.); n_D^{22} 1.5132; d_4^{19} .965
7	*p*-Cymene	250	200	75	a. Methylisopropyl-	5.0	118–122° (9 mm.); n_D^{22} 1.5120; d_4^{18} .949
					b. Methylisopropyl-	17.2	129–132° (9 mm.); n_D^{23} 1.5146; d_4^{17} .967
					c. Diisopropyl-	12.6	141–146° (9 mm.); n_D^{22} 1.5186; d_4^{18} .972
8	Pseudocumene	150	99	38	a. 2,4,5-Trimethyl-	7.2	
					b. 2,4,6-Trimethyl-	7.2	
9	Mesitylene	100	66	25	2,3,5-Trimethyl-	13.4	
10	Ethylbenzene	100	104	HCN, cc 30	a. Ethyl-	29.8	
					b. Diethyl-	24.6	See above
11	*p*-Cymene	50	52	15	a. Methylisopropyl-	12.4	110–117° (14 mm.); n_D^{24} 1.5268
					b. 5-Methyl-2-isopropyl-	24.6	126–133° (14 mm.); n_D^{25} 1.5250
					c. Methyldiisopropyl-	15.8	133–138° (14 mm.); n_D^{25} 1.5242
					d. Methyldiisopropyl-	9.8	142–150° (14 mm.); n_D^{24} 1.5190

[a] Experiments Nos. 1, 2, 3, 5, 7 were conducted for 7 hours at 95–100°. Nos. 4 and 6 were conducted for 8, and No. 8 for 6.5 hours, at 100°. Nos. 10 to 13 were conducted for 5 hours at 100°.

[b] The cumene used in this investigation was obtained through the courtesy of the Dow Chemical Company, Midland, Mich.

TABLE I—(*Continued*)

EXPERIMENT[a]	HYDROCARBON	AMOUNT CC.	$AlCl_3$ GMS.	NaCN GMS.	-BENZALDEHYDE	% YIELD BASED ON 2 MOLES CN^-	PHYSICAL CONSTANTS
12	*m*-Diisopropylbenzene	100	104	30	a. Diisopropyl-	17.2	135–139° (9 mm.); n_D^{21} 1.5194; d_4^{22} .970
					b. Triisopropyl-	16.0	145–152° (9 mm.); n_D^{24} 1.5172; d_4^{25} .940
13	*m*-Diisopropylbenzene	100	66	38	Triisopropyl-	4.6	129–133° (9 mm.); n_D^{21} 1.5182; d_4^{22} .943

benzaldehyde. An alternative path would picture the condensation of the intermediate, then migration of the methyl group, the final product corresponding to 2,4-dimethylbenzaldehyde. Phase II indicates an alkylation of the xylene, followed by condensation with the intermediate to yield the 2,4,5-trimethylbenzaldehyde.

Benzene is one of the exceptions to the applicability of sodium cyanide. This would indicate that the presence of an alkyl substituent is indispensable to effect reaction. In the case of *p*-xylene, with its zero dipole moment, the aluminum chloride rearranges the alkyl groups by migration, to yield the more highly polar hydrocarbons.

From ethylbenzene are formed di- and tri-ethylbenzaldehydes. If, however, ethylbenzene is treated according to the original procedure as extended to the aromatic hydrocarbons (3), mono- and di-ethylbenzaldehyde are obtained. The latter was found to be identical with the product obtained from the sodium cyanide modification. Thus, in these two reactions, although alkylation is extensive, migration of the ethyl group is restricted.

Cumene shows preferential formation of diisopropylbenzaldehyde; *m*-diisopropylbenzene failed to yield the higher aldehyde, forming chiefly an isomeric diisopropylbenzaldehyde. *p*-Cymene yields isomeric methylisopropylbenzaldehydes and another isomeric diisopropylbenzaldehyde.

m-Diisopropylbenzene and *p*-cymene also were treated according to the original procedure. *m*-Diisopropylbenzene forms di- and tri-isopropylbenzaldehydes. The degree of alkyl migration was determined by subjecting *p*-cymene to the reaction. It yielded two isomeric methyldiisopropylbenzaldehydes and two methylisopropylbenzaldehydes, one of the latter corresponding to an expected aldehyde, 5-methyl-2-isopropylbenzaldehyde.

Alkylation of *p*-cymene should be expected to be analogous to the Gattermann reaction, as shown by the products formed from the other hydrocarbons. However, the formation of the methylisopropylbenzaldehydes indicates that the alkylated cymene is further dealkylated:

$$RC_6H_5 + (CH_3)(C_3H_7)C_6H_3R' \rightleftharpoons RC_6H_4R' + (CH_3)(C_3H_7)C_6H_4$$

TABLE II

DERIVATIVES

EXPERIMENT	DERIVATES	M.P. °C	FOUND			CALCULATED		
			C%	H%	N%	C%	H%	N%
1	Acid	122						
	Amide	179						
2a	Acid	122						
	Amide	180						
2b	Acid	146						
	Amide	202			8.59			8.68
3a	Acid	122						
	Amide	180						
3b	Acid	146						
	Amide	201						
4a	Acid	81	74.19	7.86		74.17	7.87	
	Amide	161			7.87			7.91
	2,4-Dinitrophenylhydrazone	132			16.39			16.38
	Hydantoin (4)	175			12.16			12.07
4b	Acid	111	75.86	8.90		75.73	8.74	
	Semicarbazone	151			16.80			17.00
	2,4-Dinitrophenylhydrazone	162			15.38			15.14
5	Acid	186	75.63	8.89		75.73	8.74	
	2,4-Dinitrophenylhydrazone	133			15.36			15.14
6	Acid	181	75.94	9.15		75.73	8.74	
	2,4-Dinitrophenylhydrazone	120			15.18			15.14
7a	2,4-Dinitrophenylhydrazone	193			16.56			16.38
b	2,4-Dinitrophenylhydrazone	167			16.39			16.38
c	2,4-Dinitrophenylhydrazone	150			15.09			15.14
	Acid	181	75.69	9.04		75.73	8.74	
8a	Acid	148						
b	Acid	155	73.26	7.37		73.17	7.32	
9	Acid	124	73.09	7.40		73.17	7.32	
10b	2,4-Dinitrophenylhydrazone	135			16.31			16.38
	Acid	81						
11a	2,4-Dinitrophenylhydrazone	182			16.55			16.38
	Acid	138	74.17	8.01		74.16	7.87	
11b	2,4-Dinitrophenylhydrazone	155			16.12			16.38
	Acid (5)	83	74.22	8.08		74.16	7.87	
11c	2,4-Dinitrophenylhydrazone	129			14.61			14.63
	Acid	121	76.49	9.10		76.36	9.09	
11d	2,4-Dinitrophenylhydrazone	157			14.57			14.63
	Acid	125	76.60	9.16		76.36	9.09	
12a	2,4-Dinitrophenylhydrazone	143			15.38			15.14
	Acid	190	75.57	8.74		75.73	8.74	
12b	2,4-Dinitrophenylhydrazone	151			13.61			13.59
	Acid	182	77.33	9.75		77.36	9.75	
13	2,4-Dinitrophenylhydrazone	169			13.65			13.59

the reaction proceeding chiefly to the right when the concentration of aluminum chloride is large and the concentration of the cleaved cymene increases.

The formation of the methylisopropylbenzaldehydes and diisopropylbenzal-

dehyde obtained when using sodium cyanide is explained by an alkylation-dealkylation occurring after the primary alkylation of cymene. If the methyl group is involved in the second rearrangement, then diisopropylbenzaldehyde is the product. If, however, the second alkylation-dealkylation involves an isopropyl group, then methylisopropylbenzaldehyde results.

EXPERIMENTAL PART[3]

General method of preparation. Through a well-stirred mixture of aluminum chloride, the hydrocarbon, and sodium cyanide, dry hydrogen chloride was passed at a moderate rate (60 bubbles/min.), the whole being maintained at room temperature for 15 minutes. Then the reaction mixture was heated gradually so that after 20 minutes the maximum temperature (usually 95–100°) was attained. The hydrogen chloride was now conducted at a slow rate (15 bubbles/min.) until the reaction was terminated. The mixture, which was stirred well throughout, was kept for the period and temperature specified. The usually dark brown viscous product was poured on ice and concentrated hydrochloric acid and then allowed to stand overnight at room temperature. Usually the decomposed product was steam-distilled. If the aldehyde was nonvolatile with steam it was extracted with ether. The layers were separated, washed with potassium bicarbonate solution, and finally dried. The mixture was then fractionated through an efficient column.

SUMMARY

1. The use of sodium cyanide instead of hydrogen cyanide in the Gattermann synthesis of aldehydes has been shown to be applicable to aromatic hydrocarbons. One of the exceptions to the above is benzene. The negative polarity and lack of an alkyl substituent seem to be responsible for the lack of formation of the aldehyde intermediate.

2. Although *p*-xylene has a zero dipole moment, it can undergo alkyl migration and alkylation by the aluminum chloride to form the more highly polar hydrocarbon.

3. The yields of the aldehydes from toluene and the isomeric xylenes coincide with the polarity of the hydrocarbon reactants, the maximum being reached in *ortho*-xylene.

4. Compounds with labile alkyl groups, like ethyl- and isopropyl- radicals, show extensive alkylation and alkyl migration in the Gattermann reaction when hydrogen cyanide is employed.

5. The mechanism of the sodium cyanide reaction differs from that with hydrogen cyanide. The former modification requires the formation of the aldehyde intermediate, which appears to occur by the action of the aluminum chloride-hydrocarbon complex on the sodium cyanide. During the decomposition of the sodium cyanide, the aluminum chloride displays its side-reactions, whereby the over-all process yields products generally different from those obtained by the Gattermann reaction.

6. Solvents exert an influence on aldehyde formation. Toluene alone yields *m*- and *p*-tolualdehydes, whereas use of chlorobenzene as diluent gives the latter isomer exclusively.

[3] The microanalyses here reported were performed by Mr. Joseph Alicino of this laboratory.

7. The following compounds, not reported in the literature, were identified: Diethyl-, triethyl-, diisopropyl-, triisopropyl-, and methyldiisopropyl-benzaldehydes.

NEW YORK, N. Y.

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(3) HINKEL, AYLING, AND MORGAN, *J. Chem. Soc.*, 2793 (1932).
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF HOWARD UNIVERSITY]

THE ACETYLATION OF SOME DESOXYBENZOINS

R. P. BARNES, S. R. COOPER, VICTOR J. TULANE, AND HAROLD DELANEY[1]

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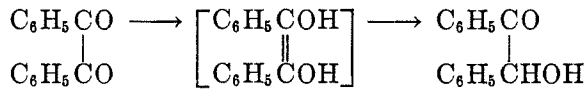
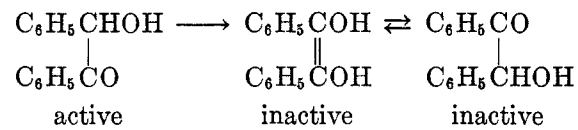
In 1899 Thiele (1) found that an acetic anhydride solution of benzil in the presence of zinc dust and a little sulfuric acid gave rise to two stereoisomeric forms of diphenylacetylene glycol diacetate, each of which upon hydrolysis with alcoholic potash yielded benzoin. He concluded therefore that the reduction of benzil occurred by way of diphenylacetylene glycol according to the following scheme:



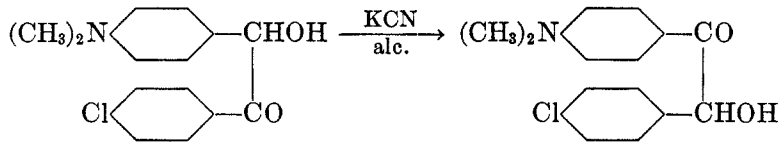
Nef (2) also in 1899 found that the product of the action of metallic sodium on an anhydrous ethereal solution of benzil when treated with acetic anhydride yielded a product which was identical with one of the stereoisomeric diphenylacetylene glycol diacetates which Thiele (1) had obtained.

In 1909 Wren (3) reported that when *l*-benzoin was boiled for one-half hour with alcoholic potash the recovered benzoin was optically inactive. He interpreted the racemization as having taken place thus:



Later McKenzie, Roger, and Wills (4) discovered that the racemization of *l*-benzoin could be effected much less drastically. Thus almost complete racemization was brought about by the use of a mere trace of potash in alcoholic solution in the cold in the course of twenty-four hours.

It was Jenkins (5) who in 1931 was first to effect the conversion of a mixed benzoin into its isomer. By treatment of an alcoholic solution of *alpha-p*-dimethylamino-*p'*-chlorobenzoin with potassium cyanide, he obtained the isomeric *beta-p*-dimethylamino-*p'*-chlorobenzoin:

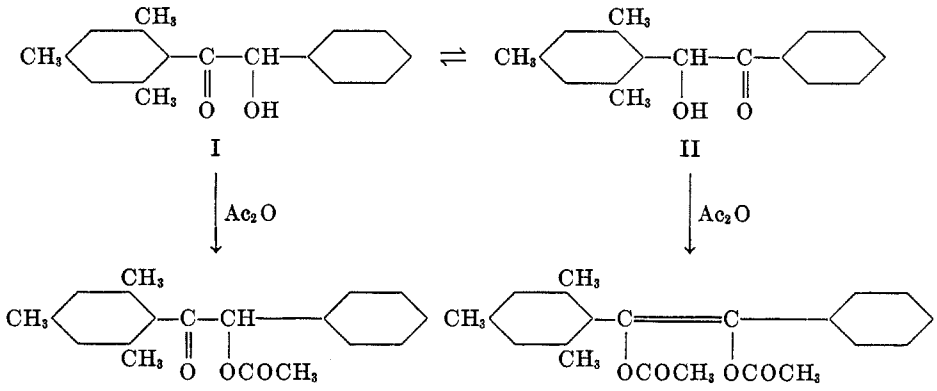


Margaret Luis (6) followed Jenkins' work with the conversion of *r*-4'-dimethylaminobenzoin and anisbenzoin into *r*-4-dimethylaminobenzoin and benzanisoin, respectively, by means of alcoholic potash at room temperature, and showed

[1] Part of this work was done by Mr. Harold Delaney in partial fulfillment of the requirements for the Master's degree.

that the reverse change did not occur under those conditions. During the same year Julian and Passler (7) reported a partial transformation of anisbenzoin into benzanisoin by distillation.

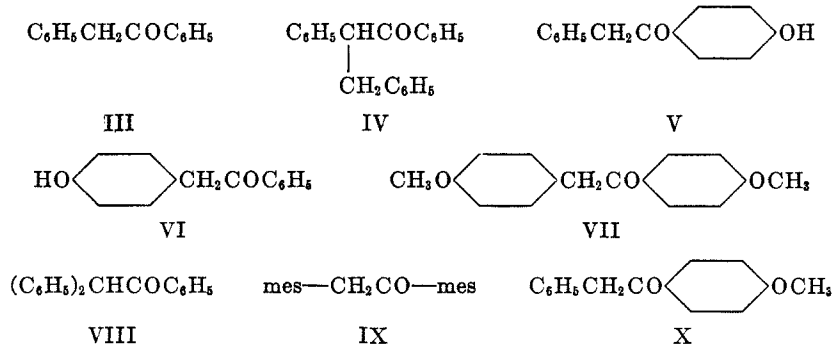
In their investigation of isomeric benzoins, Weinstock and Fuson (8) found that an equilibrium mixture resulted when either 2,4,6-trimethylbenzoin (I) or 2′,4′,6′-trimethylbenzoin (II) was heated with sodium acetate in alcoholic solution. They also found that 2,4,6-trimethylbenzoin on boiling for five hours with acetic anhydride yielded a monoacetate, whereas the 2′,4′,6′-trimethylbenzoin upon treatment under the same conditions gave the diacetate.

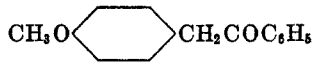


In all of these isomerizations it is assumed that under the influence of alkali or heat the rearrangement takes place through the unstable ene-diol, —C=C(OH)—.

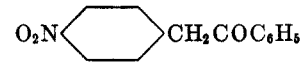
More recently still, Barnes and Tulane (9) have presented a mechanism for the interconversion of mixed benzoins; and Barnes and Lucas (10, 11) have also pointed out the stabilizing effect of the methoxyl group on ene-diols.

It is the purpose of this paper to report a series of acetates of enolic modifications of monoketones and to relate the behavior of the methoxyl substituted monoketones to the mechanism for the interconversion of mixed benzoins (9). Thus, we have prepared and acetylated (12) the following desoxybenzoins:

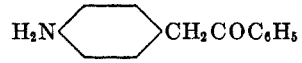




XI



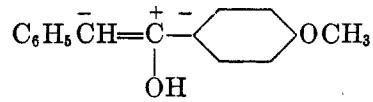
XII



XIII

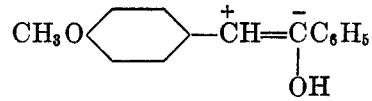
The ease with which alkyl desoxybenzoins are formed (13, 14), is indicative of the formation of metallic enolates. And so it does not seem strange that, under the proper conditions, O-acetyl derivatives of these enolates may result.

The ease with which acetylation is effected is reflected in the variations in the time of refluxing in the various cases. The fact that *p*-hydroxydesoxybenzoin (V) is practically completely converted into the acetate in one hour, whereas the *p*-methoxydesoxybenzoin (X) is not completely converted in four hours, seems very highly significant in the light of the mechanism presented on the rearrangement of mixed benzoins (9). The effect of the *p*-methoxyl group is to make the methylenic carbon relatively negative as compared with the carbonyl carbon:



Thus there is little tendency for the methylenic hydrogen to give rise to the enolic modification. It seems therefore that the *p*-hydroxyl group is no more effective in this regard than is a similarly placed hydrogen, for the ketone (V) is as easily acetylated as is desoxybenzoin (III).

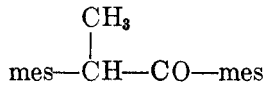
On the other hand, one would predict that *p'*-hydroxydesoxybenzoin (VI) would be as easily acetylated as desoxybenzoin (III) or *p*-hydroxydesoxybenzoin (V). In like manner, one would predict that the *p'*-methoxydesoxybenzoin (XI), because of the effect of the methoxyl in rendering the methylenic carbon relatively positive as compared with the carbonyl carbon, would tend to expel a methylenic hydrogen, thereby giving rise to the enolic modification with subsequent quantitative acetylation:



These predictions are fulfilled in that both compounds (VI) and (XI) are quantitatively acetylated in thirty minutes.

When one applies these considerations to the behavior of desoxyanisoin (VII), its behavior becomes perfectly clear. It is acetylated quantitatively in one hour, for the opposing effects of 4,4'-methoxyls render this compound of the order of activity of desoxybenzoin, whereas in the case of anisoin (10), in which a perfectly symmetrical ene-diol results as an intermediate, there is no acetylation, as predicted.

Neither steric hindrance nor the inhibiting effect on enolization by substitution of methylenic hydrogen, which is so pronounced in *alpha* and *beta* diketones and esters, seems to play a very important part in connection with the acetylation of these compounds, for phenyldesoxybenzoin (VIII) is practically quantitatively acetylated in one hour; desoxymesitoin (IX) in four hours; and benzyldesoxybenzoin (IV) in six hours. On the other hand, methyl desoxymesitoin (XIV) is the only compound investigated which was recovered unchanged even after a period of thirty-seven hours of refluxing. This behavior



XIV

of methyldesoxymesitoin is in keeping with the findings of Fuson and coworkers (15).

The *p'*-nitrodesoxybenzoin (XII) and the *p'*-aminodesoxybenzoin (XIII) are quantitatively acetylated in thirty minutes, which indicates an activating effect of both the nitro group and the amino nitrogen.

All of these desoxybenzoin acetates hydrolyze smoothly in acid medium to the parent desoxybenzoin.

This explanation applies not only to the rearrangement of Margaret Luis' *r*-4'-dimethylaminobenzoin since the dimethylamino group also possesses a strong tendency toward electron-release, but particularly well to the rearrangement of Jenkins' *alpha-p*-dimethylamino-*p'*-chlorobenzoin, for in this case also the −T-effect of the dimethylamino group and the +I-effect of the halogen atom act in the same direction and hence reinforce each other.

In relation to the findings of Weinstock and Fuson (8), it seems significant that the 2',4',6'-trimethylbenzoin (II) gives rise to a diacetate, whereas its isomer yields the monoacetate solely. For, since interconversion or diacetylation must occur by way of the ene-diolic modification, the equilibrium point must be far toward (I). This ene-diolic system is identical with that pictured for the ene-diolic modification of anisbenzoin (9), the driving force here being an inductive effect (16, 17, 18, 19, 20) of the methyl groups. This is in keeping with the report that the mesityl nucleus acts against enolization towards itself, but promotes enolization away from itself (21).

EXPERIMENTAL

p'-*Methoxydesoxybenzoin* (*XI*). Two grams of *p'*-hydroxydesoxybenzoin was suspended in 30 cc. of water, to which 2 g. of dimethyl sulfate was added. To this suspension, 1.6 g. of sodium hydroxide dissolved in 10 cc. of water was added drop-wise with vigorous shaking. The solution turned yellow. The reaction mixture became warm, and a pale yellow solid separated on the walls of the reaction flask. The reaction mixture was warmed and shaken for thirty minutes, chilled, filtered, washed with water, and recrystallized from methanol yielding 1.5 g. of pale yellow leaves, melting at 98°.

Anal. Calc'd for $C_{15}H_{14}O_2$: OCH_3, 13.7. Found: OCH_3, 13.7.

Acetylation. Each of the desoxybenzoins was refluxed with twice its weight of freshly fused potassium acetate and sufficient boiling acetic anhydride to effect solution of the

TABLE I

DESOXYBENZOIN ACETATES[a]

ACETATE	FORM	M.P. °C	FORMULA	ANALYSIS Calc'd	Found
$C_6H_5CH{=}CC_6H_5$[b] | $OCOCH_3$	Pale yellow needles	101	$C_{16}H_{14}O_2$	C, 80.67 H, 5.88	80.66 6.2
$C_6H_5C{=}CC_6H_5$[c] | | $CH_2C_6H_5$ $OCOCH_3$	Colorless needles	70	$C_{23}H_{20}O_2$	C, 84.14 H, 6.1	84.30 5.9
$C_6C_5CH{=}CC_6H_4OCOCH_3(p)$[d] | $OCOCH_3$	Colorless needles	109	$C_{18}H_{16}O_4$	C, 72.97 H, 5.4	72.83 5.6
$(p)CH_3COOC_6H_4CH{=}CC_6H_5$[e] | $OCOCH_3$	Cream colored needles	119	$C_{18}H_{16}O_4$	C, 72.97 H, 5.4	73.54 5.8
$(C_6H_5)_2C{=}CC_6H_5$[b] | $OCOCH_3$	Colorless needles	104	$C_{22}H_{18}O_2$	C, 84.07 H, 5.7	84.08 5.9
Mes—CH=C—Mes[d] | $OCOCH_3$	Colorless needles	106	$C_{22}H_{26}O_2$	C, 81.98 H, 8.1	81.83 8.3
$C_6H_5CH{=}C_6H_4OCH_3(p)$[d] | $OCOCH_3$	Colorless needles	88	$C_{17}H_{16}O_3$	C, 76.12 H, 6.0	76.3 6.2
$(p)CH_3OC_6H_4CH{=}CC_6H_5$[e] | $OCOCH_3$	Yellow needles	86	$C_{17}H_{16}O_3$	OCH_3, 11.6	11.8
$(p)CH_3OC_6H_4CH{=}CC_6H_4OCH_3(p)$[b] | $OCOCH_3$	Colorless needles	90	$C_{18}H_{18}O_4$	OCH_3, 20.8	21.0
$(p)O_2NC_6H_4CH{=}CC_6H_5$[e] | $OCOCH_3$	Yellow needles	107	$C_{16}H_{13}NO_4$	C, 67.84 H, 4.6	67.87 5.0
$(p)HNC_6H_4CH{=}CC_6H_5$[e] | | $COCH_3$ $OCOCH_3$	Cream colored needles	137	$C_{18}H_{17}NO_3$	C, 73.22 H, 5.8	73.66 6.1

[a] All of these acetates hydrolyze smoothly in alcoholic hydrochloric acid to the parent desoxybenzoins; the p'-amino acetate goes to the p'-aminodesoxybenzoin hydrochloride.

[b] Refluxed for one hour.

[c] Refluxed for six hours.

[d] Refluxed for four hours.

[e] Refluxed for one-half hour. The desoxymesitoin was graciously supplied by Professor Reynold C. Fuson.

potassium acetate. The ease with which the different reactions took place is indicated by the length of time of refluxing required. At the end of the heating period the solution was cooled and poured into a large volume of water to decompose the acetic anhydride. Invariably an oil was thrown down, which upon extraction with ether, and washing with sodium bicarbonate, was dried and evaporated. The residual oil was crystallized from methanol.

Methyldesoxymesitoin was recovered unchanged after a period of thirty-seven hours of refluxing.

SUMMARY

1. The preparation and characterization of *p'*-methoxydesoxybenzoin is given.
2. Eleven acetates of enolic modifications of desoxybenzoins are reported.
3. A mechanism presented for the benzoin rearrangement is applied to the acetylation of desoxybenzoins.

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A CONVENIENT SYNTHESIS OF *dl*-SERINE

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The increased use of synthetic amino acids in biochemical, physiological and pharmacological investigations has stimulated the study of improved methods for their syntheses. While the synthesis of *dl*-serine has been considerably improved by several investigators (1, 2, 3, 4) within the last decade, each of these methods has certain undesirable features. The method of Dunn and co-workers (1) is inconvenient because of the low yield of ethoxyacetaldehyde obtained and of the necessity of using liquid hydrogen cyanide. The procedures of Schiltz and Carter (2), and Carter and West (3) require large quantities of mercury salts, which make the process expensive regardless of whether the mercury is recovered or discarded. This difficulty was overcome by Wood and du Vigneaud (4), but as a portion of their synthesis has to be carried out in a steel pressure vessel, the runs either have to be small or else some additional investment in equipment is necessary. The present method starts with the very inexpensive "Cellosolve" (β-ethoxyethanol) and arrives at the desired *dl*-serine in what is essentially a two-step process, using only very inexpensive reagents and apparatus.

While Drake and co-workers (5) report that zinc chromite and copper chromite catalysts were unsatisfactory for the dehydrogenation of methoxy- and ethoxyethanols, in a patent issued to Drake (6) a year later, it is stated that the most satisfactory catalyst found for this dehydrogenation was one containing chromium oxide, prepared according to the method of Young (7). In a very recent patent granted Gresham (8), a copper-chromium oxide catalyst was employed for the dehydrogenation. The catalyst adopted by the authors is the standard copper chromite catalyst described by Lazier and Arnold (9). While this catalyst gives yields somewhat less than reported by Drake (5, 6), it is a standard product, kept on hand at all times by many laboratories, thus in many cases avoiding the preparation of a special catalyst. The catalyst was activated by passing isopropanol vapor over the hot catalyst prior to use in a manner similar to that of Young (7). The presence of chromium in the catalyst greatly lessens the tendency of the catalyst to become inactive in use.

The modified Strecker reaction, using sodium cyanide and ammonium chloride, has not been successfully applied to ethoxyacetaldehyde before. By combining the modified Strecker reaction and a simplified method of isolation, the time yield of *dl*-serine has been greatly improved; the percentage yield, however, is not much superior to existing methods of preparation. The best alternate method, that of Wood and du Vigneaud (4), gives the excellent over-all yield of 47%. The somewhat older method of Carter and West (3) gives an over-all yield of 30–40%, but requires 7–10 grams of mercuric acetate to produce one gram of *dl*-serine. The present method gives a 51% yield, based upon ethoxyacetaldehyde.

EXPERIMENTAL

Ethoxyacetaldehyde. Cellosolve was vaporized through an electrically heated catalyst chamber containing copper chromite catalyst (9). Two styles of catalyst chambers were tried without significant difference in results; one was a horizontal Pyrex glass tube heated in an electric furnace, the other was a vertical Pyrex glass column heated by a chromel resistance wire wrapped on asbestos paper. Only the latter will be described here.

A side arm, diameter 11 mm., and a bottom tube, diameter 16 mm., were sealed to a 60 cm. length of Pyrex glass tubing, inside diameter 28 mm., to form a large Hempel column. On the lower 45 cm. of the large tube was wound 28 feet of No. 24 B. & S. gauge chromel resistance wire over a single layer of asbestos paper moistened with a 2% solution of sodium silicate. The wire was then covered with three layers of asbestos paper in a similar manner, and the column was dried in a warm place overnight.

The catalyst was made into a thick paste with water and smeared onto 25 mm. disks of copper wire screen (copper window screen). These disks were dried in an oven at 110° and were then placed in the Pyrex glass column, spaced by 20 mm. sections of 25 mm. thin-walled brass tubing, until a catalyst zone 40 cm. in length had been formed. A 360° thermometer extended 10 cm. into the heated zone through the top of the column. The temperature of the reaction zone was adjusted with a Variac transformer.

The column was fitted to a 1-liter two-necked flask with a dropping-funnel in one neck. The vapors were condensed with a water-cooled condenser and the distillate colllected in a suitable receiver cooled by an ice-bath. About 50 g. of isopropanol was slowly distilled through the dehydrogenator while it was being warmed to the proper temperature, so that all the air was displaced and only vapor remained in the reaction zone. Hydrogen was evolved quite vigorously when the temperature reached 275–280°. When the temperature had risen to 310°, the last of the isopropanol was driven through the column and Cellosolve was then distilled at the rate of 100 g. per hour while maintaining the temperature at 310–330°. The rate of gas evolution with Cellosolve was markedly less than with isopropanol, but this rate continued without diminution during a run lasting 7 hours. When the distillation of isopropanol was omitted, the catalyst rapidly lost its activity.

The distillate from the above process was fractionally distilled through an 80 cm. Hempel column filled with 6 mm. glass Raschig rings and having a partial condenser at the head to increase the reflux ratio. The fraction collected boiled at 96–107° and showed 85% aldehyde content when analyzed by the method of Donnally (10). The yield was 30–35% based upon unrecovered Cellosolve.

dl-*Serine.* To 80 cc. of an ice-cold saturated solution of ammonia in methanol was added 68 g. of 85% ethoxyacetaldehyde, and the mixture was allowed to stand in the refrigerator for one-half hour or longer. In the meantime, a solution of 38 g. of sodium cyanide in 80 cc. of water and a solution of 46 g. of ammonium chloride in 125 cc. of water were prepared and mixed just prior to using. The aldehyde-ammonia and ammonium cyanide solutions were then mixed. The dark-colored solution which was formed, gradually became lighter in color during the first half hour. After standing at room temperature for 18 hours the clear red solution was poured, while stirring, into 400 cc. of 48% hydrobromic acid (hood: hydrogen cyanide). The nearly black solution was slowly distilled until the vapor temperature reached 110°. An additional 100 cc. of 48% hydrobromic acid was added and disdistillation was continued very slowly as long as any additional ethyl bromide was formed (4–6 hrs.). The liquid in the boiler was cooled to room temperature, the salts which separated were removed by filtering, and the filter cake was washed with ethanol until nearly colorless. The combined filtrate was evaporated to dryness under reduced pressure (boiling water-bath). An additional 100 cc. of water was added and the evaporation was repeated to remove the excess hydrobromic acid as completely as possible.

The residue was extracted with 400 cc. of 90% ethanol divided into three portions, the insoluble salts were removed by filtering and rinsed well with ethanol. The combined alcoholic solution was neutralized with concentrated aqueous ammonia until a faint permanent odor of ammonia was present, and the solution was placed in the refrigerator to cool over-

night. The crystals which separated were filtered off, sucked dry, washed with methanol until nearly colorless, and dried. The dry product weighed 35.1 g. (51% of theory based upon 85% aldehyde content).

This faintly colored product was rendered completely pure by dissolving in 150 cc. of boiling water, treating with 3 g. of decolorizing carbon and filtering while hot. The hot, crystal-clear, colorless solution was treated with an equal volume of ethanol and placed in the refrigerator to cool for several hours. The colorless crystals, which were filtered off, washed with ethanol followed by ether, and dried, weighed 33.0 g.

Anal. Calc'd for $C_3H_7NO_3$: N, 13.33. Found: N, 13.4, 13.2 (Kjeldahl).[1]

The product commenced to turn brown at 228° (corr.) and melted with gaseous decomposition at 243–244° (corr.), which is in good agreement with the value reported by Wood and du Vigneaud (4).

SUMMARY

Ethoxyacetaldehyde was prepared in 35% yield from inexpensive β-ethoxyethanol (Cellosolve) by catalytic dehydrogenation over a copper chromite catalyst at 310–330°. From this aldehyde *dl*-serine was obtained in 51% yield by the modified Strecker reaction.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

SYNTHETIC GLYCOSIDES OF STROPHANTHIDIN

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The natural cardiac drugs, with the exception of the toad venoms and a few members of the group which appear to be true alkaloids, occur as glycosides. The question of the role of the carbohydrate component of the glycosides remains unanswered. Until comparatively recently the view was fairly widely held that the function of the carbohydrate moiety was to increase the solubility of the aglycon in the aqueous body fluids, and, in the case of the polysaccharides of the aglycons, to provide a larger molecule, the speed of absorption of which into the body tissues would be slower and hence tend to produce a cardiotonic effect of longer duration. Recently, however, some evidence has been secured to the effect that, while the aglycon portion of the glycoside molecule undoubtedly plays a dominant role in determining the qualitative actions of the glycosides, the carbohydrate portion is not without influence on the quantitative action of the drugs. As illustrative of this effect, the cases of cymarin and convallatoxin may be cited. Cymarin has been shown to be the cymaroside of strophanthidin (1), whereas convallatoxin has been more recently shown to be the *l*-rhamnoside of strophanthidin (2). No information is available as to whether these two substances are α- or β-glycosides, or as to whether they possess the furanoside or pyranoside ring structure. However, it is of interest to note that, whereas convallatoxin is the most potent of the known cardiac glycosides, cymarin is significantly less active. A similar, though less striking, variation has been observed in α- and β-antiarin, which are glycosides of a common aglycon with antiarose and *l*-rhamnose respectively (3). The actual values for the minimum systolic doses for these glycosides are shown in Table I. It thus becomes apparent that the carbohydrate constituent of these pairs of glycosides, at least, plays a decidedly positive role in determining the quantitative action of the drugs. It is, therefore, of great interest to determine the effect on activity of varying the carbohydrate component of the cardiac glycosides.

In the present study the synthesis of four strophanthidin glycosides is described and quantitative data on the activity of both the glycosides and their acetylated precursors are presented. The pharmacological data were secured through the kind cooperation of Dr. K. K. Chen of the Lilly Research Laboratories, Indianapolis, Indiana; and a detailed report of the methods used has appeared elsewhere (6). It should be pointed out that, in commencing this study, we have chosen to keep constant both the aglycon component and the configuration of the glycosides prepared. The mode of synthesis, on the basis of past experience, can lead only to β-glycosides. It has thus been possible to restrict the study to the effect of variation of the carbohydrate constituent on the activity of strophanthidin β-glycosides and their acetyl derivatives. The glycosides investi-

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gated are the β-glycosides of strophanthidin with *l*-arabinose, *d*-xylose, *d*-glucose and *d*-galactose. It is planned in the future to extend the study to α-glycosides, as well as to glycosides of aglycons other than strophanthidin, in order to ascertain the effect of these variables.

The method used for the synthesis of the glycosides was a variation of the classical procedure of Koenigs and Knorr (7) embodying the condensation of an alcohol and an acetobromo sugar. The reactions were carried out in anhydrous dioxane solution in the presence of silver carbonate and anhydrous magnesium sulfate. The use of dehydrating agents more active than magnesium sulfate, such as anhydrous calcium sulfate (Drierite), led to some decomposition of the strophanthidin. It is important that the procedures detailed in the experimental part be followed closely if a crystalline acetyl glycoside is to be obtained. Numerous variations of these methods led only to complex oily mixtures from which no crystalline products could be isolated.

The acetyl glycosides thus obtained are β-glycosides by the mode of synthesis (7). Furthermore, the secondary hydroxyl group on carbon atom 3 of strophanthidin, rather than one of the tertiary hydroxyl groups, is involved in the

TABLE I

MINIMUM SYSTOLIC DOSES OF GLYCOSIDES

GLYCOSIDE	CAT UNITS (MG./KG.)	FROG UNITS (MG./G.)
Cymarin (4)	0.11	0.00060
Convallatoxin (4)	.08	.00021
α-Antiarin (5)	.13	.00050
β-Antiarin (4)	.10	.00039

glycosidic linkage. This was demonstrated by acetylation of strophanthidin *d*-glucoside with acetic anhydride in pyridine solution. The strophanthidin acetyl glucoside thus obtained was identical with the strophanthidin tetraacetylglucoside obtained from strophanthidin and acetobromoglucose. If one of the tertiary hydroxyl groups of strophanthidin had been involved in the glucoside formation, the secondary C-3 hydroxyl group would have been left unsubstituted and, under the conditions of the re-acetylation of the glucoside, a pentaacetyl derivative of the latter should result, with the four hydroxyl groups of the glucose component and the secondary C-3 hydroxyl group undergoing acetylation (8). On the basis of this proof of structure of the strophanthidin acetylglucoside, it is logical to assume that the other glycosides possess an analogous structure.

Deacetylation of the acetylglycosides was carried out catalytically with barium methoxide in absolute methanol solution (9). The resulting crystalline glycosides gave a strong positive nitroprusside (Legal) color test, thus showing that the unsaturated lactone side chain of the strophanthidin had not been altered during the treatment. Deacetylation of strophanthidin triacetyl β-*l*-arabinoside with methyl alcoholic ammonia also did not affect the lactone. However, we feel that the milder barium methoxide method is preferable.

The synthetic strophanthidin glycosides were extremely difficult to obtain in crystalline form originally. However, once they had been obtained in the crystalline state, recrystallization was readily accomplished. Strophanthidin β-*d*-galactoside has not been obtained in crystalline form as this is written. The other three glycosides all contain water of crystallization, the presence of which apparently is necessary in order to secure them in crystalline form.

TABLE II

ASSAY IN CATS (AVERAGE OF SEVERAL ANIMALS)

COMPOUND	MEAN LETHAL DOSE ● STANDARD ERROR (MICROGM./KG. CAT)
Strophanthidin	306.2 ± 38.7
Strophanthidin acetate	186.6 ± 24.6
Strophanthidin-β-tetraacetyl-*d*-glucoside	1166 ± 125
Strophanthidin-β-*d*-glucoside	91.3 ± 2.46
Strophanthidin-β-triacetyl-*d*-xyloside	591.6 ± 70.4
Strophanthidin-β-*d*-xyloside	109.5 ± 4.39
Strophanthidin-β-triacetyl-*l*-arabinoside	1230 ± 136.6
Strophanthidin-β-*l*-arabinoside	94.5 ± 2.95
Strophanthidin-β-tetraacetyl-*d*-galactoside	1692 ± 168
Cymarin	110.1 ± 3.75 (11)

TABLE III

ASSAY IN FROGS (AVERAGE OF SEVERAL ANIMALS)

COMPOUND	MEAN SYSTOLIC DOSE ± STANDARD ERROR (MICROGM./G. FROG)
Strophanthidin	2.71 ± 0.49
Strophanthidin acetate	2.19 ± 0.13
Strophanthidin-β-tetraacetyl-*d*-glucoside	18.77 ± 3.07
Strophanthidin-β-*d*-glucoside	0.583 ± 0.04
Strophanthidin-β-triacetyl-*d*-xyloside	8.07 ± 1.35
Strophanthidin-β-*d*-xyloside	0.64 ± 0.04
Strophanthidin-β-triacetyl-*l*-arabinoside	6.33 ± 0.38
Strophanthidin-β-*l*-arabinoside	0.308 ± 0.03
Strophanthidin-β-tetraacetyl-*d*-galactoside	11.29 ± 1.85
Cymarin	0.60 ± 0.006

The substances prepared have been assayed in cats and frogs, and the data thus obtained are shown in Tables II and III. The observed mean lethal doses are given (6), and the standard error is also indicated. Data obtained previously (4, 5) on the four glycosides given in Table I are presented for comparison, together with previous data on strophanthidin (10) and new data on strophanthidin acetate. It is not possible to draw any definite conclusions as to the influence of the configuration of the sugar component on the activity of the glycosides from the number of cases studied at present. However, certain

definite trends can be pointed out. The acetylglycosides are notably less potent than the glycosides, which, in turn, are more potent than the aglycon. The latter fact has previously been noted in several cases (10). However, it is interesting to note that introduction of an acetyl group directly onto the aglycon (strophanthidin acetate) results in greatly increased activity, whereas acetylation on the sugar component of the glycosides lowers activity in most cases. It is significant that, whereas the activity of the glycosides falls within the same general range, that of the acetylglycosides varies over a much wider range.

We wish to acknowledge our appreciation to S. B. Penick and Company, of New York City, for the generous gift of *Strophanthus kombe* seeds, from which the strophanthidin used in this work was prepared.

EXPERIMENTAL

All melting points are corrected for stem exposure.

Preparation of the acetylglycosides. The preparation of strophanthidin tetraacetyl-β-*d*-glucoside is given as typical of the general procedure used. The other glycosides were prepared by this general method, with the variations noted below for the individual cases.

A mixture of 4 g. (0.0097 mole) of strophanthidin, 3.5 g. (0.0127 mole) of dry silver carbonate, 6 g. of anhydrous magnesium sulfate, and 40 cc. of dioxane (which had been refluxed over and distilled from sodium) was stirred for one hour in a three-necked flask equipped with a dropping-funnel. All solutions, as well as the reaction mixture, were carefully protected from moisture by calcium chloride tubes. One-half gram of iodine was then added and a solution of 8 g. (0.0193 mole) of acetobromoglucose in 20 cc. of dry dioxane was added dropwise over a period of an hour. After the mixture had been allowed to react at room temperature for 20 hrs., the silver salts and magnesium sulfate were filtered off and the filtrate was concentrated under reduced pressure to a viscous straw-colored oil. The oil was exhaustively stirred with several portions of anhydrous ether until it had completely solidified. Three grams of solid material was thus obtained. When petroleum ether (Skellysolve B) was added to the combined ether washings, an additional 0.7 g. of solid material was obtained which was combined with the main crop. The crude acetylglucoside was crystallized from a mixture of alcohol and water. After two recrystallizations, 2 g. of product corresponding to a yield of 28%, based on the strophanthidin used, was obtained. The acetylglucoside forms long needles which tend to felt when dry. The melting point varies with the rate of heating, but the compound ordinarily begins to soften at about 165° and melts with decomposition between 240° and 250°. For analysis the substance was dried over calcium chloride at 75° and 10 mm. pressure; $[\alpha]_D^{27}$ + 24° (c = 0.978 in chloroform).

Anal. Calc'd for $C_{37}H_{50}O_{15}$: C, 60.5; H, 6.9.
Found: C, 60.3; H, 6.7.

*Strophanthidin tetraacetyl-β-*d*-galactoside* was prepared exactly as was the glucoside. The yield was 31%, and the substance crystallized from dilute alcohol as prismatic needles which sintered at 230° and melted with decomposition at 236–237°. It contains 0.5 mole of water of crystallization. For analysis it was dried over calcium chloride at 75° and 10 mm. $[\alpha]_D^{28}$ + 16° (c = 1.756 in chloroform).

Anal. Calc'd for $C_{37}H_{50}O_{15}\cdot 0.5\ H_2O$: C, 59.7; H, 6.9.
Found: C, 59.7; H, 6.7.

*Strophanthidin triacetyl-β-*d*-xyloside* was prepared in 7.5% yield, as in above cases. It crystallizes from dilute alcohol as long needles which contain two moles of water of crystallization, and melt with decomposition at 240–250° after preliminary sintering. For analysis the substance was dried at 75° and 10 mm. over calcium chloride; $[\alpha]_D^{28}$ − 10° (c = 0.676 in chloroform).

Anal. Calc'd for $C_{34}H_{46}O_{13}\cdot 2H_2O$: C, 58.4; H, 7.2.
Found: C, 58.4; H, 7.5.

Strophanthidin triacetyl-β-l-arabinoside was prepared as above, except that no iodine was used to catalyze the reaction. The yield was 14%. The glycoside crystallizes from dilute alcohol as needles, the melting point of which varies greatly with the rate of heating. Ordinarily it begins to sinter at about 155° and melts with effervescence and decomposition at about 200°. Attempts to improve the yield by the use of iodine resulted in the formation of brown oily products which could not be obtained in crystalline form. For analysis it was dried at 75° and 10 mm. over calcium chloride; $[\alpha]_D^{28}$ + 20° (c = 1.600 in chloroform).

Anal. Calc'd for $C_{34}H_{46}O_{13}$: C, 61.6; H, 7.0.
Found: C, 61.3; H, 7.2.

Strophanthidin β-d-glucoside. To a solution of 0.5 g. of strophanthidin tetraacetyl-β-*d*-glucoside in 75 cc. of absolute methanol was added 1 cc. of approximately 0.5 *N* barium methoxide solution in absolute methanol. After the solution had been allowed to stand for 8 hrs. in the refrigerator, the barium was quantitatively precipitated with dilute sulfuric acid. The filtrate from the barium sulfate was concentrated under reduced pressure, leaving an oily residue which was very soluble in water and sparingly soluble in absolute alcohol and ethyl acetate. Repeated attempts to crystallize the glucoside from the ordinary solvents yielded it only in the amorphous state. It was finally obtained crystalline from ethyl acetate which had been previously saturated with water. Once crystalline, the glucoside may be conveniently recrystallized by dissolving it in 95% alcohol and adding ether to the solution until a slight turbidity appears. The glucoside separates as fine needles which contain 0.5 mole of water of crystallization and melt with decomposition at 234–236° after sintering at 228°. For analysis it was dried at 60° and 10 mm. over calcium chloride for 8 hrs.; $[\alpha]_D^{30}$ + 21° (c = 0.620 in water).

Anal. Calc'd for $C_{29}H_{42}O_{11}\cdot 0.5\ H_2O$: C, 60.5; H, 7.5.
Found: C, 60.3; H, 7.8.

Strophanthidin β-d-xyloside was prepared and purified exactly as was the glucoside. It crystallizes as needles which contain 2.5 moles of water of crystallization and melts with decomposition at 152–154°. For analysis it was dried at 75° and 10 mm. over calcium chloride; $[\alpha]_D^{29}$ + 7° (c = 0.366 in 95% alcohol).

Anal. Calc'd for $C_{28}H_{40}O_{10}\cdot 2.5\ H_2O$: C, 57.8; H, 7.8.
Found: C, 58.0; H, 7.8.

Strophanthidin β-l-arabinoside was prepared as in the above examples, except that the substance was crystallized directly without treatment with wet ethyl acetate, by dissolving it in alcohol, adding water to the solution and then evaporating most of the alcohol. The arabinoside crystallizes in long needles containing 0.5 mole of water of crystallization. The melting point varies with the rate of heating, but ordinarily the substance melts with decomposition and effervescence at about 210° after preliminary sintering. For analysis it was dried at 75° and 10 mm. over calcium chloride; $[\alpha]_D^{30}$ 31° (c = 1.100 in 95% alcohol).

Anal. Calc'd for $C_{28}H_{40}O_{10}\cdot 0.5\ H_2O$: C, 61.6; H, 7.6.
Found: C, 61.6; H, 7.8.

The acetylarabinoside was also deacetylated with methyl alcoholic ammonia as follows: To a solution of 100 mg. of the acetylarabinoside in 20 cc. of absolute methanol was added 100 cc. of an approximately 15% solution of dry ammonia in absolute methanol. After the solution had been allowed to stand in the refrigerator for 24 hrs., it was concentrated under reduced pressure and the residue extracted with dry ethyl acetate. The product remaining from the extraction crystallized from dilute alcohol when seeded with the arabinoside obtained by the use of barium methoxide.

Reacetylation of strophanthidin β-d-glucoside. One hundred twenty milligrams of strophanthidin β-*d*-glucoside was dissolved in 5 cc. of dry pyridine, 0.25 cc. of acetic anhydride was added, and the mixture was allowed to stand twelve hours. The solution was then diluted with ice-water and concentrated under diminished pressure to one-half its volume; a crystalline precipitate separated. This was shown to be identical with strophanthidin tetraacetyl-β-*d*-glucoside by saponification equivalent. Equivalent weight: Calc'd 147; Found 152. As a control, strophanthidin tetraacetyl-β-*d*-glucoside prepared from aceto-

bromoglucose and strophanthidin was similarly saponified. Equivalent weight: Calc'd 147; Found 152.

The microanalyses reported in this paper were performed by Mr. Saul Gottlieb of these laboratories.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OKLAHOMA AGRICULTURAL AND MECHANICAL COLLEGE]

N-BENZYLAMIDES AS DERIVATIVES FOR IDENTIFYING THE ACYL GROUP IN ESTERS[1,2]

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The standard method of identifying the acyl group in esters, involving saponification, isolation of the acid or salt, and conversion to a derivative, is always time-consuming and occasionally fruitless. To obtain a derivative directly from an ester, Koelsch and Tenenbaum (1) and Hardy (2) have recommended adding the ester to the bromomagnesium salt of an arylamine, to produce the corresponding arylamide. Buehler and Mackenzie (3) carried out direct aminolysis of twelve esters with benzylamine,

$$RCOOR' + C_6H_5CH_2NH_2 \rightarrow RCONHCH_2C_6H_5 + R'OH$$

but found the method unsatisfactory for esters of higher fatty acids and halogenated acids.

Of these two procedures, that employing benzylamine has now been modified and considerably extended. Tests of six reasonably common high-boiling organic bases—benzylamine, dibenzylamine, cyclohexylamine, dicyclohexylamine, ethylenediamine, and phenylhydrazine (4)—with several esters proved benzylamine to be best in speed of reaction and ease of removal from the amide derivatives. This is in fair agreement with the findings of Smith and Adkins (5) on the relative reactivity of benzylamine in aminolyzing amides.

The principal improvements made on the procedure of Buehler and Mackenzie are the use of no water as diluent and the employment of ammonium chloride as catalyst. The absence of water permits attainment of higher temperatures and ensures homogeneity of the reaction mixture, and substituted ammonium ions are known to catalyze aminolysis of esters (6).

Esters of the higher alcohols, being less reactive, are not adequately aminolyzed by boiling for an hour with benzylamine. This difficulty may be met by longer heating or by subjecting such esters to a preliminary methanolysis, which is itself quite rapid (7) and which produces methyl esters of comparatively high reactivity (8).

Many of the N-benzylamides described in this paper were prepared by aminolysis of the acids rather than the esters, simply because the acids were already at hand. The authors know of no case in which an aminolyzable acid yields a non-reactive ester. On the other hand, reactivity of an ester does not guarantee that the free acid will aminolyze; it may undergo decarboxylation, as *p*-nitrophenylacetic acid does.

Table I includes all N-benzylamides prepared by the procedure described in

[1] Presented before the Organic Division at the Buffalo Meeting of the American Chemical Society, September, 1942.

[2] Based mainly on the M. S. thesis of Jack King, 1942.

TABLE I

MELTING POINTS OF N-BENZYLAMIDES OF CARBOXYLIC ACIDS

MELTING POINT, °C[a]	ACID
<35[b]	Pivalic, isocaproic, oleic, linoleic, linolenic, dimethylpropenylacetic (12)
36.0–38.0 (3)	*n*-Butyric
42–3, 41.1–41.8 (3)	*n*-Valeric
42–3, 42.6–43.7 (3)	Propionic
47.5–48.5	*dl*-Methylethylacetic
52–53, 50.3–51.4 (3)	*n*-Caproic
53–54	Isovaleric
59.8–60.4 (3), 49 (12)	Formic
60–61, 60.0–61.3 (3, 12)	Acetic
64 (12)	Hydroxypivalic
74.5–75.5	*m*-Toluic
76–77	Diethylacetic
82–83, 82.0–82.5 (13)	Lauric
84–85 (12)	Hydrocinnamic
84.5–86.0	Phenoxyacetic
86.5–87.5, 87–92 (3, 12)	Isobutyric
89–90	Myristic
89–90	*p*-Aminobenzoic
93–94, 90–94.4 (12, 14)	Trichloroacetic
94.5–95.0 (13), 91–92[c]	Palmitic
98.6 (15)	Stearic
100–101, 101 (12)	*m*-Nitrobenzoic
103–104	Glycolic
105.0–105.5, 104–107 (12)	Benzoic
109–110	*o*-Iodobenzoic
111.0–111.5, 110.5–111.0 (13)	2-Furoic
112.5–113.6 (3)	Crotonic
113–114	N-Phenylglycine
121–122, 122 (12)	Phenylacetic
123.0–124.5 (12), 120 (16)	Cyanoacetic
124.0–124.5	Diglycolic
124–125	Anthranilic
126.5–127.5 (17)	Piperonylic
131.0–132.5, 126–131 (12)	Anisic
133 (12)	*p*-Toluic
136.5–137.0, 134–137 (12)	Salicylic
137–138	Ethylmalonic
137.5–138.5	Diethylmalonic
137.5–138.5 (18)	2,4,6-Trimethylbenzoic
141–142, 141–143 (12)	*p*-Nitrobenzoic
141–142.5	*m*-Hydroxybenzoic
141.5–142.5, 142 (19)	Malonic

[a] The value believed most probable is listed first. Values obtained in this work are corrected and then rounded off to the nearest half-degree.

[b] These oils were not purified nor analyzed.

[c] Obtained in this work but from low grade acid.

TABLE I—*Concluded*

MELTING POINT, °C[a]	ACID
145–146	2-Furanacrylic
148–149	*n*-Butylmalonic
149–150	Maleic
153–154	Pimelic
155.5–157 (12)	*d*- or *l*-Malic
159.5–160.5 (20)	β-Phenylglutaric
166.0–167.5	Sebacic
167–168	Phenylethylmalonic
167.5–169, 167–169 (12)	Carbonic, carbamic, chloroformic
169–170	Citric
169.5–170	Glutaric
178–179, 178–179 (12)	Phthalic
185–186	*p*-Nitrophenylacetic
188–189	Adipic
189–190	Phenylsuccinic
194–195 (20)	β-Methylglutaric
196.5–197.5[d]	Naphthalic
199 (12), 197–200	*d*- or *l*-Tartaric
200–201 (21)	Saccharic
203.5–205	Fumaric
203–207 (12)	Mesotartaric
205–206, 205–206 (12)	Succinic
208–210 (12)	*dl*-Tartaric
222–223, 216–218 (12)	Oxalic
225–226	Cinnamic
236–237[e]	Acrylic
264–266	Terephthalic

[d] Melting point of the imide.

[e] Melting point of β-benzylaminopropionbenzylamide hydrochloride.

this paper; esters and acids that fail to yield satisfactory derivatives are listed in the experimental part. N-Benzylamides can be most highly recommended in qualitative analysis whenever the corresponding acid is liquid and/or water soluble, so that it cannot itself serve as a derivative. It is evident from the table, however, that the amides from the fatty acids are not at all satisfactory, partly because they are too low-melting and especially because there is too little spread in melting point values among isomers. Esters of aromatic acids yield amides far better in both respects, but the method must compete with the equally simple process of saponification and precipitation of the free acid, an obvious derivative. Esters of most hydroxy acids and particularly of polybasic acids of all types react readily to give high yields of easily purified products, whereas Koelsch and Tenenbaum (1) found their method to fail for several common esters of dibasic acids. Under the conditions used, benzylamine does not affect the double bonds in esters of cinnamic, 2-furanacrylic, maleic, and fumaric acids, but methyl acrylate produces the benzylamide of a benzylaminopropionic acid, presumably β-benzylaminopropionic acid. By comparable

treatment of ethyl crotonate Buehler and Mackenzie (3) obtained the benzylamide of crotonic acid, but Sani (9), under conditions not greatly different, produced the benzylamide of β-benzylaminobutyric acid from the same amine and the same ester.

In general, alkyl esters of inorganic acids and sulfonic acids do not react as desired, probably because they tend to alkylate the benzylamine instead of acylating it. It may be noted that aryl esters of sulfonic acids have been aminolyzed to phenols by piperidine, but the fate of the sulfonic acid was not reported (10).

Esters of keto acids and polynitro aromatic acids give only gums, no doubt because of condensation between benzylamine and the carbonyl or a nitro group. Ethyl carbonate does not react at all, although phenyl carbonate cleaves satisfactorily. Glycine and *d*-glutamic acid produce only water- or acid-soluble derivatives, if indeed they react appreciably, although N-phenylglycine yields a good product. It is noteworthy that Abderhalden and Brockmann (11) proposed benzylamine cleavage for identifying the carboxyl-bearing amino acid in polypeptides, and prepared several (oily) N-benzylamides of alpha-amino acids from the esters.

Esters of halogenated aliphatic acids cannot be treated successfully by the routine method, but it is hoped to find milder conditions suitable for producing aminolysis of the ester linkage without affecting the halogen. The benzylamino acids resulting from displacement of the halogen do not give readily purifiable benzylamides.

EXPERIMENTAL

In the standard procedure developed for the aminolysis, 1 ml. of a liquid ester (or acid), or 1 g. of a solid, is added to 3 ml. of benzylamine together with 0.1 g. of ammonium chloride. The mixture is refluxed for an hour, conveniently in a Pyrex test tube with finger condenser. It is cooled and washed with water to remove excess amine; in case no solid separates, acidification with hydrochloric acid will sometimes precipitate the desired amide. Again, if enough unreacted ester is left to keep the amide in solution, it is often possible to expel the ester by boiling the oily layer with water. The solid amide is isolated by filtration, dried, washed with ligroin to remove soluble impurities, and recrystallized, usually from aqueous acetone or ethanol.

To test the effectiveness of preliminary methanolysis, 1 ml. each of *n*-amyl valerate and *n*-butyl benzoate, esters which had not given solid derivatives by the standard procedure, were refluxed for one-half hour in 5 ml. of methanol containing a little sodium methoxide. After the excess methanol had been distilled off, the remaining ester was successfully aminolyzed by the usual procedure.

Table II presents information on the preparation and analysis of the new compounds encountered.

The following esters gave only unpurifiable gums or oils: methyl levulinate, ethyl *o*-benzoylbenzoate, ethyl acetoacetate, methyl *p*-hydroxybenzoate, methyl *o*-nitrobenzoate, ethyl 3,5-dinitrobenzoate, methyl 3,5-dinitrosalicylate, ethyl nitrate, *n*-butyl nitrite, ethyl sulfite, and coumarin. Similar useless products were formed by gallic acid, phenylarsonic acid, *dl*-tropic acid, camphoric acid, nicotinic acid nitrate, *m*-aminobenzoic acid, and tetrachlorophthalic anhydride.

Glycine, glutamic acid, ethyl chloroacetate, and methyl *p*-toluenesulfonate produced substances completely water- or acid-soluble and therefore not further investigated. Un-

changed ethyl carbonate, *o*-cresyl *p*-toluenesulfonate, and triphenyl phosphate were the only substances identified after attempted aminolyses; melting points and mixed melting

TABLE II

ANALYTICAL DATA ON NEW COMPOUNDS

N-BENZYLAMIDE[a]	FORMULA	%N, KJELDAHL	
		Found	Calc'd
Adipic	$C_{20}H_{24}N_2O_2$	8.61	8.64
p-Aminobenzoic	$C_{14}H_{14}N_2O$	12.46	12.39
Anthranilic	$C_{14}H_{14}N_2O$	12.58	12.39
β-Benzylaminopropionic[b]	$C_{17}H_{21}ClN_2O$	8.93	9.15
n-Butylmalonic	$C_{21}H_{26}N_2O_2$	8.39	8.28
Cinnamic[c]	$C_{16}H_{15}NO$	6.05	5.90
Citric	$C_{27}H_{29}N_3O_4$	9.14	9.15
Diethylacetic[d]	$C_{13}H_{19}NO$	6.74	6.83
Diethylmalonic	$C_{21}H_{26}N_2O_2$	8.14	8.28
Diglycolic[d,e]	$C_{18}H_{20}N_2O_3$	9.00	8.97
Ethylmalonic	$C_{19}H_{22}N_2O_2$	9.18	9.03
Fumaric[c]	$C_{18}H_{18}N_2O_2$	9.58	9.51
2-Furanacrylic[d]	$C_{14}H_{13}NO_2$	5.91	6.17
Glutaric[d]	$C_{19}H_{22}N_2O_2$	8.86	9.03
Glycolic	$C_9H_{11}NO_2$	5.30	5.28
m-Hydroxybenzoic	$C_{14}H_{13}NO_2$	6.08	6.16
o-Iodobenzoic	$C_{14}H_{12}INO$	4.04	4.15
Isovaleric	$C_{12}H_{17}NO$	7.27	7.33
Maleic	$C_{18}H_{18}N_2O_2$	9.58	9.51
dl-Methylethylacetic[d]	$C_{12}H_{17}NO$	7.12	7.33
Myristic	$C_{21}H_{35}NO$	4.40	4.42
Naphthalic[c,f]	$C_{19}H_{13}NO_2$[g]	4.82	4.87
p-Nitrophenylacetic	$C_{15}H_{14}N_2O_3$[h]	10.55	10.37
Phenoxyacetic	$C_{15}H_{15}NO_2$	5.68	5.81
Phenylethylmalonic	$C_{25}H_{26}N_2O_2$	7.37	7.25
N-phenylglycine[d]	$C_{15}H_{16}NO_2$	11.90	11.66
Phenylsuccinic[d]	$C_{24}H_{24}N_2O_2$	7.30	7.53
Pimelic[d]	$C_{21}H_{26}N_2O_2$	8.36	8.26
Sebacic	$C_{24}H_{32}N_2O_2$	7.34	7.36
Terephthalic[d]	$C_{22}H_{20}N_2O_2$	7.98	8.14
m-Toluic	$C_{15}H_{15}NO$	6.31	6.22

[a] Made from methyl or ethyl ester and recrystallized from aqueous alcohol or acetone unless otherwise stated.

[b] Made from methyl acrylate; isolated and analyzed as hydrochloride. This compound was analyzed also for ionic chlorine (Volhard): found, 11.6; calc'd for $C_{17}H_{21}ClN_2O$, 11.6.

[c] Recrystallized from β,β'-dichlorodiethyl ether.

[d] Made from free acid.

[e] Recrystallized from water.

[f] Made from anhydride.

[g] N-Benzylnaphthalimide was produced.

[h] Kjeldahl modified according to Eckert (22) to include nitro group.

points were the basis of identification of the two solids. *p*-Nitrophenylacetic acid yielded only *p*-nitrotoluene (identified by odor, m.p., and mixed m.p.), but the methyl ester aminolyzed normally.

N-Butyl and isopropyl formates did not produce the solid derivative described by Buehler and Mackenzie, but this failure is believed due to difficulties in purification. The derivative of ethyl lactate was similarly lost, perhaps because of solubility in water. β-Hydroxypropionic acid yielded a small amount of white solid which could not be brought to sharp melting point by recrystallization. Tricarballylic acid gave much solid product, which however could not be purified because of its enormous tendency to form rigid gels in every solvent tried.

SUMMARY

Many esters and free acids can be converted to crystalline N-benzylamides by refluxing with benzylamine in the presence of salt catalysts. Of the ninety-odd tested, sixty-eight formed such derivatives, thirty-one of them new. The method fails for esters of inorganic acids, sulfonic acids, keto acids, polynitro aromatic acids, and some halogenated aliphatic acids. Esters of alcohols of high molecular weight may require preliminary methanolysis.

The amides formed by hydroxy acids, alkoxy acids, and polybasic acids, or by their respective esters, constitute excellent identifying derivatives, whereas those from fatty acids melt too low and too close together to be useful.

STILLWATER, OKLA.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

THE ACTION OF THIONYL CHLORIDE ON URETHANS

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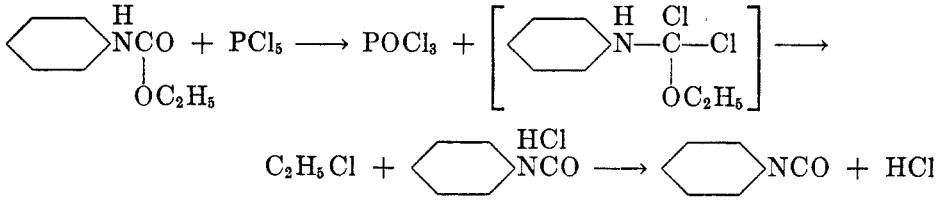
The action of acid chlorides on urethans has been studied frequently. Schroeter and Lewinski (1) heated a benzene solution of urethan and thionyl chloride under reflux on a water-bath and obtained ethyl allophanate, ethyl chloride, hydrogen chloride, and sulfur dioxide. They suggested no mechanism for the change. Lengfeld and Stieglitz (2) and later Folin (3) found that phenylurethan reacts with phosphorus pentachloride at 50–55° to eliminate ethyl chloride and leave chloroformanilide, which they found to decompose at 90–100° into hydrogen chloride and phenyl isocyanate. The reactions may be as shown below.

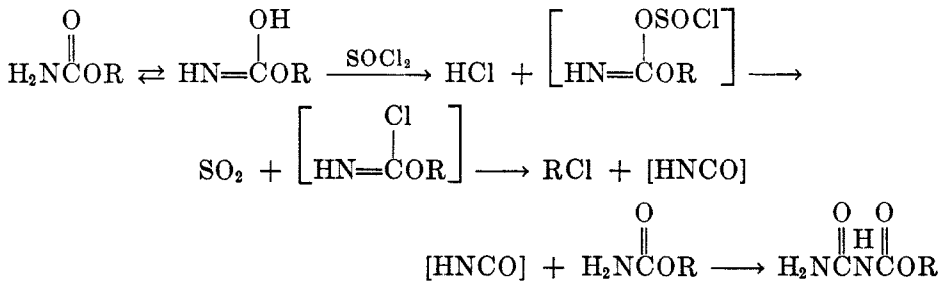


Much later Warren and Wilson (4) confirmed Schroeter and Lewinski's work with urethan but found that treatment of phenylurethan in the same way gave a tarry mass from which nothing definite could be isolated. However, they found that when a mixture of 0.2 molecular proportion of this urethan and 1 of thionyl chloride was allowed to stand at room temperature for one week, ethyl chloride, hydrogen chloride, and sulfur dioxide were eliminated and a 70% yield of diphenyl diisocyanate, more recently designated as 1,3-diphenyluretedione (5), crystallized out. Again, no mechanism was suggested.

In the present work, treatment of urethan with thionyl chloride by Warren and Wilson's method failed to give the allophanate they reported. *n*-Butyl carbamate, which they did not test, behaved in the same way. In both cases the only new product isolated in our tests of their method was a small amount of cyanuric acid, which indicates that the reaction mixture contained cyanic acid. When benzene solutions of the reactants were heated under reflux for several hours as directed by Schroeter and Lewinski, the corresponding esters of allophanic acid were obtained in yields of 71% and 51%, respectively.

These results may be explained by assuming the presence of an enolic form of the urethan which could readily be attacked by thionyl chloride. The existence of such an enol is indicated by an observation of Kraft (6) in which he found that sodium displaces hydrogen from an ether solution of urethan to give a substance that will react with methyl iodide to form methylurethan. In the first product, which was isolated and analyzed for sodium, the metallic radical was represented as attached directly to nitrogen, though it may have been on oxygen (7). The action of thionyl chloride on such an enol would give an inter-

mediate sulfur compound, for Stähler and Schirm (8) showed that propyl alcohol and thionyl chloride gave a mixture of dipropyl sulfite and the propyl ester of chlorosulfinic acid. Such a type of product derived from a urethan might be expected to lose readily sulfur dioxide and alkyl chloride, and give cyanic acid. A portion of the latter could then attack unchanged molecules of urethan and convert them into the related esters of allophanic acid, in accordance with Traube's results (9), while the remainder could, under certain conditions, polymerize to cyanuric acid, which was isolated in some of our experiments.



More direct support for the existence of an ester of chlorosulfinic acid was obtained in the present study. Thionyl chloride reacted rapidly with β-naph-

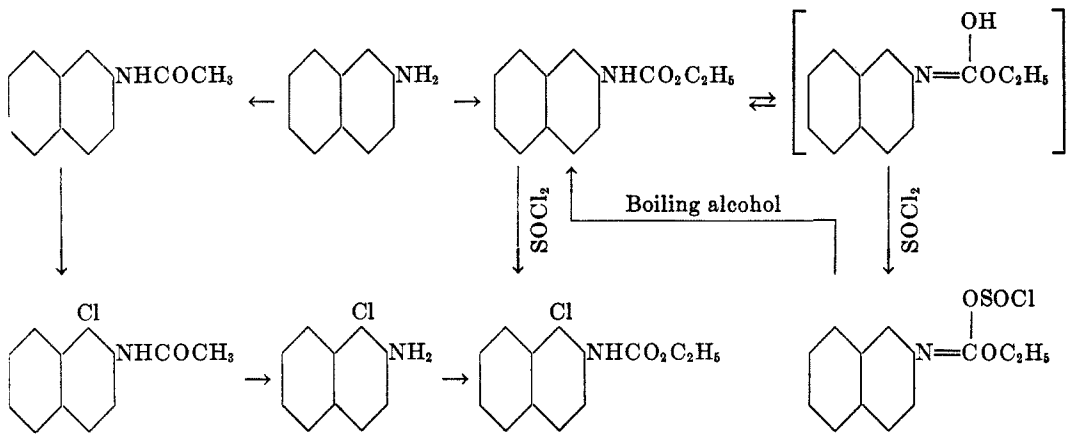


FIGURE I. PROOF OF STRUCTURE OF 1-CHLORO-2-NAPHTHYLURETHAN

thylurethan at about 0° to give two products, *viz.*, one composed of orange-red short, thick needles, m.p., 133–134°, and another in the form of colorless, silky needles, m.p., 94–95°. The higher-melting product, which separated first, was freed from foreign material with difficulty, and could not be kept without decomposition longer than two days. This change involved the elimination of sulfur dioxide and was accelerated by sunlight. Standing for two weeks caused some loss of color and the formation of a gum. The freshly-prepared purified material gave analytical data for halogen and sulfur required by the ethyl ester of β-naphthyliminochlorosulfinic acid. Boiling this product with absolute alcohol caused loss of sulfur dioxide and the formation of a viscous oil from which a 28% yield of the starting urethan was recovered.

From the original filtrate left after removal of the orange-red crystals a 56% yield of 1-chloro-2-naphthylurethan was obtained.

The action of thionyl chloride on N-aryl substituted urethans to give an isocyanate seemed to be specific for the phenyl derivative. In this case standing of the mixture at room temperature for one week gave a 65% yield of 1,3-diphenyluretedione. As indicated above, the enolic form of the urethan

$$[C_6H_5N = \overset{\overset{OH}{|}}{C}OC_2H_5]$$

could react with thionyl chloride to give an ester of chlorosulfinic acid which latter might easily lose alkyl chloride and sulfur dioxide, products identified in this reaction. The remaining isocyanate would then polymerize. Six urethans in which the phenyl group contained a substituent failed to give, at room temperature or at the boiling point of the mixture, any product that could be identified. Results are shown in Table I.

TABLE I

BEHAVIOR OF PHENYLURETHAN AND SUBSTITUTION PRODUCTS TOWARD THIONYL CHLORIDE

SUBSTITUENT IN PHENYL	TREATMENT	RESULT	STARTING MATERIAL RECOVERED
Unsubstitued	One week at room temperature	Uretedione formation	None
4-Methyl	Two weeks at room temperature	Viscous oil formation	None
	Heated	Tar formation	None
2,4-Dimethyl	Refluxed 5 hours	Tar formation	None
2-Chloro	Refluxed 6 hours	No reaction	Nearly quant.
4-Chloro	Refluxed 5 hours	No reaction	Nearly quant.
4-Nitro	Refluxed 6 hours	No reaction	Nearly quant.
2-Chloro-5-nitro	Refluxed 6 hours	No reaction	Nearly quant.

EXPERIMENTAL

n-*Butyl allophanate.* A benzene solution containing thionyl chloride and *n*-butyl carbamate in the proportion of one mole of the former and 0.2 mole of the latter was heated under reflux as directed by Schroeter and Lewinski. A small amount of cyanuric acid separated and was removed by filtration, the solvent was distilled from the filtrate, and the residue was purified. Crystallization from benzene gave a 51% yield of colorless fluffy needles that melted at 149–150°.

Anal. Calc'd for $C_6H_{12}N_2O_3$: N, 17.50. Found: N, 17.58.

Ethyl ester of 2-naphthyliminochlorosulfinic acid. Sixty-five grams of 2-naphthylurethan was dissolved in 180 g. of thionyl chloride in a suitable flask which was closed immediately by a stopper bearing a calcium chloride tube, and the flask was immersed in a bath of ice and salt. Within a few minutes evolution of hydrogen chloride was noted, and after three hours an orange-red crystalline solid began to separate. The flask was kept in the ice-bath for about 36 hours, the remaining gas was removed under partial vacuum at room temperature, the crystals were collected and the filtrate (F) was reserved. Attempts to crystallize portions of the solid were unsuccessful, and it was purified by repeated extraction with dry

ether which removed foreign material. The product was obtained in orange-red thick needles that melted at 133–134°. The yield was 20%.

Anal. Calc'd for $C_{13}H_{12}ClNO_3S$: Cl, 11.93; S, 10.75.
Found: Cl, 11.86; S, 10.88.

When the above compound was kept in a desiccator longer than two days it underwent slow decomposition with the evolution of sulfur dioxide. After two weeks the color was less pronounced and the material had become gummy. A mixture of 5 g. of freshly prepared material and 30 cc. of absolute alcohol was boiled under reflux for half an hour. Sulfur dioxide was evolved and the liquid slowly became colorless. Water was added to the hot liquid and the mixture was allowed to cool. A viscous oil settled to the bottom and long needles separated from the supernatant liquid. The solid was removed and crystallized from dilute alcohol in colorless needles that melted at 71–72°. This product did not depress the melting point of an authentic sample of 2-naphthylurethan used as starting material and melting at 71–72°. Cosiner (10) found 73° and Vittenet (11) recorded 69° for this compound.

Thionyl chloride was removed from filtrate (F) by distillation under partial vacuum, and the residue crystallized in light brown masses upon cooling. Separate portions of it were purified by recrystallization from methanol and ethanol, respectively, and in each case colorless silky needles, m.p., 94–95° were obtained. This indicated that the product in question was not an isocyanate. The total yield was 56% and the substance was identified as 1-chloro-2-naphthylamino ethyl carbonate, or α-chloro-β-naphthylurethan, by comparison of it with an authentic sample prepared in a different way.

Anal. Calc'd for $C_{13}H_{12}ClNO_2$: Cl, 14.22; N, 5.61; Mol. wt. 249.5.
Found: Cl, 14.19; N, 5.52; Mol. wt., (freezing point with benzene) 236.2.

4-Chloro-1-naphthylamino ethyl carbonate. Sixty grams of α-naphthylurethan was dissolved in 180 g. of thionyl chloride and the solution was cooled immediately in an ice-salt bath. After thirty-six hours gases were removed by a pump, and some crystalline material was collected by filtration and reserved for further study. When about 500 cc. of ligroin (35–40°) was mixed with the filtrate a yellow solid precipitated. Crystallization from dilute methanol, with Norit for decolorization, gave a nearly colorless solid that showed a melting range of 122–127°. After four further crystallizations 17% yield of small colorless leaflets that melted at 143–144° was obtained.

Anal. Calc'd for $C_{13}H_{12}ClNO_2$: Cl, 14.22; N, 5.61.
Found: Cl, 13.98; N, 5.52.

The above compound was further characterized by hydrolysis with alcoholic potash, which gave nearly a quantitative yield of a product that melted at 97–98°. This was identified by comparison with the derivative obtained by hydrolysis of 4-chloro-1-acetylaminonaphthalene, previously prepared by Reverdin and Crépieux (12).

SUMMARY

1. Thionyl chloride reacts with ethyl and *n*-butyl carbamates to give the corresponding allophanates and small amounts of cyanuric acid.

2. The action of this acid chloride with N-aryl substituted urethans to give uretediones was specific, so far as tested, for the phenyl derivative. Compounds containing "negatively" substituted phenyl suffered no change when refluxed with the reagent, but when the substituent was alkyl, tar was formed.

3. With the α- and β-naphthyl derivatives, chlorination of the ring at positions 4 and 1, respectively, took place at 0°. From the β-compound there was also isolated the unstable ethyl ester of β-naphthyliminochlorosulfinic acid.

IOWA CITY, IOWA

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[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

ON THE MECHANISM OF THE DIENE REACTION

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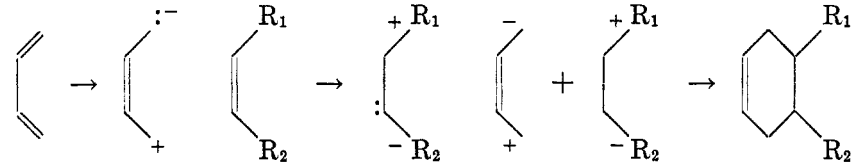
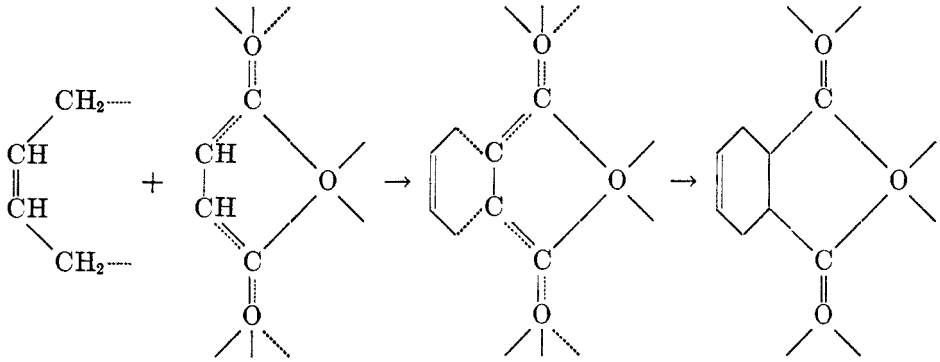
In a recent publication from this laboratory (1) the following scheme A was formulated for the Diels-Alder reaction, involving resonance forms of both com-



Scheme A

ponents. According to this scheme each partner shows at one pole an electron deficit which is remedied by the lone pair of the other partner.

At the same time, a paper by Hudson and Robinson (2) presented scheme B for the same reaction, assuming that both the α- and δ-carbon atoms of the diene function successively as electron donors, whereas the philodienic component serves as electron acceptor at both ends of its olefinic bond. The



Scheme B. A dotted line represents a single electron.

addition proceeds, therefore, in two phases, allowing a monopolar approach of the two reacting molecules. This scheme was based on the successful condensation of isoeugenol and isosafrole, and can easily be applied to other reactions such as bromination of ethylenic compounds, avoiding the breakdown of the Br_2-molecule into a positive and negative ion, which is assumed in almost all other theories.

It is, however, evident, as the authors already recognized, that scheme B cannot be applied to philodienic compounds possessing only one substituent. Diene additions must therefore proceed by different mechanisms depending on the structure of the philodiene. Furthermore, according to scheme B, the reactivity in a series of olefins $R_1CH{=}CHR_2$ should decrease gradually with

increased difference in negativity between R_1 and R_2. The end-points of such a series would be represented by $R_1 = R_2$ on one side, and by $R_1 = H$ on the other. Investigation of such complete series of olefins in the same type of reaction would shed light on the general mechanism of the Diels-Alder reaction, whether proceeding along two different ways or on a common path.

Several cases of Diels-Alder reactions seem to support the former possibility. In Tables I and II the results of a systematic study of condensations with bicyclohexenyl and 3,4,3′,4′-tetrahydro-1,1′-binaphthyl (bis-dialin) are summarized. Two groups of philodienic components are clearly discernible: with equal and different substituents.

TABLE I

ADDUCTS WITH BICYCLOHEXENYL

PHILODIENIC COMPONENT	RATIO DIENE / PHILODIENE	SOLVENT	YIELD %	REFERENCE
Maleic anhydride	1:10		95	Present authors
trans-Dibenzoylethylene	1.5:1	Ethanol	85	(1)
trans-Cinnamic acid	1:1		50	(1)
Indene	1.5:1		43	(15)
Benzalacetophenone	1:1		30	(1)
Benzalacetone	1:1.3		27	(1)
trans-Benzoylacrylic acid	1:1	Ethanol	25	(1)
Acrolein	1:1	Benzene	20	(16)

TABLE II

ADDUCTS WITH BIS-DIALINE

PHILODIENIC COMPONENT	RATIO DIENE / PHILODIENE	YIELD %	REFERENCE
Maleic anhydride	1:2	87 (nitrobenzene)	(11)
"	1:10	95	Present authors
Quinone	1:10	80	"
trans-Dibenzoylethylene	1:1	50	"
α-Naphthoquinone	1:2	50	"
Cinnamic acid, Benzoylacrylic acid, Benzalacetone, Benzalacetophenone	1:1		"

It is seen, however, that the yields vary with changes in the ratio of components, solvents etc. In many cases, the drastic conditions cause side reactions, *e.g.*, with ketones and quinones. In view of the reversibility of the diene reaction, and in order to get a sound basis for comparison, it is necessary to use a large excess of one component. This, naturally, could only be the diene, which serves as solvent and diluent for the olefin. Bicyclohexenyl was chosen because of its excellent reactivity and its being a liquid of high solvent power. Results, now obtained in 5:1 reaction mixtures, are given in Table III.

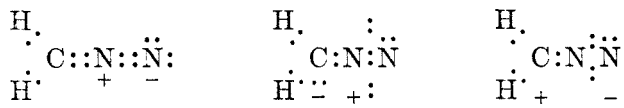
It is obvious at once, that no difference is detectable between symmetrical and unsymmetrical philodienes. Even the reaction temperature does not indicate any group difference: Fumaric acid, which should behave like its *cis* isomer, can be brought into reaction only at 200°,[1] whereas β-nitrostyrene (4) reacts as easily as quinone or maleic anhydride at 80°. If we add the recent observation of Joshel and Butz (5), that even ethylene undergoes the Diels-Alder reaction, when suitably activated, then we can safely conclude that scheme A represents satisfactorily the general reaction mechanism. This scheme has also the advantage of revealing the complete formal analogy of the Diels-Alder condensation with the reaction between philodienes and diazomethane. In certain cases, the primary addition product with diazomethane has been isolated (6, 7). The formula CH_2N_2 can be best represented as a resonance hybrid mainly between a, b, and c (besides other, less contributing,

TABLE III

ADDUCTS WITH BICYCLOHEXENYL, RATIO DIENE/PHILODIENE = 5:1

PHILODIENIC COMPONENT	TEMP. °C	YIELD, %
Maleic anhydride	80	95
Quinone	80	85
α-Naphthoquinone	100	99
Fumaric acid	200	80
Benzalacetone	180	76
Dibenzalacetone	180	95
Cinnamic acid	180	75
β-Nitrostyrene	80	95

forms), and evidently form c (or b) is able to explain the cyclization in a way corresponding to scheme A.



a b c

On the other hand, it must be conceded that scheme B may apply in extraordinary cases such as styrene derivatives, because styrene itself is entirely incapable of functioning as diene (it may, on the contrary, serve as philodienic component!). A resonance form of styrene as diene in accordance with scheme A apparently requires too great a disturbance of the aromatic nucleus.[2]

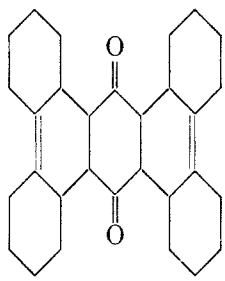
[1] As far as we are aware, this is the first case of direct condensation of free fumaric acid with dienes. Compare reference 3.

[2] When this paper was ready for publication, Allen and van Allan [*J. Am. Chem. Soc.*, **64**, 1260 (1942)] published certain experiments on the Diels-Alder reaction comprising a complete series from maleic anhydride to acetylene and showing likewise the equality of symmetrically and unsymmetrically substituted and monosubstituted ethylenes as philodienes.

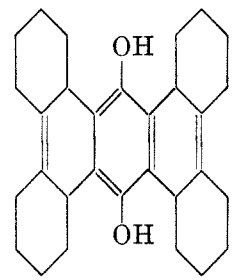
CHEMICAL REMARKS

1. Especially with quinones, the use of an excess of diene gives superior results because it avoids the dehydrogenating action of free quinone on the adduct. *E.g.*, the reaction between bicyclohexenyl and benzoquinone has been reported to yield one single and five double addition products. Barnett (8) obtained from a boiling solution of one mole of benzoquinone in 2 moles of the diene only one product of m.p. 315°. Weizmann and co-workers (9), working with the same mixture at 140°, reported an adduct of m.p. 247° (I) in 25% yield and a partially dehydrogenated product of m.p. 297° (II ?). Finally Backer (10), who used different solvents, isolated two further addition products of m.p. 217° and 137°, respectively, and one (isomerization ?) product of m.p. 304°. Under the mild conditions used in the present work, the two isomers of m.p. 248° and 217° were isolated (the large excess of bicyclohexenyl allows of course only for the formation of bis-adducts), making up together an almost quantitative yield. Ethanolic potash enolizes the higher-melting adduct to an isomer of m.p. 327° (III), and the lower-melting form to a corresponding compound of m.p. 310–312°, apparently identical with the last-mentioned product of Backer. Both enols are resistant to alcoholic ferric chloride, which would dehydrogenate them, if they were the hydroquinones II. The experiment of Barnett was repeated and the product, obtained in about 10% yield, proved to be identical with the isomerization product of m.p. 312°. This is not surprising, since spontaneous enolization of adducts has already been reported (7). The situation can, therefore, be somewhat clarified by the following statement:

Bicyclohexenyl and benzoquinone have, so far, given three bis-addition products of m.p. 137°, 217°, 248° resp. The last two give enolization products of m.p. 310° and 327° resp. under a variety of conditions.



I



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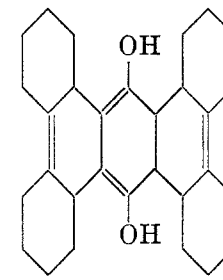
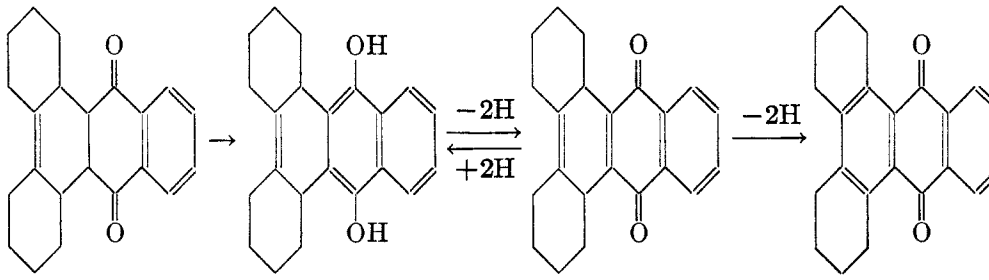


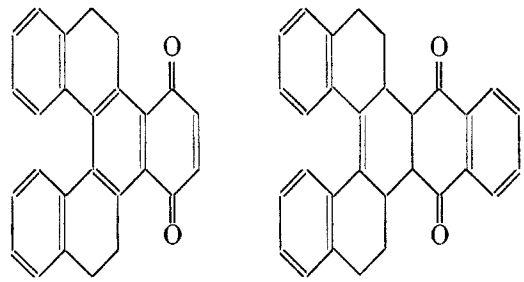
III

Similarly, α-naphthoquinone gave a quantitative yield of the primary addition compound (IV), without even a trace of dehydrogenation products. When enolization is effected by alcoholic potash or by hydrobromic-acetic acid, the intermediary hydroquinone V is extremely unstable and passes already during recrystallization into the naphthoquinone VI by autoxidation. Curiously enough, during reaction with hydrobromic acid, about 50% of the material is dehydrogenated further to the anthraquinone VII. Apparently, part of VI functions as hydrogen acceptor for the other part according to the following scheme, and V then regenerates VI by autoxidation.



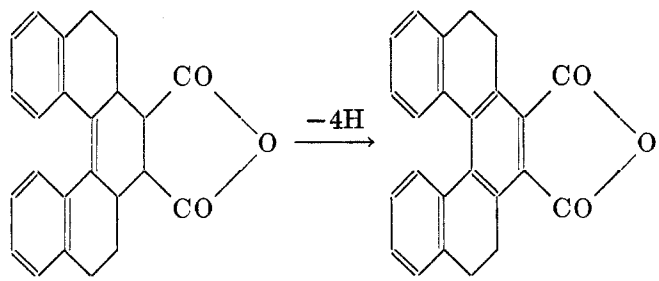
IV V VI VII

It is significant that both VI and VII were isolated by Weizmann and co-workers (9) directly in the diene reaction at a temperature of 200°, whereas Barnett (8), from a boiling mixture, obtained the primary product V. It has already been shown in other examples (7), that enolization and dehydrogenation are favored by an excess of the quinone. Bis-dialin gave, by use of an excess of benzoquinone, exclusively the compound VIII by loss of four hydrogen atoms from the primary adduct. In accordance with this structure, the compound is unable to undergo enolization. α-Naphthoquinone under the same conditions yielded the primary addition product IX, and dibenzoylethylene gave XII.

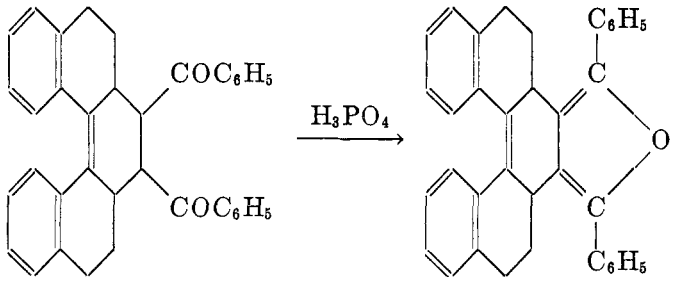


VIII IX

2. Condensation between bis-dialin and maleic anhydride in nitrobenzene was reported by Weidlich (11) to give the "tetrahydro" product X, in contradiction to the common dehydrogenating action of this solvent (12). It has now been found, that extending the reaction time from two to ten hours gives the expected "aromatized" compound XI, thus confirming our previous statement, that nitrobenzene oxidizes the already-formed adduct and does not act on some hypothetical intermediate.



X XI



XII XIII

EXPERIMENTAL PART

I. REACTIONS WITH BICYCLOHEXENYL

Reactions which mainly represent repetitions of previous experiments under altered conditions, are not recorded.

1. *With benzoquinone.* The quinone (1.1 g; 1/100 mole) and the diene (8 g.; 1/20 mole) were warmed on a water-bath for five hours. The clear solution started crystallization after three hours. The crystals (2.5 g.) showed the m.p. 235–240°. This substance was dimorphic; from butanol it crystallized in prismatic rods, m.p. 233–235°, from high-boiling petroleum ether in needles, m.p. 247° (I). The mother liquor deposited, after 24 hours, a second crop (0.8 g.), of m.p. 190–195°. From high-boiling petroleum ether, clusters of rectangular prisms, m.p. 212° (Ia).

Anal. Calc'd for $C_{30}H_{40}O_2$: C, 83.3; H, 9.3.
Found: C, 82.8; H, 9.2.

On concentrating the mother liquors, a further crop (0.4 g.) of the first isomer, (m.p. 247°) was obtained, bringing the total yield to 86%.

Enolization: 0.5 g. of I was suspended in ethanolic potassium hydroxide and left at room temperature for 24 hours. The filtered material was recrystallized twice from nitrobenzene; clusters of colorless needles, m.p. 327° (III). The substance was recovered unchanged after boiling its butanolic solution with ferric chloride.

Anal. Calc'd for $C_{30}H_{40}O_2$: C, 83.3; H, 9.3.
Found: C, 83.5; H, 8.9.

Adduct Ia, when treated in the same way, gave colorless needles (from butyl acetate), m.p. 310–312° (IIIa).

Anal. Calc'd for $C_{30}H_{40}O_2$: C, 83.3; H, 9.3.
Found: C, 83.5; H, 9.6.

According to Barnett (8), a solution of quinone (0.6 g.) in bicyclohexenyl (2 g.) was boiled for two minutes, and the mixture treated with alcohol and acetone. From butyl acetate, white needles were obtained (0.2 g., 10%); m.p. 308°, mixed m.p. with the foregoing compound (IIIa), 308–310°.

The mother liquors were concentrated and yielded, upon treatment with ligroine, 0.1 g. of a mixture of I and Ia.

2. *With α-naphthoquinone.* The quinone (1.2 g., 1/130 mole) and the diene (6 g., 1/26 mole), when heated on a water-bath, gave a clear solution, which solidified after two hours. Treatment with alcohol gave 2.5 g. (100%) of adduct, which crystallized from butanol in colorless plates, m.p. 207–208° (IV).

(a) Five-tenths gram of IV was suspended in hot alcohol and alcoholic potash added. The solution turned immediately red-yellow, and on cooling a red solid crystallized. On recrystallization, first a heterogeneous material (yellow needles, red prismatic rods) appeared, which, however, gradually changed into a pure red substance; prismatic rods (from butyl acetate), m.p. 248° (VI).

Anal. Calc'd for $C_{22}H_{22}O_2$: C, 83.0; H, 6.9.
Found: C, 82.7; H, 7.1.

(b) Five-tenths gram of IV was dissolved in glacial acetic acid (25 cc.), and at 80° five drops of conc'd hydrobromic acid were added. The colorless solution turned immediately yellow and deposited, on cooling, yellow needles (VII). From acetic acid, m.p. and mixed m.p. with a previous sample (9) 234–235°. Conc'd sulfuric acid gave a beautiful red color.

Anal. Calc'd for $C_{22}H_{20}O_2$: C, 83.6; H, 6.3.
Found: C, 83.8; H, 6.1.

From the filtrate of VII, water precipitated a brown-black material (quinhydrone of V + VI ?). Repeated recrystallization from butyl acetate gave red rods, m.p. and mixed m.p. with VI 248°.

3. *With fumaric acid.* The acid (1.25 g. 1/92 mole), suspended in the diene (8.5 g., 1/18 mole) did not react at 100°. However, reaction took place at 190–200°. The excess of bicyclohexenyl was distilled off, and the residue extracted with boiling sodium hydroxide solution. The adduct acid, which was precipitated from the filtered extract, was amorphous (2.5 g., 80%) and was therefore converted into its di-anilide. The adduct was dissolved in benzene (25 cc.) and phosphorus pentachloride (2.2 g.) added at once. An exothermic reaction occurred, and was completed by refluxing for half an hour. Solvent and phosphorus oxychloride were removed *in vacuo*, and the residue boiled with aniline (2 cc.) for two minutes. Hydrochloric acid precipitated a sirupy product, which crystallized on treatment with alcohol. From glacial acetic acid long, colorless, slender needles, m.p. 312°, were obtained.

Anal. Calc'd for $C_{28}H_{32}N_2O_2$: C, 77.8; H, 7.4; N, 6.5.
Found: C, 78.2; H, 7.8; N, 6.8.

4. *With β-nitrostyrene.* Nitrostyrene (1 g., 1/150 mole) and the diene (5 g., 1/30 mole) were warmed on a water-bath for eight hours. On cooling, the product crystallized, and was triturated with methanol. Yield, 1.9 g., 95%; from butanol beautiful rods, m.p. 187°. With hot conc'd sulfuric acid a golden-yellow solution was obtained.

Anal. Calc'd for $C_{20}H_{26}NO_2$: C, 77.2; H, 8.0; N, 4.5.
Found: C, 77.2; H, 8.3; N, 4.6.

The adduct was not attacked by catalytic hydrogenation, in accordance with observations of Alder (13). (The $C_{12,13}$ double bond in these adducts is known to be entirely refractive).

5. *With dibenzalacetone.* The ketone (1.2 g., 1/200 mole) and the diene (4 g., 1/40 mole) were heated to 180–190° during five hours. The sirupy mass crystallized on trituration with ethanol (2 g., 95%); from butanol thin long needles, m.p. 208–209°.

Anal. Calc'd for $C_{41}H_{50}O$ (double adduct): C, 88.2; H, 9.0.
Found: C, 88.5; H, 8.6.

II. REACTIONS WITH 3,4,3′,4′-TETRAHYDRO-1,1′-BINAPHTHYL

1. *Preparation of bis-dialin.* For the preparation of tetralone we used the method of Thompson (14). Contrary to this author's experience, we did not find the described treatment sufficient to remove peroxides. Eventually, the following changes were introduced: treatment with sodium hydroxide at 60° was continued for 4 hours, and shaking with ferrous sulfate at room temperature was extended at least for 24 hours.[3] The average yield was two-thirds of that reported by Thompson. Pinacolization of tetralone was best effected in the following way: to 200 cc. of dry benzene, absolute ethanol (10 cc.) was added, and about 25 cc. was distilled off. Thin aluminum foil (7 g.) was added, care being taken to expose a fresh surface of the metal, then 1 g. of mercuric chloride, and finally tetralone

[3] The tetralin-tetralone mixture was shaken with half of its volume of a saturated solution of $FeSO_4$. Practically no emulsions were formed, if this solution was filtered before use, and the layers separated within a few minutes. The absence of peroxides was proved by the negative reaction with KI in glacial acetic acid.

(20 g.). The mixture was refluxed overnight. The liquid was now decanted, the metal dissolved in dilute HCl and ice, and the solution extracted with ether. The ether extracts were combined with the benzene solution, the solvents removed, and the residue refluxed for three hours with a 1:1 mixture of acetic acid and acetic anhydride. On cooling, bis-dialin (15 g.) crystallized. Recrystallization from ethanol containing 10% benzene, gave 12 g. of pure diene, m.p. 141°. The pinacol itself, when isolated, crystallized from butyl acetate in beautiful prisms, m.p. 191–192° (8).

2. *Condensation with maleic anhydride.* The anhydride (24 g., 1/4 mole) and bis-dialine (6 g., 1/40 mole) were heated together on a water-bath for four hours. The clear solution solidified completely. The excess anhydride was removed by water. The residue, m.p. 233°, (8 g., 95%) was fractionally crystallized from xylene. The main product formed thick rectangular plates, m.p. 256° (X).

Anal. Calc'd for $C_{24}H_{20}O_3$: C, 80.9; H, 5.6.
Found: C, 81.1; H, 5.5.

The mother liquors yielded a second adduct, clusters of fine needles, m.p. 260° (Xa). Mixed m.p. with the foregoing 232°.

Anal. Calc'd for $C_{24}H_{20}O_3$: C, 80.9; H, 5.6.
Found: C, 81.0; H, 5.8.

Adduct X was transformed with diazomethane into its di-ester, which formed tetragonal pyramids from high-boiling petroleum ether; m.p. 168°.

This ester (0.9 g.) was isomerized with sodium (0.5 g.) in boiling butanol (25 cc.) during three hours (1). The sodium salt of the isomeric acid crystallized on cooling. It was decomposed with dil. sulfuric acid at 0°, and the product recrystallized from butyl acetate, m.p. 239°.

Anal. Calc'd for $C_{24}H_{22}O_4$: C, 77.0; H, 5.9.
Found: C, 76.7; H, 5.7.

Adduct Xa, on the other hand, resisted all attempts, to convert it into the free acid. Therefore the same chain of reactions could not be carried out here.[4]

3. *Condensation in nitrobenzene.* The diene (2.5 g.) and maleic anhydride (15 g.) were boiled in nitrobenzene (25 cc.). After 3 hours, the product which crystallized on cooling was identical with the above adduct X, m.p. 256°. Then boiling was extended to 10 hours, the solvent removed by steam, and the black residue dissolved in 30% aqueous KOH with addition of some alcohol, the extract boiled with charcoal and filtered. The filtrate was nearly neutralized with HCl, a small amount of tar which settled down was removed, and then excess HCl added. The orange-yellow product was recrystallized from ethyl benzoate (red solution with green fluorescence), m.p. 275° (yellow eicosihedra, XI).

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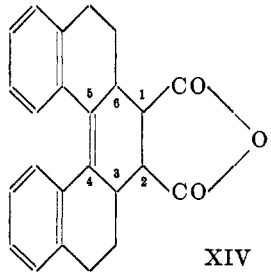
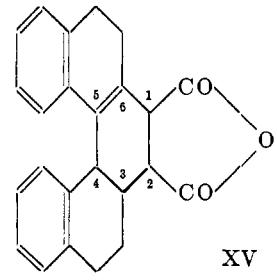
[4] The isomerization of adduct Xa was attempted in order to settle definitely the question of isomeric adducts (1). If it is assumed that the two anhydrides can be represented, *e.g.*, by formulas XIV and XV, then isomerization with sodium butoxide should give two different *trans* acids. On the other hand, if the isomerism of XIV and XV is based on the position of hydrogens at C_3 and C_6 relative to C_1 and C_2, then the same *trans* acids would be obtained from both adducts.



XIV

and



XV

Anal. Calc'd for $C_{24}H_{16}O_3$: C, 81.8; H, 4.55.
Found: C, 81.8; H, 4.2.

4. *With benzoquinone.* The diene (2.6 g.) and benzoquinone (11 g., 10 equiv.) were heated together at 125–150° for three hours. At first, a homogeneous liquid resulted, which, however, solidified later completely. After steam distillation, a dark red residue was left; crude yield, 3 g. (80%). Recrystallization from butyl acetate and acetic anhydride gave red plates, m.p. 268° (VIII).

Anal. Calc'd for $C_{26}H_{18}O_2$: C, 86.2; H, 5.0.
Found: C, 86.0; H, 4.7.

The substance was not altered when treated with HBr in acetic acid solution. No addition was observed, when 4 equiv. of the diene were heated with 1 mole of quinone, or when the components were dissolved in boiling benzene or xylene.

5. *With α-naphthoquinone.* Two moles of the quinone was heated with 1 mole of the diene at 130° for 3 hours. After steam distillation, the residue was triturated with chloroform-ethanol. From butanol, fine yellow needles, m.p. 226° (IX); yield 50%.

Anal. Calc'd for $C_{30}H_{24}O_2$: C, 86.5; H, 5.8.
Found: C, 86.6; H, 6.0.

6. *With* trans-*dibenzoylethylene.* No reaction took place in boiling benzene. If, however, the diene (2 g.) and the ethylene (2 g.) were heated to 200° for 10 hours, about 2 g. (50%) of yellow crystals was obtained by treating the reaction mixture with ethanol-acetone. From butyl acetate, quadrangular prisms, m.p. 236–238° (XII). Near the end of the crystallization a second isomer appeared in the form of needles, which, however, was not isolated.

Anal. Calc'd for $C_{36}H_{30}O_2$: C, 87.4; H, 6.1.
Found: C, 87.1; H, 6.4.

Dehydration: The adduct (1.7 g.) was dissolved in boiling acetic anhydride (25 cc.). When five drops of phosphoric acid (sp. gr. 1.75) were added, the color changed from yellow to red. The product was recrystallized from nitrobenzene, then from acetic anhydride. Yellow prismatic rods, m.p. 272–273° (XIII).

Anal. Calc'd for $C_{36}H_{28}O$: C, 90.8; H, 5.9.
Found: C, 90.2; H, 6.0.

When the product was dissolved in conc'd H_2SO_4 at 50°, no isomer analogous to the corresponding derivative of bicyclohexenyl (1) could be detected.

SUMMARY

1. High yields of adducts can be obtained from bicyclohexenyl with both symmetrically and unsymmetrically substituted ethylenes. This finding is discussed with reference to two schemes (A and B) for the mechanism of the Diels-Alder reaction.

2. The use of excess diene gives superior yields and clearer results, especially in the case of quinones.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

CONDENSATION OF EPICHLOROHYDRIN WITH ETHYLENE GLYCOL: SOME NEW POLYFUNCTIONAL DERIVATIVES

M. S. KHARASCH AND W. NUDENBERG

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Fourneau and Ribas (1) have reported the condensation of epoxyalkanes with alcohols in the presence of sulfuric acid. By suitable modifications (described in the Experimental Part), their method is here extended to the condensation of epichlorohydrin (3-chloro-1,2-epoxypropane) and ethylene glycol (1,2-ethanediol).

$$ClCH_2CH\!\!\!\diagup\!\!\!\diagdown\!\!\!CH_2 + HOCH_2CH_2OH \rightarrow \quad (I)$$
$$\qquad O$$

$$ClCH_2CHOHCH_2OCH_2CH_2OH$$

The 1-chloro-3-(β-hydroxyethoxy)-2-propanol (I) thus obtained was used to synthesize a number of new compounds.

EXPERIMENTAL PART

The preparation of 1-chloro-3-(β-hydroxyethoxy)-2-propanol (I). To 278 g. (3 moles) of epichlorohydrin (obtained from the Shell Development Company) was added 379 g. (6 moles) of ethylene glycol. Since the two liquids are immiscible, the mixture was vigorously agitated, and concentrated sulfuric acid was added a few drops at a time. The mixture became homogeneous after the addition of 1 cc. of sulfuric acid. Since further addition of acid caused a considerable rise in temperature, the flask was cooled with running water during the subsequent addition. A total of 13 cc. of sulfuric acid was added. The product was then refluxed on a steam-bath for 12 hours and neutralized with excess barium carbonate (38 g.). The material was distilled directly at 3 mm. pressure. Two main fractions were obtained: (a) unidentified material (b.p. below 135°); (b) 1 chloro-3-(β-hydroxyethoxy)-2-propanol (b.p. 135–139°) (I). The 260 g. of material in fraction (b) represents a 56% yield.

Anal. Calc'd for $C_5H_{11}ClO_3$: Cl, 22.94. Found: Cl, 22.40.

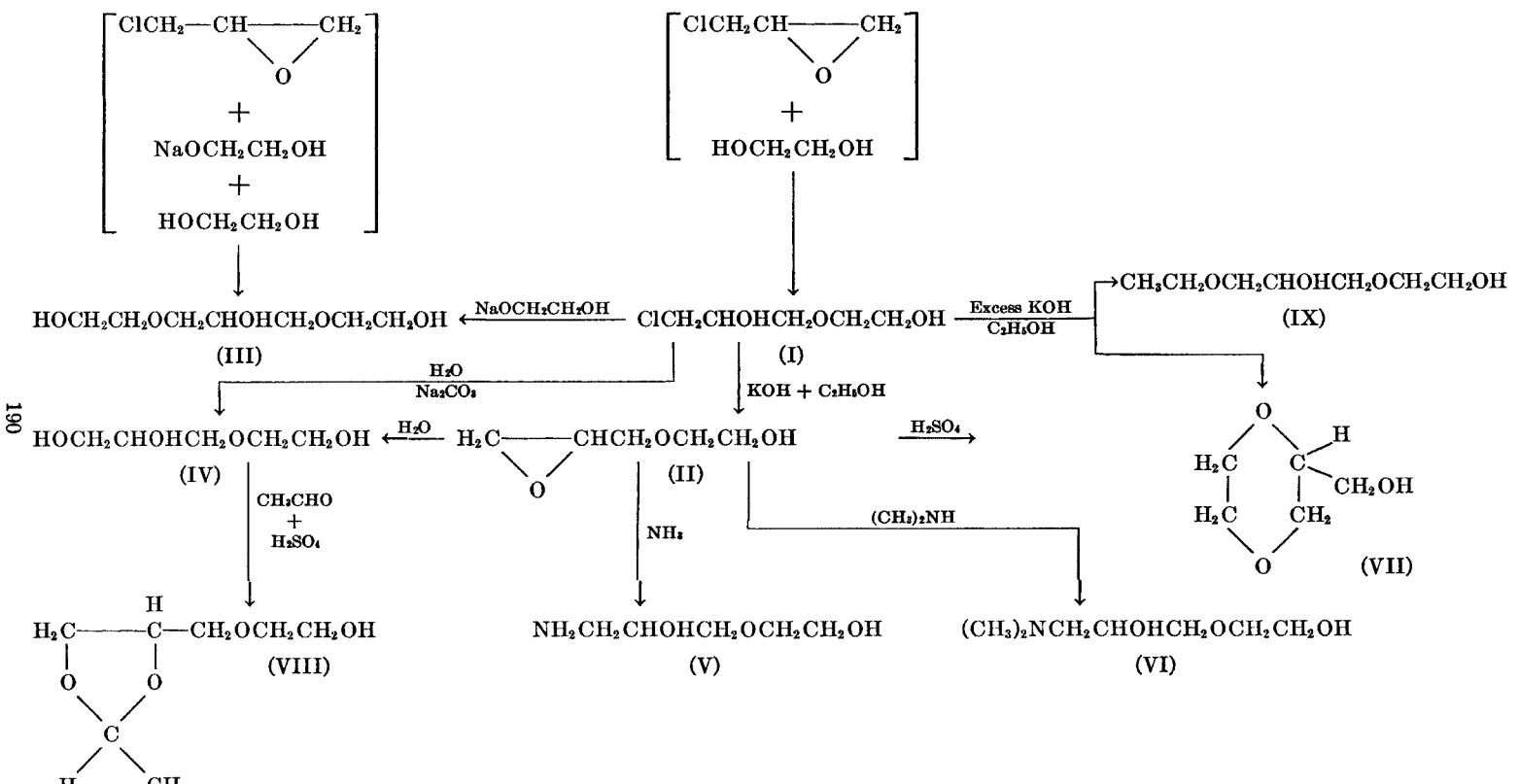
Some unidentified high-boiling material remained in the flask.

Preparation of 1,3-bis-(β-hydroxyethoxy)-2-propanol (III). This compound may be prepared by treating compound (I) with the monosodium salt of ethylene glycol. It has, however, proved more satisfactory to prepare the substance directly from epichlorohydrin by the following method. The monosodium salt of ethylene glycol was prepared by adding 23 g. of sodium (in small pieces) to 92 g. of ethylene glycol dissolved in liquid ammonia. The solvent was then removed by evaporation. To 101 g. of the monosodium salt of glycol suspended in 200 g. of glycol,was added 112 g. of epichlorohydrin (20 g. at a time). During this addition, the mixture was vigorously agitated, and heated. After the addition (which required 3 hours) was complete, the reaction mixture was refluxed for 13 hours. The fraction (48 g.) which distilled at 188–192° at 2–3 mm. was identified by its analysis and reactions as 1,3-bis-(β-hydroxyethoxy)-2-propane (III). After the liquid had stood for 24 hours at room temperature, the liquid solidified (m.p. 30°). To obtain a sample for analysis, this solid was redistilled. It boiled at 188–192° at 2–3 mm.

Anal. Calc'd for $C_7H_{16}O_5$: C, 46.65; H, 8.95.

Found: C, 46.20; H, 8.75.

Preparation of 3-(β-hydroxyethoxy)-1,2-epoxypropane (II). The method of preparation was that used by Rider and Hill (2) for the preparation of glycidol. Nineteen grams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O
+
NaOCH2CH2OH
+
HOCH2CH2OH
ClCH2CH——CH2
O
+
HOCH2CH2OH
HOCH2CH2OCH2CHOHCH2OCH2CH2OH
(III)
NaOCH2CH2OH
ClCH2CHOHCH2OCH2CH2OH
(I)
Excess KOH
C2H5OH
CH3CH2OCH2CHOHCH2OCH2CH2OH
(IX)
H2O
Na2CO3
KOH + C2H5OH
HOCH2CHOHCH2OCH2CH2OH
(IV)
H2O
H2C——CHCH2OCH2CH2OH
O
(II)
H2SO4
O
H
H2C
C
CH2OH
H2C
CH2
O
(VII)
CH3CHO
+
H2SO4
NH3
(CH3)2NH
H
H2C——C—CH2OCH2CH2OH
O
O
C
H
CH3
(VIII)
NH2CH2CHOHCH2OCH2CH2OH
(V)
(CH3)2NCH2CHOHCH2OCH2CH2OH
(VI)

DIAGRAM I

(0.33 mole) of potassium hydroxide pellets was added to 135 cc. of absolute alcohol in a 500-cc. round-bottom, three-necked flask fitted with a stirrer and dropping-funnel. The alcoholic potassium hydroxide solution was cooled to 2°. Then 54 g. (0.33 mole) of 1-chloro-3-(β-hydroxyethoxy)-2-propanol (I) dissolved in 67 cc. of absolute alcohol was slowly added. Stirring was continued for one hour after the addition of the chloro compound. The precipitated potassium chloride was collected on a filter and washed several times with absolute alcohol; the washings were added to the main filtrate. The alcohol was removed from this filtrate by distillation at 76 mm. through a one-foot column. The residue was distilled at 1–2 mm., and the portion of the material boiling at 90–94° was collected. This portion (32 g.) was redistilled, and the fraction boiling at 92–94° was collected. This portion (32 g.) was redistilled, and the fraction boiling at 92–94° at 2 mm. was used for analysis; n_D^{20} 1.4480.

Anal. Calc'd for $C_5H_{10}O_3$: C, 50.80; H, 8.55.
Found: C, 50.44; H, 8.39.

Preparation of 3-(β-hydroxyethoxy)-1,2-propanediol (IV). To 9 g. of twice distilled 3-(β-hydroxyethoxy)-1,2-epoxypropane (II) was added 19 g. of distilled water. The mixture was refluxed for 5 hours, and the water then removed by evaporation on a steam-bath. The residue was distilled at 3 mm. The material boiling at 162–164° at 3 mm. (n_D^{20} 1.4723) was collected as the desired product.

Anal. Calc'd for $C_5H_{12}O_4$: C, 44.09; H, 8.88.
Found: C, 43.07; H, 8.36.

This ether was also prepared directly from 1-chloro-3-(β-hydroxyethoxy)-2-propanol (I). To 161 g. (1.04 mole) of (I) was added a solution of 60 g. (0.5 mole) of sodium carbonate in 1200 cc. of water. The mixture was heated on a steam-bath for 16 hours. Water was removed by evaporation on a steam-bath. Methyl alcohol was added to the residue, and the sodium chloride removed by filtration. The filtrate was concentrated on a steam-bath, and the residue distilled. A considerable amount of sodium chloride separated during distillation. The portion boiling at 161–191° at 2–5 mm. was collected. This portion was submitted to a slow distillation and the fraction (90 g. = 66% yield) boiling at 145–150° at 1 mm. was collected (n_D^{20} 1.4722).

Preparation of 2-methyl-4-(β-hydroxyethoxymethyl)-1,3-dioxolene (VIII). To 52 g. (0.382 mole) of (IV) in a 500-cc. round-bottom, three-necked flask was added 2 cc. of 50% sulfuric acid. Then 18 g. of paraldehyde was slowly added while the reaction flask was heated on a steam-bath and its contents stirred. After the addition of the paraldehyde was complete, heating was continued for three hours. Then the reaction mixture was extracted with ether. The ether extract was dried with anhydrous potassium carbonate, and the ether removed by distillation on a water-bath. The residue was distilled, and the fraction boiling at 112–114° (8 mm.) was collected. The yield was 27 g. (43% of the calculated amount). This material was subjected to another distillation, and the fraction boiling at 113–115° (8 mm.) (n_D^{20} 1.4453) was used for analysis.

Anal. Calc'd for $C_7H_{14}O_4$: C, 51.82; H, 8.63.
Found: C, 51.92; H, 8.26.

Preparation of 1-amino-3-(β-hydroxyethoxy)-2-propanol (V). Twenty-five grams of (II) was added to 2.5 liters of concentrated ammonium hydroxide. The reaction mixture was allowed to stand at room temperature for 5 hours; then the water and ammonia were removed by evaporation on a steam-bath. The residue was distilled. A very small amount (1 g.) distilled below 141° at 2–4 mm. The main portion (23 g., 81% yield) distilled from 141–144° at 2–4 mm. The amine is extremely hygroscopic and readily absorbs carbon dioxide from the air. These properties may account for the somewhat low nitrogen content of the substance.

Anal. Calc'd for $C_5H_{13}NO_3$: N, 10.35. Found: N, 9.44.

Preparation of 1-dimethylamino-3-(β-hydroxyethoxy)-2-propanol (VI). The method used for this preparation was similar to that which Rider and Hill (2) used for the preparation of 1-dimethylamino-2,3-propanediol. Thirty grams (0.25 mole) of epoxide (II) was slowly added to 60 g. of dimethylamine solution (30% solution obtained from Commercial Solvents

Corporation) in a 200-cc. three-necked flask fitted with a stirrer and a reflux condenser. Since the reaction was slightly exothermic, the reaction vessel was cooled with ice-water. The reaction mixture was stirred for two hours at room temperature after the addition of the epoxide was complete; then the water was removed on a steam-bath. The residue was distilled at 1–2 mm. A few cubic centimeters boiled below 102°. The main fraction, 34.5 g., distilled at 102–105°; (n_D^{20} 1.4638). The yield was 85%. This material was analyzed without further purification.

Anal. Calc'd for $C_7H_{17}NO_3$: N, 8.57. Found: N, 7.87.

Preparation of 2-hydroxymethyl-1,4-dioxane (VII). Thirty-nine grams of epoxide (II) was placed in a flask fitted with a reflux condenser, and 1.3 cc. of concentrated sulfuric acid was added, a few drops at a time. Much heat was evolved at each addition of sulfuric acid. The reaction mixture was then heated on a steam-bath for 6 hours. The thick, syrupy reaction product was transferred to a Claisen flask and 4 g. of barium carbonate added. After the evolution of carbon dioxide had ceased, the material was distilled. Two fractions were collected: (a) 10 cc. (b.p. 94–96° at 9 mm.); (b) higher-boiling material which appeared to decompose when heated to 200° at 3–4 mm. Fraction (b) was probably a linear condensation product of the epoxide compound. Fraction (a) was the 2-hydroxymethyl-1,4-dioxane (VII). This fraction was redistilled, and the material which boiled at 92–93° at 8 mm. was used for analysis; n_D^{20} 1.4617.

Anal. Calc'd for $C_5H_{10}O_3$: C, 50.80; H, 8.55.
Found: C, 50.57; H, 8.34.

Preparation of dinitrobenzoate of 2-hydroxymethyl-1,4-dioxane. Two cubic centimeters of the material boiling at 92–93° under 8 mm. pressure was treated with 0.7 g. of 3,5-dinitrobenzoyl chloride in the manner of Shriner and Fuson (3). The 3,5-dinitrobenzoate was crystallized three times from alcohol-water. The compound melted at 106–108° (dec.).

Anal. Calc'd for $C_{12}H_{12}N_2O_8$: N, 8.97. Found: N, 9.27.

Preparation of 1-ethoxy-3-(β-hydroxyethoxy)-2-propanol (IX) and 2-hydroxymethyl-1,4-dioxane (VII). Potassium hydroxide pellets (85 g.) were added to 370 cc. of 95% ethyl alcohol. To the stirred solution (cooled to 0°), 200 g. of 1-chloro-3-(β-hydroxyethoxy)-2-propanol (I) in 100 cc. of alcohol was slowly added. The reaction mixture was stirred for 14 hours, after which the potassium chloride which had formed was removed by filtration. This potassium chloride was washed several times with ethyl alcohol, and the washings added to the original filtrate. The excess potassium hydroxide in the filtrate was neutralized (phenolphthalein) with alcoholic hydrogen chloride. The alcoholic solution was then treated with an excess of solid anhydrous potassium carbonate. The solid was collected on a filter, and the alcohol removed from the filtrate by distillation through a one-foot column at 30° and 76–78 mm. pressure. After most of the alcohol had been removed, the solution was transferred to a modified 500-cc. Claisen flask and distilled at 2 mm. pressure. The following major fractions were collected: (a) 40.1 g. = 27% (b.p. 88–93°) identified as 2-hydroxymethyl-1,4-dioxane; (b) 31 g. = 15% (b.p. 115–122°) identified as 1-ethoxy-3-(β-hydroxyethoxy)-2-propanol (IX); (c) (b.p. 137–165°) identified as material consisting largely of unreacted chloro compound. There was a higher-boiling residue which was not distilled. Fraction (a) was redistilled at 87–88° at 1–2 mm. It had the correct index of refraction (n_D^{20} 1.4611) and composition for IX.

Anal. Calc'd for $C_7H_{16}O_4$: C, 51.19; H, 9.81.
Found: C, 50.61; H, 9.41.

In order to prove the structure of VII, 25 g. of fraction (a) (b.p. 88–93° at 2 mm.) was treated with 2.5 liters of concentrated ammonium hydroxide. After the mixture had stood for 7 hours, the ammonia and water were removed by evaporation. The residue was distilled. Practically all of it distilled at 88–93° under 2 mm. pressure (n_D^{20} 1.4618). Since this material was not the amino compound (b.p. 141° at 1 mm.), the original material must have been the dioxane derivative rather than the epoxide.

An attempt was made to effect the isomerization of the epoxide (II) to 2-hydroxymethyl-1,4-dioxane by refluxing the material at atmospheric pressure (220–230°) for 1.5 hours. A

fraction boiling at 78–82° under 3–4 mm. pressure (n_D^{20} 1.4618) was thus obtained; this material was presumably the dioxane derivative or the isomeric 3-(β-hydroxyethoxy)-2-propional derivative. The yield was 30%. The major portion of the epoxy compound was converted to higher-boiling materials.

Other attempts to convert the epoxide to the dioxane derivative were made by using acids or bases in ether solution. In these experiments, the major portion of the starting material was recovered practically unchanged.

SUMMARY

Eight new compounds derived from 1-chloro-3-(β-hydroxyethoxy)-2-propanol are described.

CHICAGO, ILL.

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[Contribution from the Bureau of Entomology and Plant Quarantine, Agricultural Research Administration, U. S. Department of Agriculture]

THE INSECTICIDAL PRINCIPLE IN THE FRUIT OF THE AMUR CORKTREE[1]

MILTON S. SCHECHTER and H. L. HALLER

Received February 4, 1943

The Amur corktree, or velvet tree (*Phellodendron amurense* Rupr.), native to several Asiatic countries, was introduced into this country in 1856 (1). Specimen trees may be found in Washington, D. C., and Boston, Mass. The dioecious flowers appear in May and June, and the fruit ripens in September and October.

From the bark of the tree, used in Japan as a tonic and stomachic, the alkaloids berberine and palmatine, a phytosterol, the ketone obacunone, and the dilactone obaculactone have been isolated (2, 3, 4). Obaculactone has been shown to be identical with limonin, a constituent of citrus pulp and seeds (5). Under present conditions the bark may be useful in the cork industry (6).

The habits of the tree indicate that it has possibilities as a soil-erosion-control plant, but commercial uses for the fruit, which has a pronounced aromatic odor, remain undeveloped. The volatile oil of the fruit has been shown to consist principally of myrcene, together with a small amount of methyl-*n*-nonyl ketone and geraniol (7); and an extract of the nonvolatile residue was found to be toxic to mosquito and codling moth larvae and houseflies (8). The insecticidal value was sufficient to warrant further studies of the fruit, and this paper reports the progress that has been made.

The active principle has not been isolated, but a fraction highly toxic to houseflies[2] has been prepared by the following procedure: The crushed fruit was washed with warm water to remove water-soluble material, and then dried, ground, and extracted with low-boiling petroleum ether. The oily extract remaining after removal of the solvent was shaken with ethanol, which preferentially dissolved the toxic constituent. On saponification of the ethanol solution, the unsaponifiable portion was toxic, and the acids relatively nontoxic. Cooling a methanol solution of the unsaponifiable matter to 0° and centrifuging removed some waxy material, which was probably a mixture of sterols and hydrocarbons. The remaining unsaponifiable portion was allowed to react with phthalic anhydride to remove alcohols. The fraction that did not react was found to be toxic, and the alcohol fraction regenerated from the half-esters was not. The toxic fraction, upon distillation in a modified pot-type of molecular still, yielded several fractions, the one distilling with the bath temperature at 100–150° being the most toxic. This fraction was a yellow oil which could not be made to crystallize and

[1] The chemical tests reported in this paper were made by the Division of Insecticide Investigations, and the entomological tests by the Division of Control Investigations, of the Bureau of Entomology and Plant Quarantine. The fruit of the Amur corktree was supplied by the Division of Hillculture of the Soil Conservation Service.

[2] For convenience the preliminary tests were carried out in acetone solution. It was later found that all the fractions showed little or no toxicity when tested in highly refined kerosene, such as is used in household fly sprays.

from which no crystalline derivative, such as a semicarbazone, 2,4-dinitrophenylhydrazone, phenylurethan, or 3,5-dinitrobenzoate, could be prepared.

While the above procedure gives a highly potent fraction and permits an insight into the chemical nature of the toxic principle, a highly toxic fraction has also been obtained by directly distilling the petroleum-ether extract in a molecular still.

The toxic principle, not being inactivated by treatment with alkali, is different from other naturally occurring insecticides, such as the pyrethrins and rotenone, the absence of which was confirmed by qualitative tests.

Extracts of the fruit were also highly toxic to goldfish. Five milligrams of a petroleum-ether extractive dissolved in 1 cc. of acetone and diluted to 1 liter with water (5 p.p.m.) killed a goldfish in 1 hour; 20 mg. per liter killed a goldfish in 15 minutes.

EXPERIMENTAL

The small, berrylike fruit, collected from trees in Washington, D. C., was crushed in a meat grinder, placed in cloth bags, and washed with warm water to remove water-soluble materials. After being dried and ground, it was extracted with low-boiling petroleum ether. Removal of the solvent left an oily extract having the following properties: d^{26} 0.937; n_D^{26} 1.487; iodine number 184; unsaponifiable matter 21%. The yield of oil ranged from 3 to 19% of the washed and dried fruit, depending on the time of year, the yield being highest when the fruit was collected in October and November. Limonin (obaculactone) (3), $C_{26}H_{30}O_8$, m.p. 299–300°, was obtained from the petroleum-ether-extracted marc by extraction with acetone and recrystallization from acetone plus ethanol. This compound is insecticidally inert.

Unsaponifiable fraction. One hundred fifty grams of a petroleum-ether extractive was shaken with three successive 200-cc. portions of 95% ethanol and centrifuged to break emulsions. The ethanol solutions were combined, and 15 g. of potassium hydroxide in 25 cc. of water was added. The solution was refluxed for several hours, and after standing at room temperature overnight most of the alcohol was removed by steam distillation, the volume being reduced to about 450–500 cc. at the same time. The solution was cooled and extracted with ether for about 5 hours in a continuous extractor. The ether was changed and the extraction was continued overnight. The ether solutions were thoroughly washed with water, combined, and dried over anhydrous sodium sulfate, and the solvent was removed. About 15 g. of the unsaponifiable fraction was obtained. It was considerably more toxic to houseflies than the original extract.

Acidic fraction. The ether-extracted alkaline solution was made acid to Congo red paper with dilute sulfuric acid, a slight excess being added. It was then extracted with ether in a continuous extractor; the ether solution was washed and dried over anhydrous sodium sulfate, and the solvent was removed. About 33 g. of an acidic brown oil was obtained, which, being nontoxic, was not further investigated.

Reaction with phthalic anhydride. Fifty-eight grams of the unsaponifiable fraction was dissolved in 150 cc. of hot methanol, cooled to 0°, and centrifuged at that temperature to remove several grams of waxy material, probably a mixture of sterols and hydrocarbons. The waxy material gave a strong Lieberman-Burchard test, and by fractional crystallization from methanol-acetone a small amount of phytosterol (probably a sitosterol), m.p. 137–138°, was obtained. Evaporation of the methanol left 52.3 g. of a brown, viscous liquid, which in acetone solution was toxic to flies. Forty-one and one-half grams of this liquid was allowed to react with 42 g. of phthalic anhydride and 20 cc. of pyridine for 24 hours at 120°. The warm reaction mixture was poured into 500 cc. of hot dilute hydrochloric acid (25 cc. conc'd HCl + 475 cc. H_2O). The solution was heated to boiling with stirring, and then cooled and decanted from the brown gum. The gum was extracted with three 500-cc.

portions of boiling water and then dissolved in 1500 cc. of warm ether. The ether solution was extracted three times with 5% sodium carbonate solution and then twice with water. The combined sodium carbonate solutions were extracted with ether to remove any contamination mechanically entrained. The ether solutions were combined, washed successively with dilute hydrochloric acid (1:20) and water, and dried over anhydrous sodium sulfate, and the solvent was removed. Fourteen and eight-tenths grams of brown viscous oil was obtained. This portion of unsaponifiable fraction, which did not react with phthalic anhydride, was very toxic to flies.

The sodium carbonate solution was kept ice-cold and carefully neutralized with sulfuric acid (1:1), with stirring, and then 10 cc. excess was added. A brown gummy oil separated. The mixture was extracted with ether, the ether solution washed with water and dried over anhydrous sodium sulfate, and the solvent removed. Thirty-two and nine-tenths grams of a dark brown gum consisting of phthalic half-esters was obtained. This gum was saponified by dissolving in 500 cc. of ethanol and adding 30 g. of potassium hydroxide in 15 cc. of water. After the mixture had stood at room temperature overnight, 30 cc. of water was added to dissolve the crystals (probably potassium acid phthalate) and the solution refluxed for two hours. Much of the ethanol was removed by distillation, and the remainder by steam distillation. The oil left in the distillation flask was extracted with ether. The ether solution was washed, dried, and evaporated; 17.4 g. of a brown viscous liquid, which consisted of the regenerated alcohols, remained. This fraction was nontoxic to flies.

Molecular distillation of fraction that did not react with phthalic anhydride. Thirteen grams of the portion of unsaponifiable matter that did not react with phthalic anhydride was distilled in a modified pot-type of molecular still. Three fractions and the still residue were obtained as follows (temperatures refer to bath temperatures, not to boiling points):

(A) 85–100°, oil-pump alone, 5.1 g. of pale green, fluid oil, nontoxic to flies.

(B) 100–150°, oil-pump plus mercury-pump, 2.4 g. of yellow viscous oil, very highly toxic to flies.

(C) 150–200°, oil-pump plus mercury-pump, 2.1 g. of yellow, viscous oil, nontoxic to flies.

(D) Still residue, nontoxic to flies.

Fraction A seemed to consist largely of sesquiterpenes. It gave a strong positive Sabetay azulogenic test (9).

Fraction B contained practically all the toxic principle. It could not be made to crystallize, nor could any crystalline derivative, such as a semicarbazone, 2,4-dinitrophenylhydrazone, phenylurethan, or 3,5-dinitrobenzoate, be prepared from it.

It is of interest that by the Lieberman-Burchard test the petroleum-ether extracts and many of the fractions obtained therefrom, including all the toxic ones, gave a characteristic red color with green fluorescence, with an absorption band in the green at 550 mμ. This color reaction is very similar to that given by many triterpenoids, such as *alpha-* and *beta-*amyrin and hederagenin. The amount of red color, as measured by a photometer with appropriate filters, could not be correlated with toxicity to flies.

The relative toxicities of some of the fractions to houseflies are given below. The tests were carried out in acetone solution, because even the most potent fractions exhibit little or no toxicity in high-boiling kerosene. The fractions were tested at a concentration of 50 mg. per cubic centimeter.

Petroleum-ether extractive	Slightly toxic
Unsaponifiable fraction	Toxic
Unsaponifiable fraction freed of waxes	Toxic
Fraction of unsaponifiable that did react with phthalic anhydride (regenerated alcohols)	Nontoxic
Fraction of unsaponifiable that did not react with phthalic anhydride	Highly toxic
Fraction A, molecular distillate	Nontoxic
Fraction B, molecular distillate	Very highly toxic
Fraction C, molecular distillate	Nontoxic
Still residue of molecular distillate	Nontoxic

The toxicity of the petroleum-ether extractives varies with the source and with the time of year at which the fruit is collected and may range from 25 to 80%. The fruit of a related species, *Phellodendron lavallei*, has also been found toxic. More complete entomological results will be published elsewhere.

SUMMARY

1. An attempt has been made to isolate the insecticidal principle from the fruit of the Amur corktree (*Phellodendron amurense* Rupr.).
2. The unsaponifiable portion of the oil is very toxic to houseflies in acetone solution but not in high-boiling kerosene.
3. The toxic principle does not react with phthalic anhydride.
4. No crystalline derivatives of the toxic constituent could be obtained.
5. Potent concentrates may be obtained by molecular distillation.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BOSTON UNIVERSITY]

REACTIONS OF 4-(2-CHLOROETHYL)MORPHOLINE AND RATES OF REACTION OF 4-(2-CHLOROETHYL)MORPHOLINE AND OTHER HALIDES WITH SODIUM PROPOXIDE

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Since the observation by Mason and Block (1) that 4-(2-chloroethyl)morpholine reacts with alcohols and water, it has been found that this halide reacts fairly readily with sodium alkoxides, ammonia, and amines (2). This paper describes the reactions of 4-(2-chloroethyl)morpholine with (a) sodium sulfite to form sodium 2-(4-morpholino)ethyl sulfonate, (b) phenylmagnesium bromide to form 4-(2-phenylethyl)morpholine and (c) diethyl malonate to form diethyl-2-(4-morpholino)ethyl malonate.

TABLE I

COMPOUND	AVERAGE VELOCITY CONSTANT	HALF-LIFE PERIOD (MINUTES)
Benzyl chloride	170×10^{-6}	93
4-(2-Chloroethyl)morpholine	33×10^{-6}	530
2-Chloroethylbenzene	23×10^{-6}	700
1-Chlorobutane	2.3×10^{-6}	5,300
2-Chloroethoxybenzene	1.9×10^{-6}	8,200
2-Chloroethyl ether	1.1×10^{-6}	15,300

Since 2-chloroethyl ether was found to be comparatively unreactive (3), it was thought desirable to determine the relative rates of reaction of 4-(2-chloroethyl)morpholine, 2-chloroethyl ether, benzyl chloride, 2-chloroethylbenzene, 1-chlorobutane, and 2-chloroethoxybenzene with sodium propoxide. The reaction was found to be a second-order reaction, and the velocity constants were calculated from the equation $k = \frac{x}{ta(a - x)}$. The half-life period was calculated from the equation $t_{\frac{1}{2}} = \frac{1}{ka}$. The average velocity constants and the half-life periods are given in Table I. These results, shown graphically in Figure 1, indicate that 4-(2-chloroethyl)morpholine is less reactive than benzyl chloride toward sodium propoxide. However 4-(2-chloroethyl)morpholine is more reactive than 2-chloroethylbenzene and very much more reactive than 1-chlorobutane, 2-chloroethoxybenzene and 2-chloroethyl ether toward sodium propoxide.

EXPERIMENTAL

Sodium 2-(4-morpholino)ethyl sulfonate. One-tenth mole (14.95 g.) of freshly distilled 4-(2-chloroethyl)morpholine (1) was added to a solution of 0.15 mole (18.9 g.) of sodium sulfite dissolved in 200 cc. of water. The mixture was heated on a hot-plate under a reflux

condenser for one and one-half hours. This solution was transferred to a large evaporating dish and was evaporated to dryness on a steam-bath. The residue was dried in an oven at 105° for about two hours. The solid was finely ground and extracted with 150 cc. of boiling 95% alcohol, followed by seven more extractions with boiling alcohol, using 50 cc. for each extraction. The alcohol was removed from the combined extracts, and the residue was dissolved in the minimum amount of boiling alcohol. The solution was decolorized with

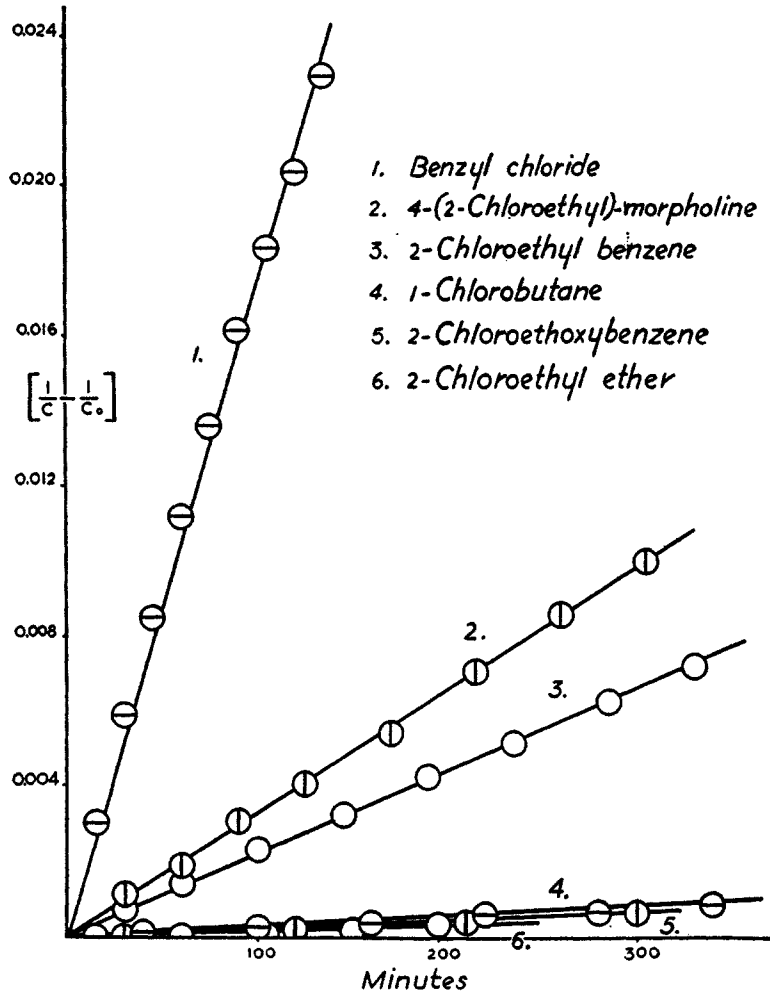

FIG. 1

Norit and filtered hot. From the cold filtrate, 17.5 g. (81%) of white crystals was obtained. An additional 2 g. was obtained from the mother liquor by evaporation, redissolving, and decolorizing with Norit. Total yield, 90%.

Anal. Calc'd for $C_6H_{12}NNaO_4S$: N, 6.45. Found: N, 6.40, 6.41.

Picrate of 2-(4-morpholino)ethylsulfonic acid. Ten cubic centimeters of a saturated alcoholic solution of picric acid was added to 0.5 g. of sodium 2-morpholinoethyl sulfonate dissolved in 5 cc. of hot alcohol. The mixture was heated to boiling on the steam-bath and

allowed to cool. The crystals which separated were recrystallized from ethyl alcohol, and melted at 178.8–182.0°.

Anal. Calc'd for $C_{12}H_{16}N_4O_{11}S$: N, 13.20. Found: N, 13.33, 13.24.

4-(2-Phenylethyl)morpholine. Phenylmagnesium bromide was prepared from 6 g. of magnesium, 39.3 g. of bromobenzene, and 150 cc. of absolute ether. After complete addition of the bromobenzene, the reaction mixture was refluxed on a water-bath for one hour. Most of the ether was removed by distillation. The reaction mixture was heated on a steam-bath under a reflux condenser while 14.95 g. (0.1 mole) of freshly distilled 4-(2-chloroethyl)morpholine was added slowly with constant stirring. The mixture was refluxed for an additional hour and then decomposed with dilute sulfuric acid. The small upper layer was removed and the aqueous layer was extracted several times with ether. After filtering the aqueous layer, 25 g. of ammonium chloride was dissolved in it, and the solution was made strongly alkaline by the addition of concentrated ammonium hydroxide. The light yellow, upper layer was extracted with 50 cc. of ether, and the water layer was extracted with three 20-cc. portions of ether. After drying the ether extracts over calcium chloride, the ether was distilled and the residue distilled under reduced pressure. The 4-(2-phenylethyl)morpholine (4) distilled at 132–135° (5 mm.). The yield was 5.9 g., or 31%. The picrate melted at 170° and a mixed melting point determination with some known 4-(2-phenylethyl)morpholine picrate (4) was also 170°.

Diethyl-2-(4-morpholino)ethyl malonate. Two-tenths of a mole (4.6 g.) of sodium was added to 125 cc. of absolute ethyl alcohol in a 500 cc. round-bottomed, three-necked flask equipped with a mechanical stirrer, a dropping-funnel, and a reflux condenser. After the solution had cooled, 0.6 mole (96.0 g.) of diethyl malonate was added. A substantial excess of diethyl malonate was found to be necessary in order to obtain a satisfactory yield. The mixture was heated in an oil-bath to refluxing temperature, and 0.2 mole (29.9 g.) of freshly distilled 4-(2-chloroethyl)morpholine was added dropwise, with constant stirring, finally refluxing for twenty minutes. Dry hydrogen chloride gas was passed into the reaction mixture until the solution was acidic. As much alcohol as possible was removed by distillation under reduced pressure, keeping the flask in a water-bath heated to 45°. To the residue was added 150 cc. of water. The upper layer of unreacted diethyl malonate was removed and the aqueous layer was extracted several times with ether. The solution was made strongly alkaline with 30% sodium hydroxide solution. The upper layer was removed, and the alkaline solution was extracted with five 25-cc. portions of ether. The ether extracts and the upper layer were combined, dried over Drierite and the ether removed by distillation. The residue was fractionally distilled under reduced pressure. A fraction weighing 33 g., (60% yield) was collected at 168–176° (4 mm.). Diethyl-2-(4-morpholino)-ethyl malonate is a viscous, slightly yellow liquid which is insoluble in water, but readily soluble in alcohol, ether, and benzene.

Anal. Calc'd for $C_{13}H_{23}NO_5$: N, 5.13; Neut. equiv. 273.
Found: N, 4.96, 5.09; Neut. equiv. 269, 268.

Attempts to make a picrate, 3,5-dinitrobenzoate, *p*-toluenesulfonate, and a quaternary methyl *p*-toluenesulfonate of diethyl-2-(4-morpholino)ethyl malonate resulted in the formation of liquids. However, a solid derivative was obtained with methyl iodide.

Diethyl-2-(4-morpholino)ethyl malonate methiodide. Equivalent parts of diethyl-2-(4-morpholino)ethyl malonate and methyl iodide were mixed and warmed over a flame for several minutes. After standing in the refrigerator overnight, a solid separated. This was filtered and recrystallized from ethyl acetate; m.p. 92.2° (corr.).

Anal. Calc'd for $C_{14}H_{26}INO_5$: N, 3.37. Found: N, 3.38, 3.41.

Apparatus used for determining reaction rates. The constant-temperature bath was a large porcelain crock which was placed in a wooden box and insulated with asbestos. The bath was heated with a heating coil which was controlled by a thermostat, the masthead of which was in the bath. A mechanical stirrer was used to maintain a uniform temperature throughout the bath. The temperature was kept constant at 50.6° ± 0.2°. The reaction flask was a 500 cc. Morton (5) creased flask which was partially immersed in the water-bath.

The flask was equipped with a reflux condenser, a mechanical stirrer, and a short water condenser, the inner tube of which was so arranged that it dipped beneath the surface of the liquid contained in the flask. This inner tube was wide enough and of sufficient length to admit a pipette so that samples could be withdrawn at any desired time without any appreciable loss due to vaporization.

TABLE II

BENZYL CHLORIDE

TIME, MIN.	$a-x$	x	$\frac{1}{a-x}$	$\frac{1}{a-x}-\frac{1}{a}$	k
0	62.84		0.01591		
5	59.23	3.61	.01688	0.00097	1.9×10^{-4}
10	55.50	7.34	.01802	.00211	2.1
15	52.85	9.99	.01892	.00301	2.0
20	50.42	12.42	.01983	.00392	2.0
25	48.09	14.75	.02079	.00488	2.0
30	46.00	16.84	.02174	.00583	1.9
35	44.21	18.63	.02262	.00671	1.9
40	42.64	20.20	.02345	.00754	1.9
45	41.15	21.69	.02430	.00839	1.9
50	39.95	22.89	.02503	.00912	1.8
55	38.18	24.66	.02619	.01028	1.9
60	37.14	25.70	.02692	.01101	1.8
65	35.65	27.19	.02805	.01214	1.9
70	34.91	27.93	.02865	.01274	1.8
75	34.09	28.75	.02933	.01342	1.8
80	33.07	29.77	.03024	.01433	1.8
85	32.20	30.64	.03106	.01515	1.8
90	31.42	31.42	.03183	.01592	1.8
95	30.41	32.43	.03288	.01697	1.8
100	30.11	32.73	.03321	.01730	1.7
105	29.42	33.42	.03399	.01808	1.7
110	28.64	34.20	.03492	.01901	1.7
115	28.20	34.64	.03546	.01955	1.7
120	27.39	35.45	.03651	.02060	1.7
125	27.12	35.72	.03687	.02096	1.7
130	26.54	36.30	.03768	.02177	1.7
135	25.94	36.90	.03855	.02264	1.7
140	25.48	37.36	.03925	.02334	1.7
145	24.79	38.05	.04034	.02443	1.7
150	24.17	38.67	.04137	.02546	1.7

Procedure. One-tenth mole (2.3 g.) of sodium was added to 190 cc. of *n*-propyl alcohol. While the sodium was reacting and the solution was reaching the temperature of the bath, 0.1 mole of the halide and 10 cc. of *n*-propyl alcohol, in separated containers, were also allowed to reach the temperature of the bath. At minus thirty seconds, the halide was poured down the tall reflux condenser and the inner tube was washed with the 10-cc. portion of *n*-propyl alcohol. At zero time and after desired intervals, a sample of a little more than 5 cc. was withdrawn through the short water condenser. The samples were placed immediately in an ice-cold test tube immersed in an ice-bath, in order to stop the reaction.

After standing in the ice-bath for twenty minutes, exactly 5 cc. of the cold sample was withdrawn from the test tube in a volumetric pipette, and the sample was allowed to drain into 25 cc. of water in a 250 cc. Erlenmeyer flask. The free alkali was titrated with standard hydrochloric acid, using methyl red as the indicator. Typical experimental results are given in Tables II and III. In the tabulations of the results, a represents the mg. of sodium hydroxide present at zero time, $a - x$ the mg. of sodium hydroxide present in subsequent samples, and x the mg. of sodium hydroxide representing the amount of sodium propoxide which has reacted. The reciprocal of $a - x$ is given in the tables and also the difference

TABLE III

4-(2-CHLOROETHYL)MORPHOLINE

TIME, MIN.	$a-x$	x	$\frac{1}{a-x}$	$\frac{1}{a-x}-\frac{1}{a}$	k
0	56.99		0.01755		
10	55.65	1.34	.01797	0.00042	4.1×10^{-5}
20	54.64	2.35	.01830	.00075	3.8
30	53.51	3.48	.01869	.00114	3.8
40	52.79	4.20	.01894	.00139	3.5
50	52.07	4.92	.01920	.00165	3.3
60	51.46	5.53	.01943	.00188	3.1
70	50.82	6.17	.01968	.00213	3.0
80	49.14	7.85	.02035	.00280	3.5
90	48.56	8.43	.02059	.00304	3.4
100	47.73	9.26	.02095	.00340	3.4
110	46.97	10.02	.02129	.00374	3.4
125	46.39	10.60	.02156	.00401	3.2
140	45.35	11.64	.02205	.00450	3.2
155	44.25	12.74	.02260	.00505	3.3
170	43.72	13.27	.02287	.00532	3.1
185	42.71	14.28	.02341	.00586	3.2
200	41.95	15.04	.02384	.00629	3.1
215	41.19	15.80	.02428	.00673	3.1
230	40.17	16.82	.02489	.00734	3.2
245	39.56	17.43	.02528	.00773	3.2
260	38.45	18.54	.02601	.00846	3.3
275	37.70	19.29	.02653	.00898	3.3
290	37.30	19.69	.02681	.00926	3.2
308	36.53	20.46	.02737	.00982	3.2
320	35.76	21.23	.02796	.01041	3.3

between the reciprocal of $\frac{a-x}{1}$ and the reciprocal of a. This difference is plotted in Figure 1 as $\frac{1}{c} - \frac{1}{c_0}$ against time.

One experiment was performed to determine the identity of the product. One-tenth of a mole (14.95 g.) of freshly distilled 4-(2-chloroethyl)morpholine was added to 200 cc. of n-propyl alcohol to which 2.3 g. of metallic sodium had been added. The mixture was heated in a water-bath at 50° for eleven hours. The reaction mixture was treated according to the method described by Mason and Malkiel (2). An 82% yield of morpholinoethyl n-propyl ether was obtained.

SUMMARY

The reactions of 4-(2-chloroethyl)morpholine with sodium sulfite, phenylmagnesium bromide, and diethyl malonate have been reported.

A comparison has been made of the rates of reaction of 4-(2-chloroethyl)morpholine and five other halides with sodium propoxide.

BOSTON, MASS.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

THE PORPHYRIN-LIKE PRODUCTS OF THE REACTION OF PYRROLE WITH BENZALDEHYDE[1]

S. ARONOFF AND M. CALVIN

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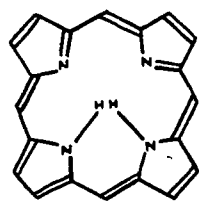
Following the verification (5, 6) of Küster's general conception of the porphyrin ring, chemists have sought for the two isomers:



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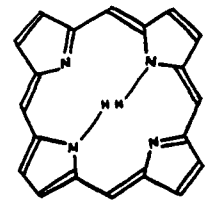

II

Rothemund (12) announced the separation of porphine into two isomers and later (13, 14) extended the porphyrin isomers to embrace various meso-[2] (methine-C) substituted compounds, including the tetraphenylporphyrins. In the latter cases, however, the actual isolation and analysis of the several forms has not been reported. The existence of the isomerism is inferred from differences in absorption spectra and acidity. The representation of these forms as isomers of the type of I and II is open to numerous objections and it was the purpose of the present research actually to isolate and establish the nature of the various forms.

The yields of porphine from pyrrole and formaldehyde are so poor that an investigation is extremely tedious. On the contrary, the yields of tetraphenylporphine are sufficiently large to permit of a relatively large source of material. The latter compound was therefore chosen for investigation.

Preparation of material. In a bomb tube of *ca.* 40 cc. capacity were mixed 5 cc. of redistilled pyrrole, 10 cc. of pyridine,[3] and 10 cc. of benzaldehyde. Nitrogen was bubbled through the solution for one-half hour to remove the oxygen and the tubes were sealed. The bombs were placed in a pipe jacket which was in turn suspended in a larger Pyrex tube containing a high-boiling liquid, whose b.p. determined the temperature of the bath. Temperatures tested included 100°, 165°, 190°, 220°, and 245°. The time for which experiments were run varied from five days at the first temperature to eighteen hours at the last. Optimum yields (*ca.* 10% on the basis of pyrrole) were obtained in 48 hours at 190–220°. Filtra-

[1] Abstracted from the thesis submitted by S. Aronoff in partial fulfillment of the degree of Doctor of Philosophy, May, 1942.

[2] The implications of the term "meso" used in this connection have no relation to its use for the vinyl-hydrogenated chlorophyll derivatives.

[3] Although pyridine was used as solvent in most preparations, the substitution of pyridine by quinoline did not alter the product. These bases therefore do not enter into the structure of the end-products.

tion of the tube contents resulted in purple crystals with properties very similar to those described by Rothemund except for the variable height of band 1 in the absorption spectrum. The products obtained at different temperatures were analytically identical and corresponded to $C_{44}H_{30}N_4$.

For analysis, material was twice recrystallized from benzene with the following results:

Anal. Calc'd for $C_{44}H_{30}N_4$: C, 85.96; H, 4.92; N. 9.12.

Found: (for prep'n at 245°) C, 86.10, 85.99; H, 4.74, 4.73; N, 9.29, 9.46.
(for prep'n at 220°) C, 85.75, 85.80; H, 4.75, 4.81; N, 9.24, 9.33.
(for prep'n at 190°) C, 85.7, 85.6; H, 4.94, 4.89;
(190°, quinoline) C, 85.7, 85.6; H, 4.95, 4.92.

Spectroscopically they ranged from types 4,3,2,1[4] (at 100° and 165°) to 1,4,3,2 (at higher temperatures). It was therefore certain that at least two substances were being formed.

The crystals obtained from the original reaction mixture were further separated into components by chromatographic adsorption on talc using trichloroethylene as solvent. At least six zones appear in the chromatogram (Plate 1) four of which could be separated mechanically. These were eluted with pyridine and the eluate transferred to benzene. The latter was washed with water, dried with sodium sulfate, and concentrated, resulting in crystals of the separate components. Rechromatogrammed individually, these gave only single bands. The spectra of the various components are shown in Figs. 1 and 2. The ratio of the yields of components A:B:(C + D + E + F) is about 10:4:1. It is obvious that the first published (1) curve for "*ms*-tetraphenylporphine" is the result of low temperature preparation, being almost pure component A (see Table I). The second published (2) curve contains considerable quantities of the other components since it represents a preparation at a higher temperature. The various components also show different crystalline structure when rapidly crystallized from methyl iodide (no quaternary nitrogen formed!) (See Plate 2).

Only components A and B were obtained separately in amounts sufficient to permit the determination of properties in addition to the absorption spectrum. The results are summarized in Table I.

Absorption spectra. The differences between the components are shown in their absorption spectra in the visible region. Rothemund has proposed H isomerism primarily on the similarity of the form of the absorption spectra, the essential difference between the isomers being a shift of all the bands of one of the compounds with respect to those of the other.

Isomeric fractions A and B (see Fig. 1) show, however, relatively small shifts in band positions but extreme variations in intensity of the first band. We are not aware of any true porphyrin which shows a 1,4,3,2 spectral type, as does fraction B. Type 4,3,2,1 on the contrary, as shown by fraction A, is similar to that shown by all etioporphyrins and other porphyrins with non-chromophoric β-substitutions (except porphine, which, as noted in the discussion, may itself be a mixture).

The spectra of the other fractions are intermediate between these two extremes. Most interesting is fraction F, in which the narrowness of the bands, characteristic of true porphyrins, is beginning to be lost.

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[4] In this paper verbal nomenclature of porphyrin spectral types will be replaced by numerical, as follows. The bands are numbered 1,2,3,4, on the basis of increasing frequency. Band types are then denoted by arranging band numbers in order of decreasing absorption coefficient. Thus:

"Etio" type, 4,3,2,1


"Chloro" type, 4,2,3,1


"Rhodo" type, 3,4,2,1

Experimental. Absorption spectra were measured in the usual manner with benzene as solvent. Two instruments were used, the Beckman photoelectric spectrophotometer, and the visual Bausch and Lomb Universal spectrophotometer. The spectra obtained checked closely both in positions and height of the maxima and minima.

Acid numbers. These were determined by extraction of ether solutions with aqueous HCl. The acid number is defined as the per cent of acid to extract two-thirds of the pig-

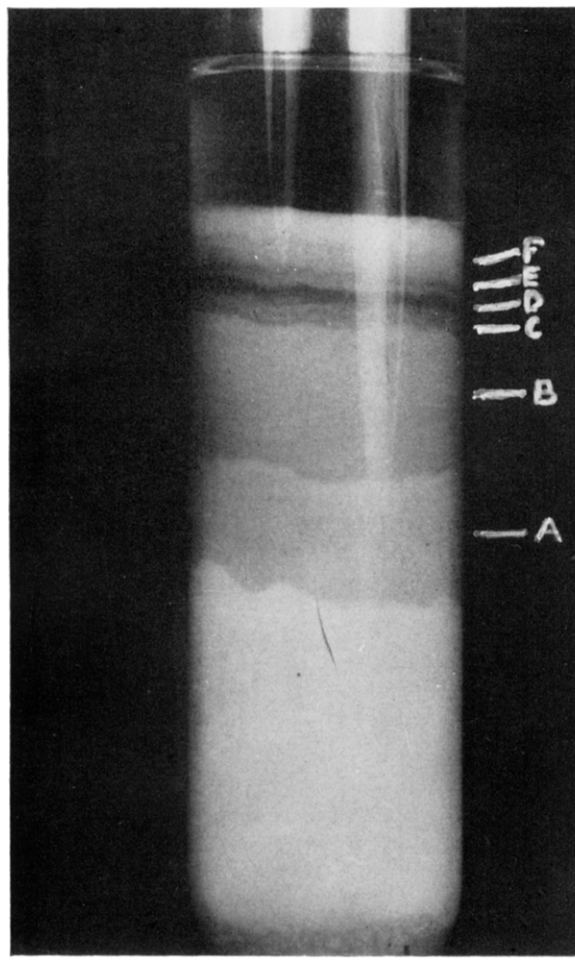


PLATE 1

MIXTURE CHROMATOGRAMMED ON TALC WITH TRICHLOROETHYLENE

Components as indicated

ment from ether (equal volumes of acid and ether). The results indicate, inasmuch as the hydrochloride of A is less soluble than B, that component B is a weaker base than component A. As a result of the spectroscopic titration it was found that the first acid dissociation constant of the disalt of B was greater than that of A. Since the monosalt of A exists over such a short range the acid number appears to be determined by the second acid dissociation constant of the salt, which is greater for A than for B.

Both components show reversible dissociation on heating their glacial acetic acid solutions, *i.e.*, when cool, the solution has an acid spectrum, when hot, a free base spectrum.

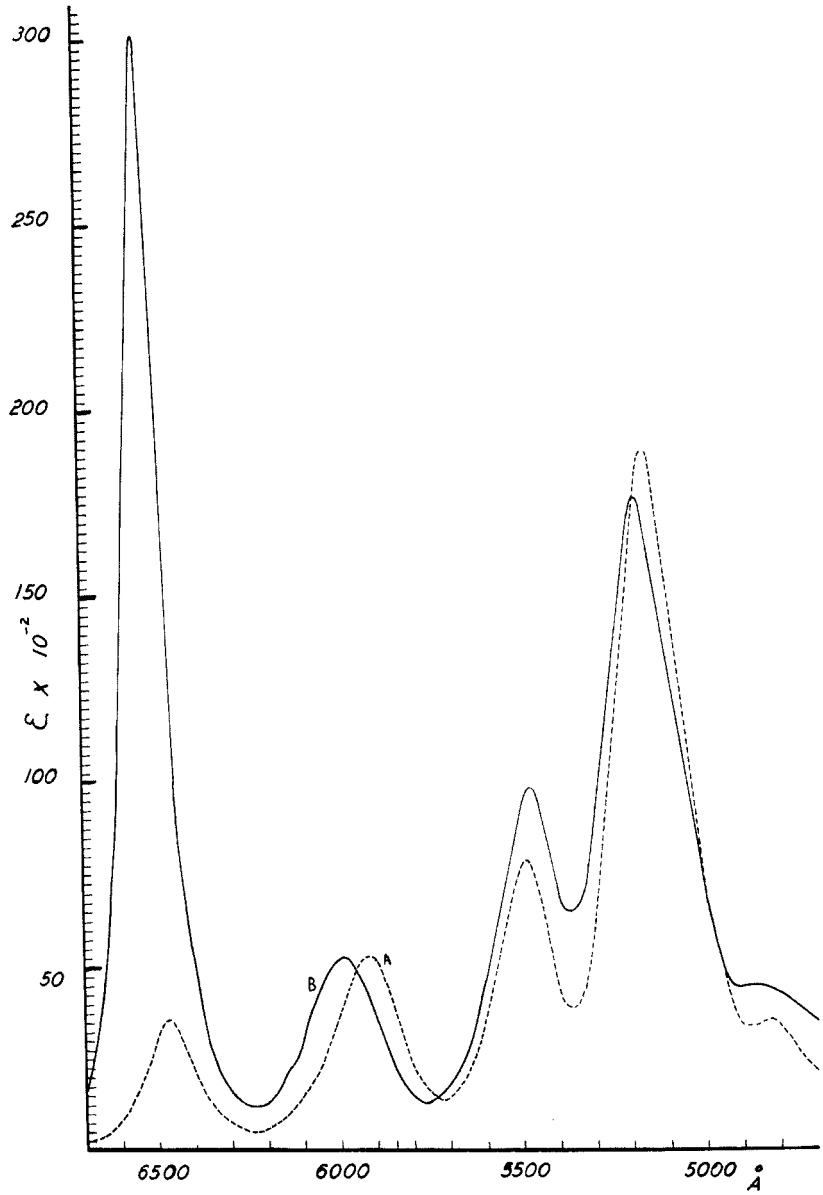


FIG. 1. FREE BASES
Components as indicated. Bands at 4000 Å not shown

Hydrochlorides. In contrast to Rothemund's results the hydrochlorides, prepared in the following manner, of the mixture were found to approach a disalt more closely than either a tri- or tetra- salt. The hydrochlorides of the original mixture were prepared by permitting the HCl extract of the ether solutions to stand a few days, at the end of which the salts had

completely precipitated, leaving a colorless aqueous acid solution. (The use of $CHCl_3$ and dry HCl gas as a means of hydrochloride preparation was avoided, since that solvent occasionally tends to add Cl to the molecule, aside from invalidating the analysis itself.)

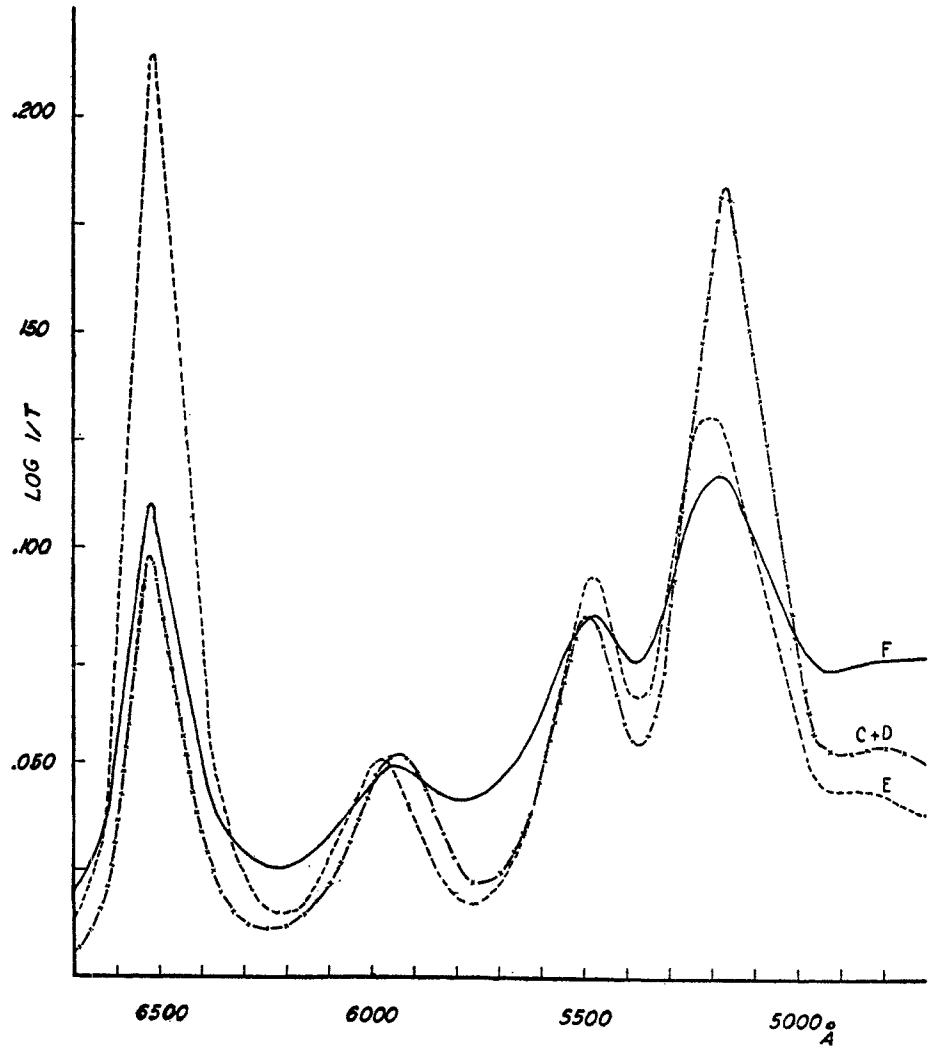


FIG. 2. FREE BASES

Components as indicated. Bands at 4000 Å not shown. Transmission plotted as log $1/T$ in a 1 cm. cell, since absolute concentration not known. Plotted for approximate equivalence at band 2.

The precipitate was washed until virtually acid-free, dried at 100° *in vacuo* (no dissociation occurred), and then analyzed.

Anal. Calc'd for P·HCl: C, 81.2; H, 4.61; Cl, 5.44.
for P·2HCl: C, 76.9; H, 4.40; Cl, 10.3.
for P·3HCl: C, 73.0; H, 4.18; Cl, 14.7.
Found: C, 74.8, 75.0; H, 4.61, 4.57; Cl, 8.12, 7.88.

The analysis for chlorine was done by the alkalimetric titration method, and is known to be giving low values.

On heating the hydrochlorides at atmospheric pressure, the HCl dissociates from the molecules and the original porphyrin is regenerated. The hydrochlorides of components A and B were separately prepared and then reconverted into the free base by heat. In each case the original free base was regenerated, as recognized by its absorption spectrum.

TABLE I

PROPERTIES OF COMPONENTS A AND B

PROPERTY	COMPONENT A	COMPONENT B
Spectral Type (free base)	4,3,2,1	1,4,3,2
Acid Number	13.5	19.5
Salt	(a) Hydrochloride extremely insoluble in H_2O (b) Regenerates original porphyrin on heating (c) $K_2 = 10^{-2}$; $K_1 = 10^{-2}$ (d) P·xH_2SO_4 stable in conc'd H_2SO_4	(a) Hydrochloride somewhat soluble in H_2O (b) Regenerates original porphyrin on heating (c) $K_2 \geqq 10^{-5}$; $K_1 \geqq 10^{-1}$ (d) P·xH_2SO_4 less stable in conc'd H_2SO_4
Cu Salts	1 band; 5400 Å	2 bands; 6150, 5400 Å
Solubility (in EtOH)	ca. 3×10^{-6} M/l	*ca.* 6×10^{-4} M/l
Crystal forms (from CH_3I)	prisms; twinned at *ca.* 110°	octahedral
Temp. of formation	lower temp. required	higher temp. required
Yields (% of total at optimum condition)	*ca.* 67%	*ca.* 27%

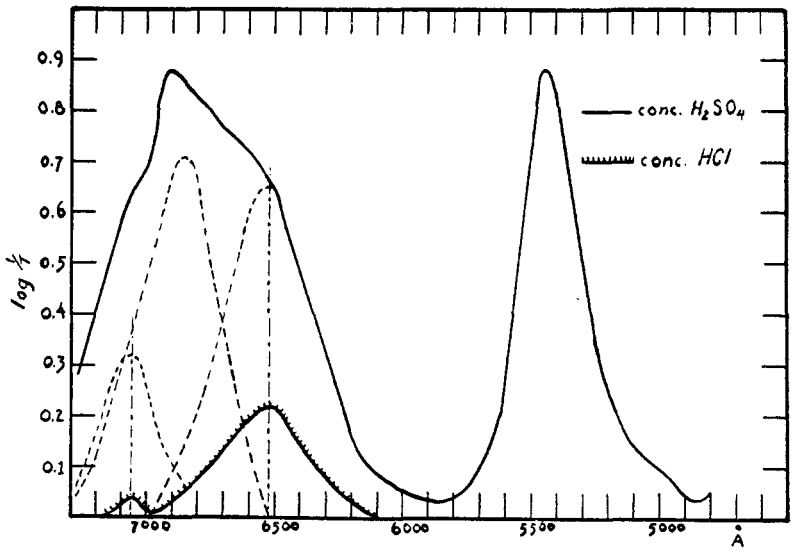


FIG. 3. SPECTRA OF EITHER A OR B IN CONC'D SULFURIC ACID AND CONC'D HYDROCHLORIC ACID

Dotted line indicates possible resolution of new band in conc'd sulfuric acid

Polyacid basicity. In addition to the spectrum of the free base of component A in an inert solvent, a different spectrum appears in dilute sulfuric acid or concentrated hydrochloric acid (see Fig. 3), and still a different one in concen-

trated sulfuric acid. Dilution of the conc'd acid solution results in reappearance of the dilute acid spectrum. Since these differences are far too great to be accounted for as mere physical effects of changing solvent, on this basis the com-

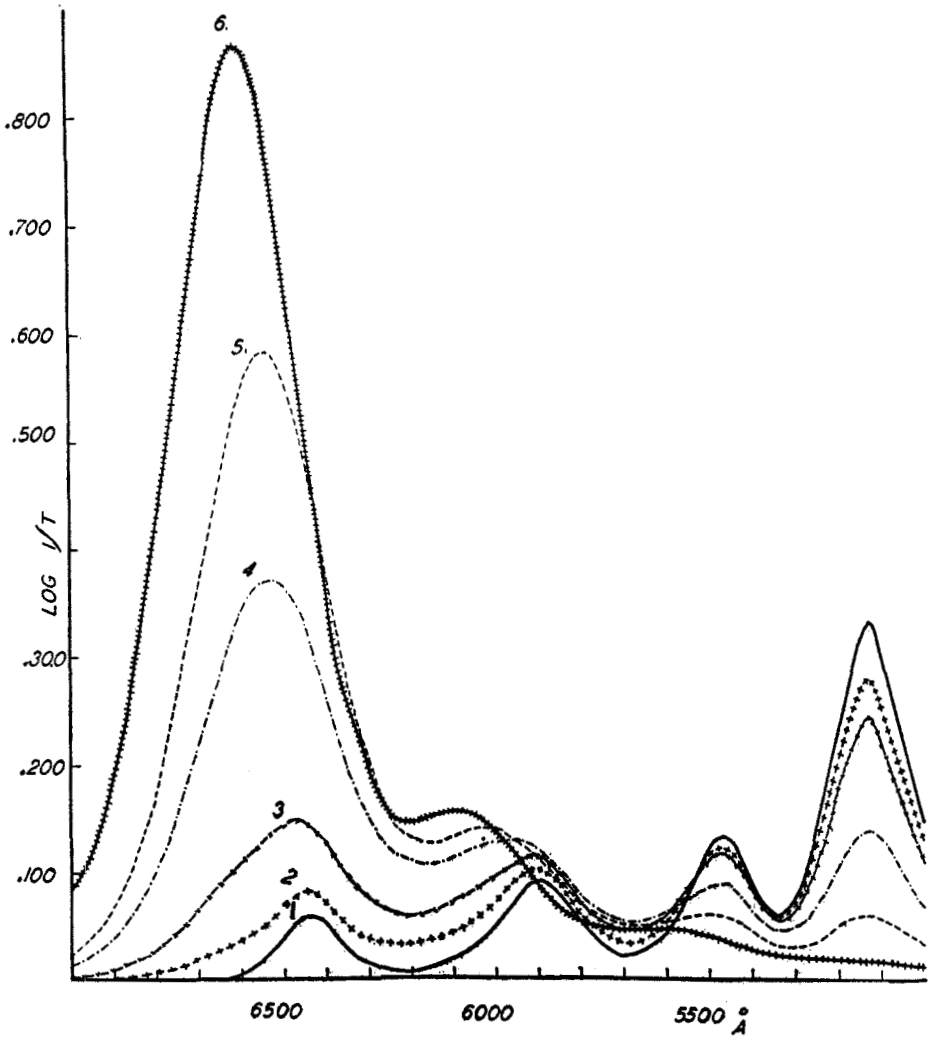


FIG. 4. COMPONENT A (FREE BASE) + VARYING AMOUNTS OF ALCOHOLIC HCl

Initial conc'n of free base identical in all cases (= 3×10^{-3} M/1.) (1) Free base (5 cc. dil. to 10 cc. with alc.); (2) free base (5 cc.) + 0.50 cc. 0.0204 *N* HCl sol'n dil. to 10 cc.; (3) free base (5 cc.) + 1.00 cc. 0.0204 *N* HCl sol'n dil. to 10 cc.; (4) free base (5 cc.) + 2.00 cc. 0.0204 *N* HCl, sol'n dil. to 10 cc.; (5) free base (5. cc.) + 3.50 cc. 0.0204 *N* HCl sol'n dil. to 10 cc.; (6) free base (5 cc.) + 5.00 cc. 6.3 *N* HCl sol'n. Taken in 1 cm. cell.

pound must have at least two basic centers. However, as the analysis of the hydrochloride showed two HCl per molecule, and there is a third salt formed in concentrated sulfuric acid, it must have at least three basic centers. The ab-

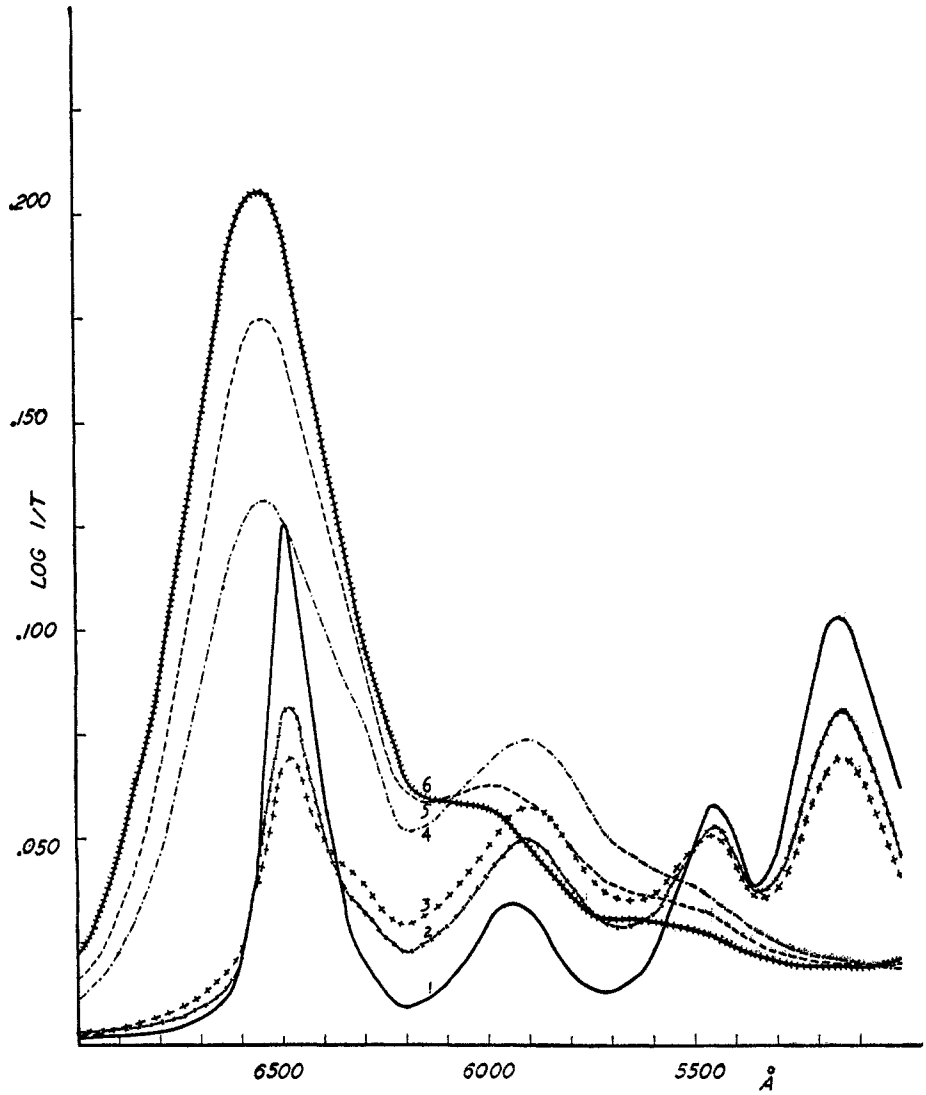


FIG. 5. COMPONENT B (FREE BASE) + VARYING AMOUNTS OF ALCOHOLIC HCl

Initial conc'n of free base identical in all cases (= 6×10^{-4} M/1.) (1) Free base (2 cc. dil. to 10 cc. with alc.; (2) free base (2 cc.) + 0.25 cc. 0.0204 *N* HCl sol'n dil. to 10 cc.; (3) free base (2 cc.) + 0.50 cc. 0.0204 *N* HCl sol'n dil. to 10 cc.; (4) free base (2 cc.) + 5.00 cc. 0.0815 *N* HCl sol'n dil. to 10 cc.; (5) free base (2 cc.) + 3.00 cc. 6.3 *N* HCl sol'n dil. to 10 cc.; (6) free base (2 cc.) + 5.00 cc. conc. *N* HCl sol'n (aq.) dil. to 10 cc. (These six curves were chosen from eleven obtained. Additional curves were omitted for the sake of clarity.) Taken in 1 cm. cell.

sence of an intermediate spectrum between the free base and the disalt shows that the first dissociation constant[5] (K_2) lies very near the second ($K_1 = 10^{-2}$)

[5] The discussion of dissociation constants does not include that of the sulfuric acid salt → disalt. The first dissociation constant (K_2) is disalt → monosalt.

(See Fig. 4) and cannot be estimated separately. Component B shows, in addition to the three spectra corresponding to those just mentioned of component A, a new spectrum at very low acid concentrations (see Fig. 5). It has therefore at least three basic centers. The presence of a different salt formed at low concentration is obvious from the drop in log $1/T$ at 6500 Å and the increase at 5900 Å. (T is the % transmission). Qualitatively, the intermediate form of a component B has a spectrum consisting of at least a single band with a maximum near 5800 Å. The spectrum may be evaluated quantitatively as follows.

Let the concentration of the free base, A = u_0, monosalt, $AH^+ = u_1$, disalt, $AH^{++} = u_2$, so that the acid dissociation constants, K_2 and K_1 may be defined as

1. $$K_2 = \frac{u_0 x}{u_1}; \qquad K_1 = \frac{u_1 x}{u_2}.$$

We know that at any x (hydrogen ion concentration)

2. $$\log \frac{1}{T} = k_0 u_0 d + k_1 u_1 d + k_2 u_2 d$$

where k_0, k_1, k_2 are the corresponding molar extinction coefficients and d is the thickness of the absorption cell.

3. $$u_0 + u_1 + u_2 = c$$

where c is the total concentration of the porphyrin. It has been shown by Hill (9)[6] that the concentrations of the ions and undissociated fraction may be expressed by the relations

4. $$u_0 = \frac{\frac{c}{x^2} K_1 K_2}{1 + \frac{K_1}{x} + \frac{K_1 K_2}{x^2}}; \qquad u_1 = \frac{\frac{c}{x} K_1}{1 + \frac{K_1}{x} + \frac{K_1 K_2}{x^2}}; \qquad u_2 = \frac{c}{1 + \frac{K_1}{x} \frac{K_1 K_2}{x^2}}$$

By using the proper combination of the above four equations the following relationship is obtained.

$$\left(\frac{k_0}{x^2} - \frac{\log \frac{1}{T}}{cx^2}\right) K_2 + \left(\frac{1}{x}\right) k_1 + \left(k_2 - \frac{\log \frac{1}{T}}{c}\right) \frac{1}{K_1} = \frac{\log \frac{1}{T}}{cx}$$

Thus by selecting, at some particular wave length, three values of log $1/T$ and the corresponding values of x it is possible to solve the resulting set of three simultaneous equations for the unknowns k_1, K_1, K_2, since k_0, x, and c are known and k_2 can be taken from the spectrum in the most concentrated acid solution.

A complete solution of the curve demands a set of simultaneous equations at every point. A minimum solution demands only a single set from which u_0 and u_2 are obtained. Knowing the values of k_2 and k_0 the curve corresponding

[6] A joint paper by one of us (S. A.) with this author dealing with the general application of equilibria in polycomponent spectroscopic systems will be published shortly.

to their sum is erected and the curve corresponding to u_1 is obtained by subtraction of the erected curve from the experimental one at the chosen x (see Fig. 6).

In the actual experiment, the pure components were dissolved in ethanol and titrated with known concentrations of dry hydrogen chloride (see Figs. 4 and 5). Using the data at four wave lengths, we obtained the results of Table II.

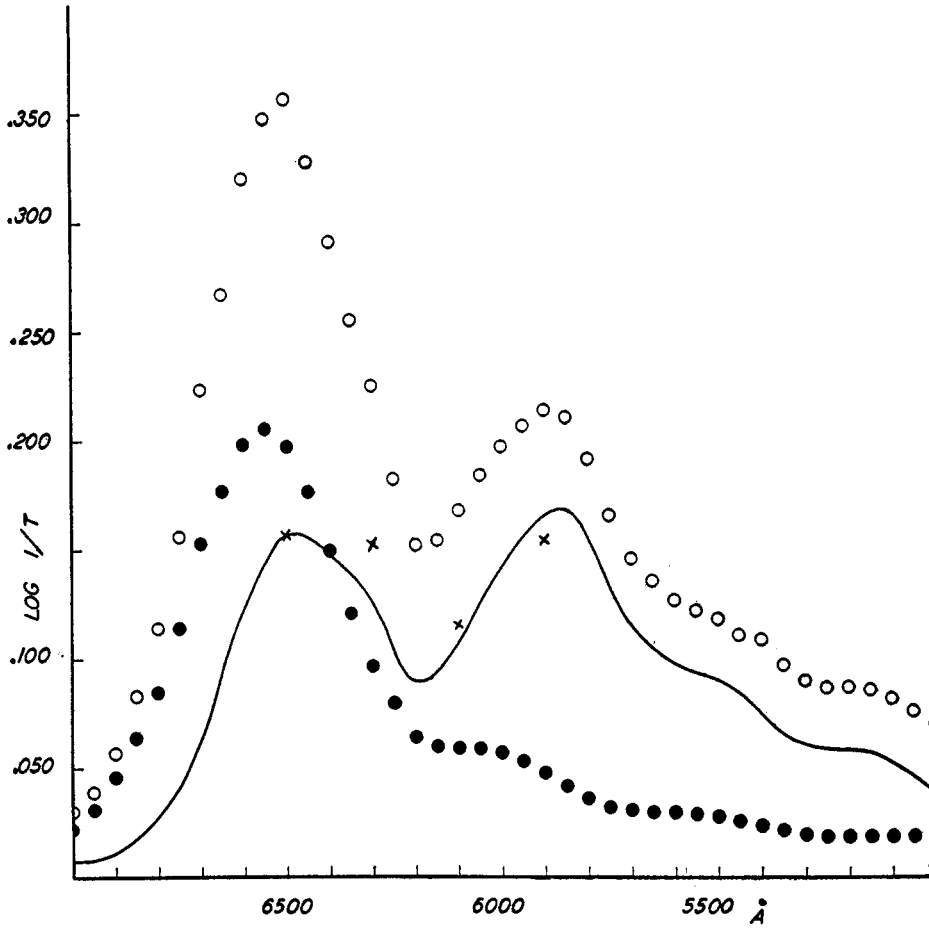


FIG. 6. CONTRIBUTION OF DISALT TO OBSERVED SPECTRUM
●, Observed spectrum. Solid line, monosalt spectrum obtained by subtraction

The absorption coefficients calculated independently (Table II) fall on the spectrum obtained by subtraction (points designated by x).

Cu complex. Most Cu-porphyrins show an absorption spectrum containing two primary bands in positions similar to that of the Cu salt of B (see Fig. 7). Fraction A has only one primary, its position being identical with the corresponding band of component B. The published data (2) show the influence of Cu-B in the spectrum of Cu-A.

TABLE II

	K_2[a]	K_1[a]	$k_1(\times 10^{-4})$
650	0.91×10^{-4}	3.63×10^{-2}	1.75
630	0.14×10^{-4}	5.25×10^{-2}	1.70
610	0.09×10^{-4}	0.13×10^{-2}	1.29
590	4.64×10^{-4}	114×10^{-2}	1.71
Geometric mean	2.3×10^{-5}	1.7×10^{-1}	

[a] Expressed as basic dissociation constants the first one becomes 10^{-9} and the second 10^{-13}. The spread in the values is to be interpreted in the nature of the curves, not the method of calculation.

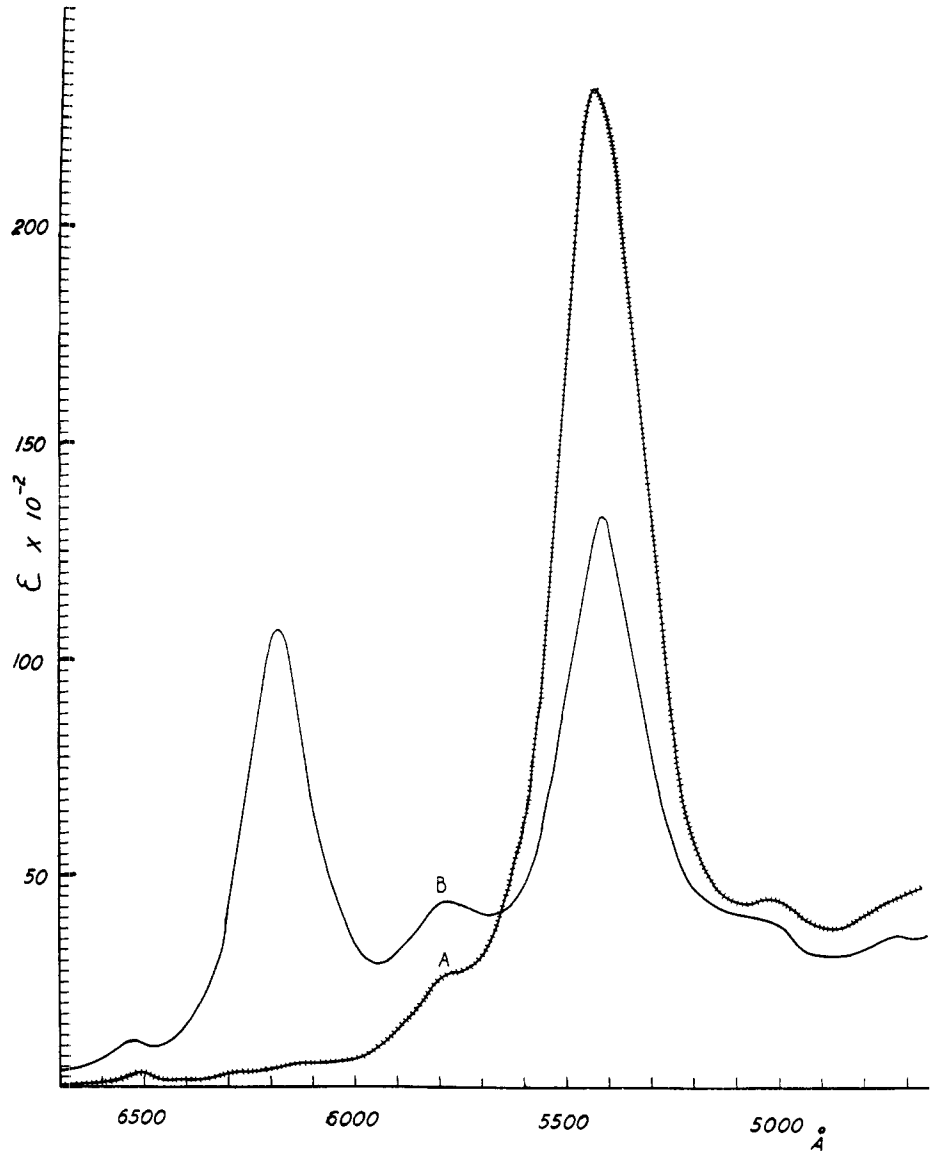


FIG. 7. Cu-COMPLEX
Components as indicated

These complexes are, like those of the porphyrins, stable in concentrated sulfuric acid, and boiling in the solvent does not remove the metal.

The complexes were prepared in the usual manner: 5 mg. of the porphyrin was heated to boiling in 1 cc. of glacial acetic acid. Fifty milligrams of copper acetate and 150 mg. of

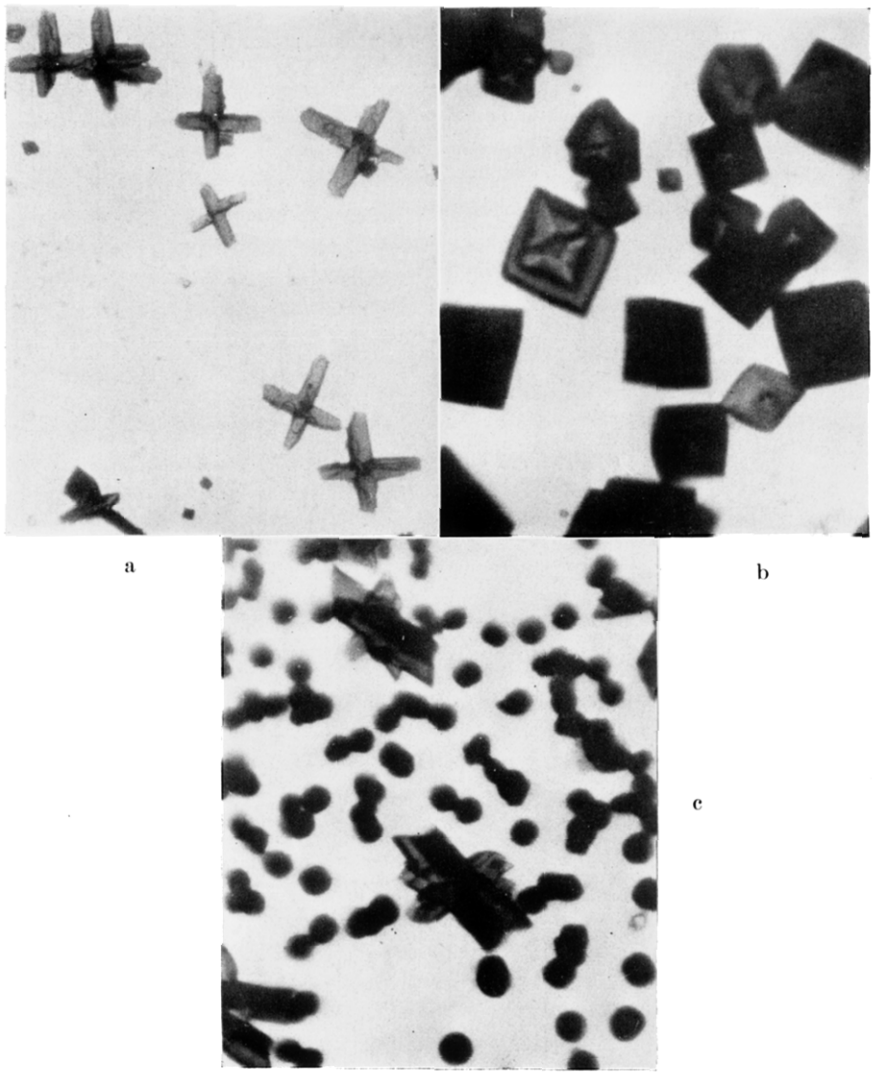


PLATE 2

(a) COMPONENT A; (b) COMPONENT B; (c) COMPONENTS C + D

sodium acetate were added, and the mixture boiled 2–3 minutes. After cooling, 25 cc. of ether and 50 cc. of water were added and the mixture shaken. The ether layer, containing the Cu-complex, was washed 2–3 times with water and then with 25% hydrochloric acid until free of unreacted free base (*i.e.*, until the acid washes were colorless). The ether was

then washed again, dried, and concentrated, resulting in beautiful orange crystals of component A and purple crystals of component B.

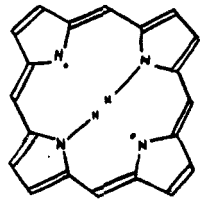
Crystal form. Still additional differences of the fractions are found in their crystal forms (Plate 2). Fraction A crystallizes in twinned prisms, the twinning angles being *ca.* 110°. The tendency to multiple twinning is small. Fraction B appears to crystallize primarily in an octahedral form. Fraction C occurs as multiple twinned prisms, and fraction D in very dense rosettes of small, lobe-like prisms. Crystals of fractions E and F have not yet been obtained.

DISCUSSION

It should be emphasized at the outset that the second form upon which the H isomerism of tetraphenylporphine was postulated has not been found under the conditions used in this investigation. That is, we have not isolated an isomeric compound of chemical composition conforming to tetraphenylporphine, $C_{44}H_{30}N_4$, of acid number 8, and absorption spectrum similar to the compound with acid number 13.5 but shifted to the blue. (No analytical data were presented in the original publication to indicate a true isomerism, reference being made to the absorption spectra and the analogous porphines.) We have found, instead, at least two (and possibly six) isomers with empirical formula corresponding to that of tetraphenylporphine. The higher number of isomers is a distinct possibility, since fractions C to F (together) formed approximately 10% of the yield of porphyrin-like material, and since the analysis for the unseparated components corresponded to that of $C_{44}H_{30}N_4$. That this analysis might be the result of a fortuitous mixture of different substances is recognized as a possibility, though not a likely one. In this case, a type of isomerism must be proposed which is different from that of mere H isomerism, where only two possibilities have been proposed.

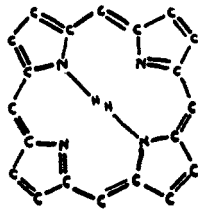
Numerous investigations (for example, refs. 4, 5, 7, 10) of the fine structure of the porphyrin nucleus have not yet brought about complete agreement. Indeed, only two facts have been universally accepted, the empirical formula and the complete conjugation of the ring. The difficulties revolve about the equivalence of the pyrrole nuclei and, as a corollary, the nitrogens within them. The fact that fully symmetrical porphyrins such as 1,2,3,4,5,6,7,8-octamethylporphine (7) exist only as a single compound, and on the other hand, the expected number of isomers (on a resonance basis) are obtained from the unsymmetrical, *e.g.* copro-porphyrins I, II, III, and IV (7), shows that (a) the pyrroles are equivalent, (b) the double bonds are not static. The latter is also inferred from the general "aromatic" character of porphyrins. The appearance of two spectral types for dicarbonyl-substituted porphyrins (16) (depending on whether they are on opposite or adjacent nuclei) is to be expected, in a manner corresponding to spectral differences of homologous *o*-, *m*-, and *p*-benzene derivatives, and does not demonstrate, as Fischer, and Stern and Wenderlein (16) claim, the inequality of the pyrrolic nuclei.

In an effort to represent the complete equivalence of the pyrroles, Clar and Haurowitz (4) proposed the biradical structure.

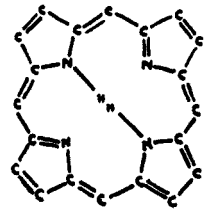


III

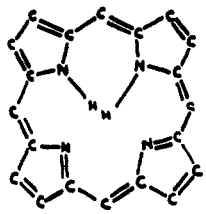
The diamagnetic nature of the porphyrins (8) has shown this to be incorrect as such. To account for the diamagnetism they proposed a resonating molecule with one N having an unshared pair of electrons and the other N being only divalent. It is indeed sufficient to represent the equality of the pyrrolic nuclei by describing the actual molecules as being in a state of resonance between the four main forms and various ionic and separated electron forms (3).



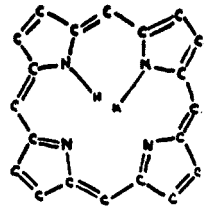
IV



V

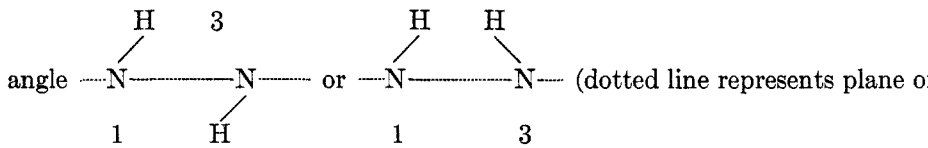


VI

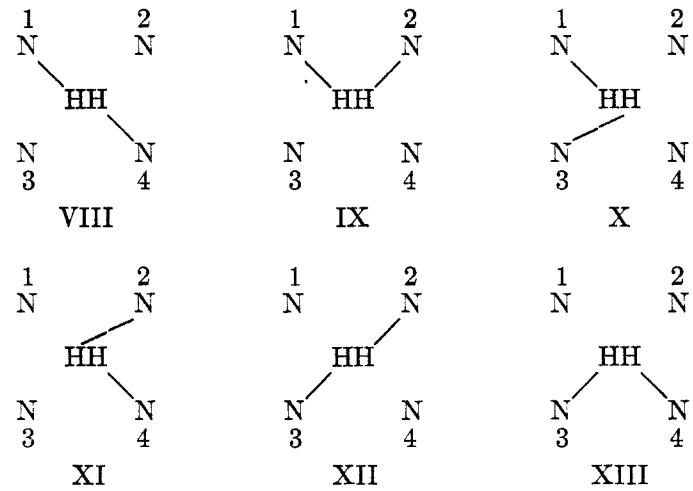


VII

If the hydrogen atoms are centrally located, all four structures (IV, V, VI, and VII) will be equivalent. If, however, they are not centrally located then IV and V would constitute the resonance pair of one isomer, while VI and VII would constitute the other. Therefore conjugation and resonance do not, *per se*, preclude the possibility of H isomerism. It does fix the isomerism to either of two types, (a) the adjacent-opposite type (VI, VII and IV, V), or (b) a planar



angle (dotted line represents plane of ring) type. This latter type would necessitate a directional rigidity of the bonds from nitrogen far beyond any possible extrapolation of what has been found. [Witness the inability to obtain geometrical or optical isomers of any primary, secondary, or tertiary nitrogen based upon the tetrahedral or pyramidal allocation of nitrogen valence (15)]. Were the isomerism to be of the adjacent or opposite type, then in an unsymmetrical porphyrin we would expect not two, but six isomers (only two in a symmetrical).

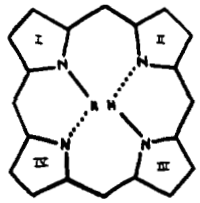


Isomers of this type have never been isolated. Nor are they to be expected since the energy barrier between two such similar forms would hardly seem sufficient to permit separation. Known cases of H isomerism usually involve considerable migration of that atom, whereas in this case it would not even move the entire distance of its Van der Waal's radius.

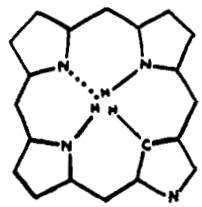
Two additional facts may be noted from Robertson's (11) x-ray data on the similar phthalocyanins. First, the evidence is that the hydrogen atoms are bonded to a pair of nitrogen atoms rather than to any single nitrogen atom and, secondly, that all C—N distances in the conjugated ring are the same. This indicates that the pyrrolic nitrogen atoms are equivalent.

We are confronted by the existence of at least two, and possibly six isomers for the porphyrin-like substances of empirical formula $C_{44}H_{30}N_4$. From the chemical and physical properties we would presume that the molecules are highly conjugated, aromatic, ringed, generally dibasic, or tribasic. They need not all

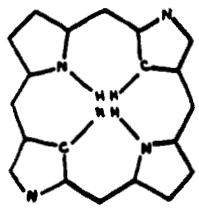
be porphyrins. Indeed, the following seven methine substituted compounds corresponding to $R_4C_{20}H_{10}N_4$ may be postulated[7]:



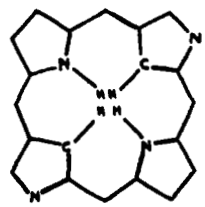
XIV



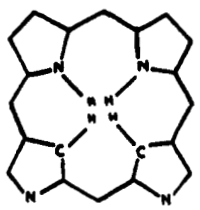
XV



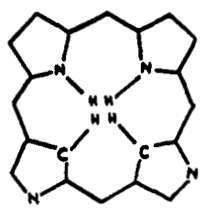
XVI



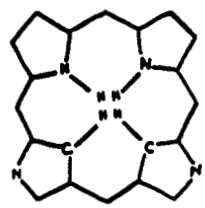
XVII



XVIII

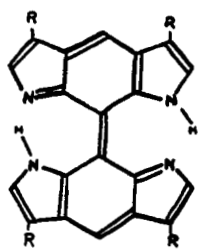


XIX

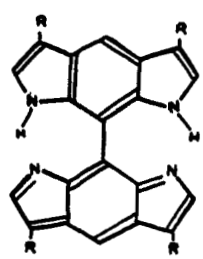


XX

The formulas shown above do not exhaust the structure corresponding to $R_4C_{20}H_{20}N_4$. *E.g.*, there are XXI and XXII.



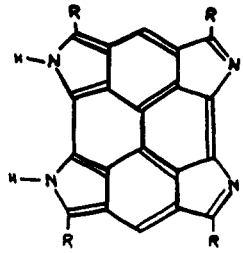
XXI



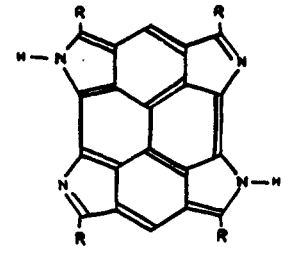
XXII

[7] Were the porphyrin-like components B, C, D, E, F, to correspond to XV, XVI, XVII, XVIII, and XIX or XX, the term carboporphyrins would be proposed. XVI would be carbo-III-porphine, XVII would be carbo-II,IV-porphine, etc.

These compounds, however, are in themselves much less stable than those predicted above, and involve rearrangements exceeding the present known types. More probable than these would be isomers involving phenyl substitution on the β-pyrrole positions, *e.g.*, XXIII and XXIV.



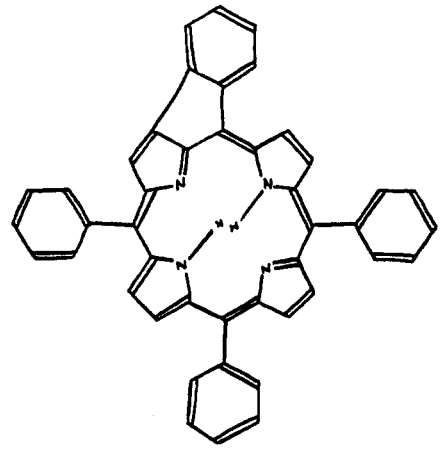
XXIII



XXIV

These rearrangements are also considered as too drastic to have occurred to any appreciable extent.

Another possibility for component B is XXV.



XXV

Although this is not isomeric with the porphin, differing by 2 hydrogen atoms (H, 4.61 as compared with H, 4.92), analysis of the mixture would not distinguish it, since it would be present at a maximum of about one-third the total yield. The analysis of the separated B however, gives H, 4.89, 4.95, and hence eliminates XXV as a possibility.

Since the α positions in pyrrole are more reactive than the β, formula XIV is assumed to be the main product. A single condensation in the β-position produces formula XV, and this would then be the most likely formula for component B. The statistical probability of two β-condensations would be much

smaller than that for one, a fact which conforms with the low yields of components C, D, E, and F.

The assignment of formula XIV to component A as compared with component B is based on the following facts: (a) the similarity of its absorption spectrum to those of known porphyrins having no chromophoric β substituents. It is to be noted that porphine itself not only has not a 4,3,2,1 spectrum, but Rothemund's and Fischer's compounds differ in the presence of a double band in the former's products at *ca.* 6800 Å. There remains the possibility that these are still mixtures of the types indicated above; (b) the much smaller separation of the first two dissociation constants of the symmetrical form represented by XIV (A) as compared with the wider separation to be expected from XV and found in B; (c) the greater base strength of B is more reasonably to be expected from the unsymmetrical form (XV); (d) the greater stability of the symmetrical form in concentrated sulfuric acid; (e) the smaller solubility of the hydrochloride in water and the free base in ethanol as compared with component B, (f) the smaller number of absorption bands of the Cu-complex might also be correlated with a more symmetrical compound.

Were one to prepare sufficient amounts of both components, one could distinguish between them by the following additional methods:

1. *Dipole moments.* Component A would be zero, B would be $\neq 0$. In the latter, however, the dipole moment might not be very large.

2. *X-ray data.* Component A should show the space-group of a centro-symmetrical molecule; component B might not. It is felt that the substitution of —C(H)= for —N= in the nucleus would result in greater x-ray changes than the corresponding replacement in the outer portion of the conjugated ring [which is known to have very little effect (17)].

3. *Rate of formation of metal complexes.* Component A would be expected to be more rapid than B (also more stable.)

4. *Isomerism of mono-β-substituted compounds.* Component A would produce one; component B would produce seven.

5. *Oxidation.* Oxidation of component A would not yield β-substituted pyrroles; component B would.

SUMMARY

1. The reaction of pyrrole with benzaldehyde yields six porphyrin-like compounds which may be separated chromatographically. At present they may be distinguished, when separated, by absorption spectra and crystal forms.

2. At least two of these, and possibly all six, are isomeric. The two known isomers are not interconvertible by means of their copper complexes or their hydrochlorides. Their acid numbers (for the respective fractions A and B) are 13.5 and 19.5. Various distinguishing properties, including polybasicity are discussed. A method for spectroscopic determination of polybasic ionization constants in a system with more than two molecular species is presented. The absorption spectra of the copper salts of fractions A and B are given.

3. The nature of the porphyrin nucleus is discussed. The possible structure of these isomers is presented and a new class of compound, carboporphines, is proposed.

BERKELEY, CALIF.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

THE REDUCTION OF CHLORAL BY ORGANOMETALLIC COMPOUNDS. 1-TRICHLORO-2-BUTANOL[1]

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As a broad generalization, it may be stated that organometallic compounds show essentially the same reactions, but at different rates. On such a basis it is possible that organolead compounds, although quite low in the reactivity-series of organometallic compounds, will add to some typical functional groups like the carbonyl group. In connection with a comprehensive study on the reducing action of alkylmetallic compounds, Meerwein and co-workers (1) called attention in a footnote to a reaction between chloral and tetraethyllead. They reported a 20% yield of 1-trichloro-2-butanol, which may have resulted from the following addition reaction:

$$CCl_3CHO + (C_2H_5)_4Pb \longrightarrow CCl_3\overset{H}{\underset{OPb(C_2H_5)_3}{C}}C_2H_5 \xrightarrow{H_2O} CCl_3\overset{H}{\underset{OH}{C}}C_2H_5$$

They found no trichloroethanol, a product of reduction isolated when some other ethylmetallic compounds were used. Under corresponding conditions, they noted that no reaction took place between chloral and tetraethyltin, an observation that is quite reasonable in view of the known significantly lower reactivity of R_4Sn compounds as compared with the corresponding R_4Pb types.

However, we were unsuccessful in obtaining any 1-trichloro-2-butanol from the reaction of chloral with tetraethyllead. Subsequently we were informed[2] that the 1-trichloro-2-butanol distilled at 68–70°/13 mm.; contained 60.19% chlorine (calc'd 60.0%); but that no derivatives of the alcohol were prepared.

As an aid to the isolation and characterization of the 1-trichloro-2-butanol that might be contained in some of our reaction products, we set out to prepare the alcohol from chloral and an ethylmagnesium halide. Iotsitch (2) investigated the action of ethylmagnesium bromide on chloral and obtained two fractions: one, distilling at 149.5–150.5°/765 mm., which was identified as trichloroethanol; the second, distilling at 77–80°/10 mm., which was obtained in 15% yield and assumed to be 1-trichloro-2-butanol. We investigated this reaction under a variety of experimental conditions and likewise obtained trichloroethanol, in yields as high as 65%. We did not obtain a definite high-boiling fraction; the material boiled over a wide range, depending on the experimental conditions used, and showed varying halogen content.

Then Hébert (3) treated chloral with ethylmagnesium iodide and, like Iotsitch, obtained trichloroethanol as the principal reaction product. He reported also

[1] Paper L in the series "Relative Reactivities of Organometallic Compounds"; the preceding paper is *J. Am. Chem. Soc.*, **65**, 435 (1943).

[2] Communication from Professor Meerwein.

a 16% yield of 1-trichloro-2-butanol, distilling at 82–84°/22 mm. Identification was established by sodium carbonate hydrolysis to give propionaldehyde and α-hydroxybutyric acid. From several experiments we did not observe any appreciable quantity of material distilling higher than 72°/22 mm., and the amount of tarry products was increased when ethylmagnesium iodide was used instead of ethylmagnesium bromide.

Later, Howard (4) reported 1-trichloro-2-butanol as the *principal* product of the reaction between chloral and ethylmagnesium bromide. His reported boiling point (99°/680 mm.) may be a typographical error.[3]

Although it does appear that Hébert (3) had 1-trichloro-2-butanol in hand, our experiments with ethylmagnesium chloride, bromide, and iodide indicate that no appreciable quantities of the alcohol were formed. It is possible that special catalytic influences may account for the variations in results. Incidentally, the reaction with ethyllithium appeared to be complicated by secondary transformations with the chlorine in chloral.

We prepared 1-trichloro-2-butanol by the following sequence of reactions:

$$CCl_3CHO + CH_2N_2 \longrightarrow CCl_3CH\text{—}CH_2 \quad (O)$$

$$CCl_3CH\text{—}CH_2 \ (O) + CH_3Li \xrightarrow{H_2O} CCl_3\overset{H}{\underset{OH}{C}}CH_2CH_3$$

1-Trichloro-2-butanol gave α-hydroxybutyric acid on treatment with sodium carbonate solution. New derivatives are described both for trichloroethanol and 1-trichloro-2-butanol.

Methylmagnesium iodide could not be used in this synthesis because the magnesium iodide contained in the complex reacted as follows to give 1-trichloro-3-iodo-2-propanol:

$$CCl_3CH\text{—}CH_2 \ (O) + MgI_2 \xrightarrow{H_2O} CCl_3\overset{H}{\underset{OH}{C}}CH_2I$$

Reaction of chloral with benzylmagnesium chloride. The reduction of chloral by numerous Grignard reagents and other RM compounds is one of a series of competitive reactions shown with a variety of carbonyl groups.[4] In general, if simple oxidation of the RMgX compound is possible (accomplished by the essen-

[3] In a private communication Professor Howard mentioned that a repetition of his reaction showed the boiling point to be about 150°. This is the boiling point to be expected of trichloroethanol. His boiling point of trichloromethylbenzyl carbinol (from chloral and benzylmagnesium chloride) is undoubtedly in error, for one would not expect it to be almost the same as his reported boiling point for 1-trichloro-2-butanol.

[4] For a general discussion and some leading references see Gilman, "Organic Chemistry", John Wiley and Sons, New York (1943), Second Edition, Chapters 5 and 7.

tial loss of two hydrogen atoms and the formation of a carbon-carbon double bond), the preponderant reaction will be the reduction of chloral to trichloroethanol. With RMgX compounds having groups like methyl, benzyl, and phenyl, the main reaction is addition to the carbonyl group. This is strikingly illustrated by the formation of the secondary alcohol with benzylmagnesium chloride,

$$CCl_3CHO + C_6H_5CH_2MgCl \xrightarrow{H_2O} CCl_3\underset{\displaystyle OH}{\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}CH_2C_6H_5$$

whereas other related phenyl-substituted alkylmagnesium halides like β-phenylethylmagnesium bromide, γ-phenylpropylmagnesium bromide, and δ-phenylbutylmagnesium bromide reduce chloral to trichloroethanol (5).

The availability of suitable derivatives for the characterization of trichloroethanol suggested a re-examination of the reaction between chloral and benzylmagnesium chloride. We have found that a small quantity of trichloroethanol is produced in this reaction, and the filtered, clear solution of Grignard reagent that was used decreases the possibility that this reduction was due to unused magnesium (6).

EXPERIMENTAL

Chloral and ethylmagnesium bromide. To the Grignard solution prepared from 24 g. (1.0 g. atom) of magnesium and 120 g. (1.0 mole plus 10%) of ethyl bromide in 400 ml. of absolute ether and cooled to −25° was added 140 g. (0.95 mole) of chloral in 100 ml. of absolute ether. The addition was performed dropwise over the course of one hour; a steady gas evolution was observed, and a white precipitate separated. The reaction mixture was allowed to warm up to room temperature, where it was held under continuous stirring for one hour. Hydrolysis was then effected by the gradual addition of 300 ml. of iced 2 *N* hydrochloric acid to the reaction mixture held at 0°. The ether layer was then separated, washed with water, and dried over anhydrous sodium sulfate. After removing the ether under reduced pressure, the residue was distilled under 11 mm. pressure, the temperature of the bath being allowed to rise constantly until no more material would distill. Thus 102 g. of distillate boiling at 48–69° was collected as a slightly yellowish oily liquid with a sharp odor. When shaken with water it imparted an acid reaction to the aqueous layer. The residue in the distilling flask was a dark thick tar. The distillate was refractionated at 6 mm. pressure, and three fractions were collected which showed the following properties:

	TEMP.	WEIGHT	n_D^{25}	d_{25}^{25}	M. R. (7)
I	43–45°	58 g.	1.4848	1.5033	33.8
II	45–47°	23 g.	1.4847	1.4945	34.0
III	47–49°	19 g.	1.4838	1.4528	34.9

All fractions acquired a violet color upon standing overnight.

The last two fractions were recombined and distilled under 0.6 mm. pressure into three fractions with the following properties:

	TEMP.	WEIGHT	n_D^{25}	d_{25}^{25}	M. R.
I	32–33°	20 g.	1.4849	1.4920	34.0
II	33–34°	9 g.	1.4848	1.4712	34.4
III	34–37°	7 g.	1.4826	1.4490	34.9

All three fractions gave a *p*-nitrobenzoate, the last two fractions, however, in poor yield. Recrystallized twice from petroleum ether (b.p. 68–70°), it melted at 71° (8) and showed no depression in a mixed melting point with the *p*-nitrobenzoate prepared from an authentic sample of trichloroethanol.[5] None of the above fractions gave a positive Lucas reaction (9). For additional confirmation the 3,5-dinitrobenzoate was prepared from each fraction. Recrystallized three times from petroleum ether (b.p. 68–70°), in which it is not very soluble, it melted at 142–143°. Further recrystallization failed to raise the melting point. There was no depression in the mixed melting point with the 3,5-dinitrobenzoate prepared from the authentic sample of trichloroethanol.

Anal. Calc'd for $C_9H_5Cl_3N_2O_6$: Cl, 31.0. Found: Cl, 31.1.

The last gram of the highest-boiling fraction was analyzed with the following results:

Anal. Calc'd for $C_4H_7Cl_3O$: C, 27.07; H, 3.98; O, 9.02; Cl, 59.94.
Found: C, 22.41; H, 3.47; O, 8.80; Cl, 65.32.

By fractionating under normal pressure and collecting the fraction boiling at 148–152° it was possible to obtain trichloroethanol in 54% yield.

Various modifications of the above reaction have been tried, including the use of ethylmagnesium chloride, ethylmagnesium iodide, and ethyllithium. A total of seventeen different runs were made, employing temperatures from −75° to 34°, inverse order of the addition of the reactants, reaction times from 15 minutes to 24 hours, etc., without essential deviation from the above results.

Chloral and tetraethyllead. To 32.3 g. (0.1 mole) of carefully purified tetraethyllead was added 14.7 g. (0.1 mole) of chloral which had been freshly distilled from phosphorus pentoxide and carefully fractionated from low-boiling material. Upon mixing there was no evidence of reaction. Heated under nitrogen, the solution became slightly greenish-yellow at 130°, and a small amount of white solid deposited. At 145° the solution turned slightly brown; at 150° dark brown. At 165° gas evolution was noticed. In another experiment the addition of a small amount of silica-gel produced no perceptible difference in these phenomena. Heating was continued for one hour at 170°, after which time there was no appreciable gas evolution. After the reaction mixture had cooled, it was hydrolyzed with water and then with dilute acetic acid. Large quantities of triethyllead chloride remained undissolved. The dark red ether layer was dried with anhydrous sodium sulfate, and the ether was carefully removed on a water-bath at 60°. Further separation of triethyllead chloride took place, and the solution was filtered into a distilling flask.

Two fractions of approximately equal size were cut at 63–64° and 65–66° at 14 mm. pressure. Material boiling lower than this was found to be principally tetraethyllead. The two fractions together weighed 3.5 g.; this would be a 19.8% yield of 1-trichloro-2-butanol, but the following physical constants for the two fractions show, together with the chlorine analysis and the failure of the product to give the Lucas reaction for secondary carbinols, that the material was not the desired product:

	n_D^{25}	d_{25}^{25}
I	1.4788	1.382
II	1.4822	1.404

These two fractions were free of lead and contained 65.6% chlorine. Comparison should be made with the authentic properties of 1-trichloro-2-butanol described below. Repeated variations in other experiments of the quantities, time of heating, and temperature failed to give fractions approximating more closely the properties of the veritable carbinol.

Trichloropropylene oxide. This compound was prepared in essential accordance with the directions of Arndt and Eistert (10) from chloral and diazomethane. In a typical run employing 44.0 g. (0.3 mole) of chloral, the yield was 23.2 g. (48%). Trichloropropylene oxide was found to boil at 39–40° under 11 mm. pressure, and to have these constants: n_D^{25} 1.4737, d_{25}^{25} 1.4921.

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[5] Kindly provided by Dr. C. S. Marvel.

1-Trichloro-3-iodo-2-propanol. To 21.0 g. (0.13 mole) of trichloropropylene oxide in 75 ml. of ether at −15° was added 0.13 mole of methylmagnesium iodide in 125 ml. of ether. A white solid rapidly separated. The reaction mixture was allowed to warm up to room temperature. It was then stirred for one-half hour, when it was hydrolyzed by the addition of 100 ml. of 2 *N* hydrochloric acid. There was a vigorous gas evolution. The ether layer was washed with 5% sodium bicarbonate and dried over sodium sulfate. The ether was removed under reduced pressure, and the residue dried at 2 mm. and 30° overnight. Oily crystals formed which weighed 31.1 g. Pressed out to dryness on a clay plate, the crystals weighed 22.2 g., which represents a 59% yield. After three recrystallizations from petroleum ether (b.p., 68–70°), the hard white crystals melted at 54–55°. Qualitative analysis showed both chlorine and iodine to be present. The Lucas test for a secondary carbinol was positive. A similar reaction is known between epichlorohydrin and methylmagnesium iodide (11).

Anal. Calc'd for $C_3H_4Cl_3IO$: I, 43.8. Found: I, 43.6.

1-Trichloro-2-butanol. To 22.0 g. (0.14 mole) of trichloropropylene oxide in 75 ml. of ether at −75° was added 140 ml. of 1.0 *N* methyllithium. The solution turned slightly yellow, and the color darkened as the reaction was allowed to warm up to room temperature. No precipitate separated. The reaction product was worked up by conventional procedures and distilled under 3 mm. pressure: 21.0 g. (85%) was collected boiling at 44–46°. The boiling point under 738 mm. pressure was found to be 169–171°. Physical constants taken on the liquid were n_D^{25} 1.4901, d_{25}^{25} 1.3760.

Anal. Calc'd for $C_4H_7Cl_3O$: Cl, 59.9; M. R., 36.9.
Found: Cl, 59.8; M. R., 37.3.

The compound readily formed a *p*-nitrobenzoate, which after two crystallizations from petroleum ether (b.p. 68–70°) melted at 70–71.5°.

Anal. Calc'd for $C_{11}H_{10}Cl_3NO_4$: Cl, 32.6. Found: Cl, 32.6.

Two isomers are possible: 1-trichloro-2-butanol and 3-trichloro-2-methyl-1-propanol. The above compound responds readily to the Lucas test for secondary carbinols. It also was readily oxidized: a mixture of one part carbinol, 1.3 parts of potassium dichromate in 8% aqueous solution, and 2.0 parts of conc'd sulfuric acid yielded a product which readily gave an addition compound with saturated sodium bisulfite solution, but which gave a negative reaction with Schiff's reagent.

Conversion into a known compound as more definite proof of structure was accomplished by refluxing 17.7 g. (0.1 mole) of the compound with 100 ml. of 5% sodium carbonate in 50% aqueous alcohol for ten hours. The acid was isolated as the zinc salt which, when decomposed with dilute hydrochloric acid, gave an acid boiling at 138–141°/11 mm. The distillate solidified to light colored crystals which melted at 41–43°. Sublimation was noticed in the vicinity of 70°. The anilide melted at 89–90°. The yield was 3.4 g. or 46.2%. A mixed melting point of the acid with α-hydroxybutyric acid, and of the respective anilides showed no depression.

1-Trichloro-2-chlorobutane. In the Lucas reaction a hydroxyl group is replaced by a chlorine atom. The alkyl halide separates gradually as the upper layer. In our above-mentioned test the reaction was allowed to stand for one hour, and then the upper layer was separated, dried, and distilled. It boiled at 134–135°/742 mm. and showed these physical constants: n_D^{25} 1.4920, d_{25}^{29} 1.3932.

Anal. Calc'd for $C_4H_6Cl_4$: Cl, 72.5; M. R., 40.4.
Found: Cl, 72.4; M. R., 40.7.

Chloral and benzylmagnesium chloride (I). To a Grignard solution, prepared from 48.6 g. (2.0 g. atom) of magnesium and 253 g. (2.0 moles) of benzyl chloride in 1200 ml. of ether and cooled to −20°, was added dropwise over a period of three hours 250 g. (1.7 moles) of chloral in 750 ml. of ether. The reaction mixture was then allowed to warm up to room temperature and stand overnight. Hydrolysis was carried out at 0° by the addition of 1000 ml. of 5% aqueous acetic acid, cooled to 0°. The ether layer was washed twice with 100-ml. portions of water, dried over anhydrous sodium sulfate, and the ether was then removed on the steam-bath. The dark fluid remaining was distilled under 10 mm. pres-

sure, and the cut was taken between 30° and 80°. This cut was then refractionated under normal pressure and the fraction 148–152° taken; weight 2.7 g.

This small fraction formed a fairly pure *p*-nitrobenzoate which after two recrystallizations from petroleum ether (b.p. 60–68°) melted at 70–71° and showed no depression in a mixed melting point with the *p*-nitrobenzoate prepared from an authentic sample of trichloroethanol. The yield, assuming purity of the small fraction, was 1.06%. This would require 0.44 g. of magnesium, as colloidal magnesium, to perform the reduction.

A second cut was made at 18 mm. pressure and 157–161°. The yield was 110 g. or 26%. The acetate was prepared with acetic anhydride and crystallized from alcohol, m.p. 109–110° (12). This indicated trichloromethylbenzyl carbinol.

Chloral and benzylmagnesium chloride (II). The Grignard solution prepared from 50.0 g. (2.06 g. atom) of magnesium and 253 g. (2.0 moles) of benzyl chloride was allowed to settle overnight. The clear supernatant liquid was carefully decanted and filtered through an "Ace C" sintered-glass filter to give an absolutely clear solution with a slight yellow-green color. The solution was cooled to −20° (further cooling causes a separation of solid on the walls of the flask) and 250 g. (1.7 moles) of chloral (dried over phosphorus pentoxide and freshly distilled with careful fractionation) in 700 ml. of ether was added dropwise. The reaction was extremely vigorous. The adduct was quite insoluble and soon separated as a heavy white precipitate; accordingly, the stirring must be efficient. After addition was completed (four hours), the mixture was allowed to warm up to room temperature, and then stirred for one hour. It was then cooled to 0° and hydrolyzed by iced ammonium chloride (300 g. in 1000 ml. of water). The ether layer was separated, washed with water three times, dried over anhydrous sodium sulfate, and the ether was removed on a bath at 60°.

Distillation was carried out at 10 mm. pressure, and the fraction boiling between 30° and 80° collected. This was refractionated at normal pressure and the fraction boiling 148–152° collected. The yield was 2.1 g. or 0.82%. The *p*-nitrobenzoate melted at 71° and showed no melting point depression in mixture with an authentic sample.

SUMMARY

In the reaction between chloral and ethylmagnesium halides, no significant quantities of 1-trichloro-2-butanol were isolated. The chief product is trichloroethanol, formed by reduction. 1-Trichloro-2-butanol has been synthesized, and suitable derivatives are described for this alcohol and for trichloroethanol.

A small quantity of trichloroethanol is formed by interaction of chloral with benzylmagnesium chloride.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

FORMATION AND PROPERTIES OF SOME URETEDIONES

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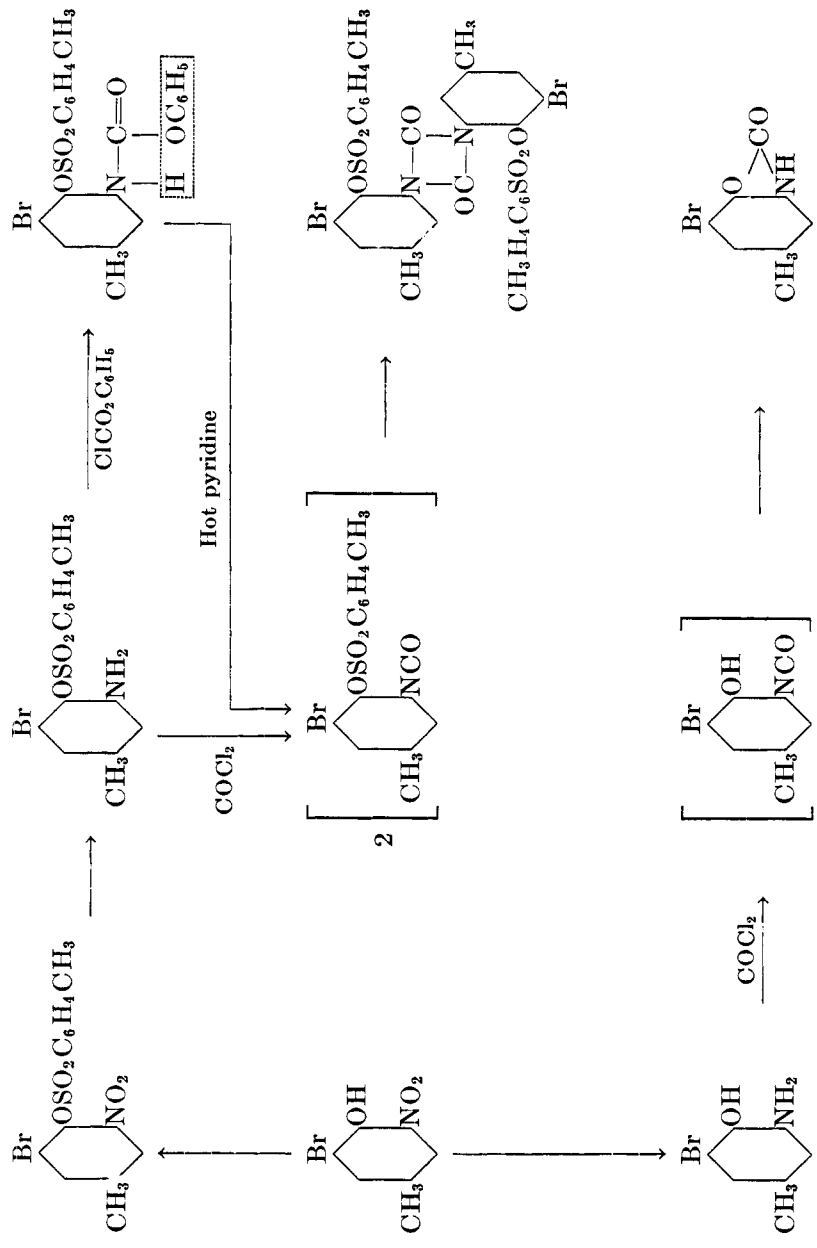
Hofmann (1) found that triethylphosphine converts phenyl isocyanate into a crystalline solid, m.p. 175°, which he called phenyl dicyanate and to which he assigned the formula $C_{14}H_{10}N_2O_2$, though he recorded no analytical data to support it. Snape (2) obtained the same compound by boiling a mixture of the isocyanate and pyridine, and analyzed his product for nitrogen only, which gave no information concerning the molecular weight of the polymer. Hofmann had previously attempted to fix this value by a vapor density determination, but was unsuccessful. He states, however, that treatment of the diisocyanate with alcohol converted it into the ester of the corresponding allophanic acid, which indicated that the polymer represented two molecules of the isocyanate. Dennstedt (3) and Frentzel (4) obtained similar results with 4-bromophenyl and 4-tolyl isocyanates, respectively. Structures for the polymers were not suggested.

Much later Warren and Wilson (5) reported that phenylurethan reacts with thionyl chloride to eliminate ethyl chloride, sulfur dioxide, and hydrogen chloride, and produces diphenyl diisocyanate, which they identified with Hofmann's product by melting point determination and analysis for nitrogen. Again, molecular weight measurements were not made, mechanism of formation, and structure for final product were not suggested.

At this point it should be noted that Raiford and Freyermuth (6) have recently shown that Warren and Wilson's observation is specific for phenylurethan. When the aryl radical contained a "negative" substituent, a mixture of the urethan and thionyl chloride underwent no change on standing at room temperature or upon refluxing for several hours. Compounds containing alkyl in the aryl radical formed tars from which nothing could be isolated.

Interest in further study of the formation and properties of such polymers resulted from an observation of Raiford and Shelton (7), who found that hot pyridine caused 2-carbophenoxyamino-4-methyl-6-bromophenyl 4-tolylsulfonate to lose phenol and give a polymerization product. It was assumed that loss of phenol from the starting material left 3-methyl-5-bromo-6-(4-tolyl)sulfonyloxyphenyl isocyanate (not isolated), and that two of these molecules united to give a derivative of the four-membered ring assigned by Staudinger (8) to Hofmann's polymerization product. Analyses of the compound in question for bromine, nitrogen, and sulfur, and molecular weight measurements supported this view. The product was designated as 1,3-di-(3-methyl-5-bromo-6-*p*-tolylsulfonyloxyphenyl) uretedione. The work of Hale (9) and of Hale and Lange (10) indicates that the existence of four-membered rings of this type is well established.

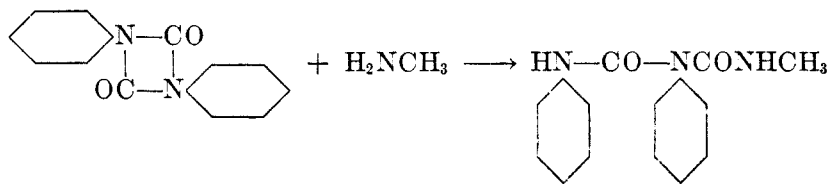
FIGURE 1


Br
OSO2C6H4CH3
NO2
CH3
Br
OH
NO2
CH3
Br
OH
NH2
CH3
COCl2
Br
OSO2C6H4CH3
NH2
CH3
ClCO2C6H5
Br
OSO2C6H4CH3
N—C=O
H OC6H5
CH3
Hot pyridine
COCl2
Br
OSO2C6H4CH3
NCO
CH3
2
Br
OH
NCO
CH3
Br
OSO2C6H4CH3
N—CO
CH3
OC—N
CH3H4C6SO2O
CH3
Br
Br
O
CO
NH
CH3

It was of interest to try to prepare by other means and isolate, if possible, the isocyanate mentioned above. To do this 2-nitro-4-methyl-6-bromophenyl 4-tolylsulfonate (11) was reduced to the corresponding amino compound, and a boiling toluene solution of the latter was saturated with phosgene. There was obtained in this way a 43% yield of purified material that melted at 208–209°, and which was identified by mixed melting point determination and molecular weight measurement as Raiford and Shelton's uretedione. When the amine had in the ortho position an exposed hydroxyl group a different type of product was obtained. When 2-amino-4-methyl-6-bromophenol was used as starting material, the isocyanate that was probably formed rearranged immediately into 5-methyl-7-bromobenzoxazolone previously obtained in a different way by Raiford and Inman (12). In no case could the isocyanate be isolated. The relationships are indicated in Figure 1.

In the work now reported the number of molecules of isocyanate involved in this polymerization was determined in most cases by molecular weight measurement. Two difficulties were met with in these experiments. Some of the products were practically insoluble in liquids that could be used for freezing-point determinations, and others were partially depolymerized at the high temperatures required for boiling-point determination in the liquids in which they were soluble. In such cases attempts were made to learn the molecular weights indirectly by study of some derivative of the polymer that was more soluble than the starting material.

Hofmann (13) noted that the phenyl diisocyanate he studied would react with ammonia and primary amines to give biurets, but he recorded no analytical data to support the composition of these products. In the present work it was found that aliphatic amines open the uretedione ring to give the related biurets. The cleavage involved must occur at but one place, otherwise there would be formed



some isocyanate and this would interact with a portion of the amine to give an unsymmetrical urea. To test that possibility here, the melting points, analytical data, and values for molecular weight measurements of the products in question were compared with those required by the related ureas. The importance of this consideration was illustrated in several cases as detailed below.

The action of *n*-propylamine on 1,3-diphenyluretedione gave a 96% yield of a product that melted at 115–116°. But Oliveri-Mandala' and Noto (14) recorded 114–116° for 1-*n*-propyl-3-phenylurea which they had obtained by a method quite different from the one employed here. A sample of their urea, prepared by the interaction of *n*-propylamine and phenyl isocyanate, melted at 115–116°, while a mixture of this and the compound here in question

melted with a depression of 26°. In addition, a molecular weight measurement of the biuret obtained from our polymer gave a value of 284 which compared favorably with the theoretical one of 297, while that required by the urea is 178. The interaction of the above uretedione with *n*-butylamine gave a compound that melted at 79–80°, which suggested that it might be a purer form of a by-product, m.p. 65°, obtained by Davis and Blanchard (15) by heating a mixture of *sym*-di-*n*-butylurea and aniline, and which they supposed might be 1-*n*-butyl-3-phenylurea, but which they did not characterize further. To show that our substance was not the urea just named, the latter was prepared by the action of *n*-butylamine on phenyl isocyanate and was found to melt at 129–130°, and to depress the melting point of our biuret.

Difficulties with molecular weight measurements, noted above, were illustrated by the behavior of a compound, m.p. 196–197°, obtained by polymerization of 2-naphthyl isocyanate. Attempts to determine the freezing point of a 1,4-dioxane solution were unsuccessful because the solute crystallized out. But partial support for the view that the polymer was a dimer was indicated by noting that it is quite different from a product of the same composition which showed no melting point but began to decompose at 220°, and which was synthesized by Otto (16) by a method which shows that the latter compound is β-trinaphthyl cyanurate, a trimer. Further proof that our product was a dimer was furnished by its interaction with *n*-butylamine, which gave an almost quantitative yield of a compound that gave nitrogen analyses and a molecular weight measurement in close agreement with values required by 1,3-di-(2-naphthyl)-5-*n*-butylbiuret, as shown below.

EXPERIMENTAL

With the exceptions of the *o*- and *p*-chlorophenyl, the *p*-xenyl and the phenyl-*p*-azophenyl derivatives, the isocyanates used in this study were Eastman's purest products. Those prepared in this laboratory were made by Hardy's method (17) with such modifications as were required in individual cases.

4-(Phenylazo)phenyl isocyanate. A solution of 35 g. of 4-aminoazobenzene in 400 cc. of toluene was placed in a 500 cc. three-necked flask fitted with a mercury sealed mechanical stirrer, and return condenser. Dry hydrogen chloride was bubbled through the gently boiling liquid until the amine had been converted into the hydrochloride, which separated in finely divided form. Phosgene was then passed in at the rate of about four bubbles per second for three hours, which caused all solid to dissolve. The mixture was cooled and filtered to remove about 2 g. of solid that melted with decomposition at 270°, and which was identified as di-(4-phenylazophenyl)urea (18). About two-thirds of the solvent was distilled from the filtrate, and ligroin (65–70°) was added to the residue to precipitate the isocyanate. In a second experiment the filtrate left after removal of di-(4-phenylazophenyl)urea was mixed with 500 cc. of ligroin and the liquid was saturated with ammonia. This caused the separation of 38.5 g. of orange-yellow solid. Crystallization from ethanol gave orange plates that melted at 231° and which were identified as 4-phenylazophenylurea, previously obtained by Pierron (19) in a different way. The amount of urea isolated corresponded to a 90% yield of isocyanate in the reaction mixture. The isocyanate isolated from the first experiment was crystallized from ligroin and was obtained in very small orange needles that melted at 94–95°.

Anal. (Dumas) Calc'd for $C_{13}H_9N_3O$: N, 18.83. Found: N, 18.54.

The catalyst, triethylphosphine, was prepared by the interaction of ethylmagnesium bromide and phosphorus tribromide in accordance with Slotta and Tschesche's (20) adaptation of Hibbert's (21) method, but with the further modification that our product was finally purified by distillation in an atmosphere of nitrogen. It boiled at 126–128°.

1-n-Butyl-3-phenylurea. A solution of 5 g. of phenyl isocyanate in 10 cc. of anhydrous ether was cooled in an ice-bath, and 15 cc. of an ether solution containing 5 g. of *n*-butylamine was slowly added. After ten minutes the solvent was distilled off, the remaining solid was crystallized from ethanol, and was obtained in colorless needles that melted at 129–130°, which is quite different from that of the product mentioned by Davis and Blanchard (15). A mixture of this urea and 1,3-diphenyl-5-*n*-butylbiuret shown in Table II melted at 73–74°. Their analyses, also, show that they are different.

Anal. Calc'd for $C_{11}H_{16}N_2O$: N, 14.58. Found: N, 14.52.

Formation of uretediones. When the starting material was a liquid, two or three drops of the catalyst was added to about 30 g. of the isocyanate under an atmosphere of nitrogen in a suitable vessel. In many cases crystals appeared on the surface of the liquid in a few moments, and within half an hour some mixtures had solidified with the evolution of considerable heat. In a few cases solid isocyanates were melted and the catalyst was mixed with the liquid; while in others it was added to a dry, saturated 1,4-dioxane solution of the isocyanate prepared at room temperature. In all cases the mixtures were allowed to stand overnight in closed vessels, after which the solids were powdered, washed with anhydrous. ether to remove unchanged starting materials, and crystallized from suitable solvents.

1-(4-Chlorophenyl)-3-(4-tolyl)uretedione. To a mixture of 10 g. of 4-tolyl isocyanate and an equimolecular proportion of 4-chlorophenyl isocyanate a few drops of triethylphosphine was added, the mixture was allowed to stand, and was worked up as indicated above. Crystallization from *n*-butyl ether gave an 88% yield of colorless glistening scales that melted at 195°. Mixtures of this product with 1,3-di-(4-chlorophenyl)- and with 1,3-di-(4-tolyl)-uretediones, respectively, melted with pronounced depression.

Anal. Calc'd for $C_{15}H_{11}ClN_2O_2$: Cl, 12.39; N, 9.77; Mol. wt. 286.5.
Found: Cl, 12.38; N, 9.45; Mol. wt. (freezing point in 1,4-dioxane) 291.

1,3-Di-(1-naphthyl)uretedione. A few drops of triethylphosphine was added to 30 g. of 1-naphthyl isocyanate, the mixture was allowed to stand four days, and the resulting solid was crystallized from nitrobenzene. A 52% yield of colorless microscopic needles was obtained. The product sublimed at about 296°, and the odor of the isocyanate was detected in the vapor. Its insolubility in 1,4-dioxane prevented a molecular weight determination with that solvent, but the difference in properties between this substance and that of the same composition with a melting range of 160–225°, synthesized by Otto (16), shows that they are not identical. Since Otto's product was prepared by a method that proves it to be a cyanurate or trimer, this is partial support for the view that the one here in question is a dimer.

Anal. Calc'd for $C_{22}H_{14}N_2O_2$: N, 8.28. Found: N, 8.49.

1,3-Di-(2-naphthyl)uretedione. Thirty grams of the related isocyanate was melted on an oil-bath and was polymerized by triethylphosphine as described previously. Crystallization from 1,4-dioxane gave large colorless plates that melted at 196–197°. The yield was 87%. Attempts to determine the molecular weight in dioxane solution were unsuccessful because the solute crystallized out. Again, the present product is quite different from Otto's β-trinaphthyl cyanurate (16) which showed no melting point, but began to decompose about 220°.

Anal. Calc'd for $C_{22}H_{14}N_2O_2$: N, 8.28. Found: N, 8.41.

Hydrolysis of 1,3-di-(4-ethoxyphenyl)uretedione. A mixture of 10 g. of this compound and 200 cc. of 10% alcoholic potash was heated on a steam-bath, under reflux, for about ten minutes, the mixture was cooled, the colorless solid that separated was collected and washed with dilute hydrochloric acid. Crystallization from acetic acid gave a 55% yield of colorless needles that melted at 225–226°, and which were identified as *sym-bis*-(4-ethoxyphenyl)urea, previously obtained by Gattermann and Cantzler (22) by a different reaction.

TABLE I

SUBSTITUTION PRODUCTS OF 1,3-DIPHENYLURETEDIONE

SUBSTITUENTS IN PHENYL	YIELD, %[a]	SOLVENT	CRYSTAL FORM	M.P., °C	FORMULA	ANALYSES				MOL. WT. DETERMINATION	
						Halogen		Nitrogen			
						Found	Calc'd	Calc'd	Found	Calc'd	Found
Unsubst.	80	*n*-Butyl ether	Colorless plates	175	$C_{14}H_{10}N_2O_2$				[b]	238	237
3-Methyl-	67	*n*-Butyl ether	Colorless leaflets	159–160	$C_{16}H_{14}N_2O_2$			10.52	10.57	266	264
4-Methyl-	70	*n*-Butyl ether	Colorless needles	185	$C_{16}H_{14}N_2O_2$				[b]	266	277
4-Ethoxy-	95	*n*-Butyl ether	Colorless prisms	181–182	$C_{18}H_{18}N_2O_4$			8.58	8.54	326	332
2-Chloro-	37	Acetic acid	Colorless plates	234–235	$C_{14}H_8Cl_2N_2O_2$	23.12	23.12	9.12	9.20	[c]	
3-Chloro-	72	*n*-Butyl ether	Colorless needles	153–154	$C_{14}H_8Cl_2N_2O_2$	23.12	23.04	9.12	9.20	307	314
4-Chloro-	85	*n*-Butyl ether	Colorless plates	155–156	$C_{14}H_8Cl_2N_2O_2$	23.12	22.91	9.12	9.12	307	293
4-Bromo-	87	*n*-Butyl ether	Colorless leaflets	203–204	$C_{14}H_8Br_2N_2O_2$	40.40	40.42			396	435
4-Nitro-	67	Nitrobenzene	Yellow needles	Subl. at 300	$C_{14}H_8N_4O_6$			17.07	16.78	[c]	
4-Phenyl-	38[d]	Nitrobenzene	Colorless flakes	270 (dec.)	$C_{26}H_{18}N_2O_2$			7.18	7.24	[c]	
4-Phenylazo-	Nearly quant.	Nitrobenzene	Orange prisms	281–282 (dec.)	$C_{26}H_{18}N_6O_2$			18.83	18.95	[c]	

[a] Refer to purified materials.

[b] Previously analyzed.

[c] Due to insolubility in 1,4-dioxane and other suitable solvents molecular weights could not be determined.

[d] High temperature required caused partial depolymerization, and a low yield of product.

TABLE II

DERIVATIVES OF 1,3-DIPHENYLBIURET

SUBSTITUENTS IN PHENYL RADICALS	SUBSTITUENT ON NITROGEN IN POSITION 5	YIELD, %[a]	CRYSTAL FORM[b]	M.P., °C	FORMULA	ANALYSES				MOL. WT.	
						Halogen		Nitrogen			
						Calc'd	Found	Calc'd	Found	Calc'd	Found
Unsubst.	Methyl	57	Colorless needles	144–145	$C_{15}H_{15}N_3O_2$			15.61	15.57	269	271
	Ethyl	61	Colorless needles	88–89	$C_{16}H_{17}N_3O_2$			14.84	14.90	283	284
	n-Propyl	96	Colorless needles	115–116[c]	$C_{17}H_{19}N_3O_2$			14.14	14.13	297	284
	n-Butyl	68	Colorless needles	79–80[d]	$C_{18}H_{21}N_3O_2$			13.50	13.50	311	308
	iso-Amyl	73	Colorless prisms	62–64	$C_{19}H_{23}N_3O_2$			12.92	13.07	325	332
	Allyl	40	Large colorless prisms	94–95	$C_{17}H_{17}N_3O_2$			14.23	14.05	295	285
	5,5′-Ethylene	45	Small colorless prisms	171–172	$C_{30}H_{28}N_6O_4$			15.67	15.70	[e]	
	Piperidyl	83	Colorless needles	135–136	$C_{19}H_{21}N_3O_2$			13.00	12.76	323	316
3-Methyl-	*n*-Butyl	86	Colorless needles	102–103	$C_{20}H_{25}N_3O_2$			12.38	12.22	339	339
4-Methyl-	*n*-Butyl	94	Colorless needles	131–132	$C_{20}H_{25}N_3O_2$			12.38	12.46	339	332
4-Methyl-	4-Tolyl[f]	53	Colorless needles	265	$C_{23}H_{23}N_3O_2$			11.26	11.40		
4-Ethoxy-	Methyl	90	Nearly colorless needles	110–111	$C_{19}H_{23}N_3O_4$			11.76	11.54	357	346
3-Chloro-	*n*-Butyl	37	Colorless needles	119–120	$C_{18}H_{19}Cl_2N_3O_2$	18.67	18.61	11.05	11.05		
4-Chloro-	*n*-Butyl	57	Colorless square columns	104–105	$C_{18}H_{19}Cl_2N_3O_2$	18.67	18.67	11.05	11.04	380	373
4-Bromo-	*n*-Butyl	84[g]	Small colorless prisms	118–120	$C_{18}H_{19}Br_2N_3O_2$	34.11	34.03	8.95	8.74	469	415

[a] Values represent purified material unless otherwise indicated.

[b] All products were crystallized from ethanol.

[c] A mixture of this product and 1-propyl-3-phenylurea, m.p. 114–116° (14), which could have been formed here if the uretedione ring had opened at two places, melted with a depression of about 26°.

[d] A mixture of this and 1-*n*-butyl-3-phenylurea, synthesized especially for this comparison, melted at 73–74°.

[e] Solute crystallized out in attempted freezing point determinations.

[f] Reaction mixture was refluxed twenty-four hours.

[g] Crude yield.

Action of Grignard reagent on uretedione. When a solution of 20 g. of 1,3-diphenyluretedione in 250 cc. of anhydrous pyridine was slowly dropped into an ether solution containing somewhat more than two molecular proportions of ethylmagnesium bromide, a colorless solid precipitated. The mixture was poured into cracked ice and an excess of dilute hydrochloric acid was added with constant stirring. The ether layer was separated and the remaining solid was collected on a filter. Crystallization from ethanol gave long colorless needles that melted at 238–240°. The product was identified as *sym*-diphenylurea. Hentschel (23) recorded 235° for this product made in a different way.

Anal. Calc'd for $C_{13}H_{12}N_2O$: N, 13.20. Found: N, 13.28.

The use of methylmagnesium iodide as reagent gave the same result.

Data for other uretediones are shown in Table I.

Preparation of biurets. These compounds were usually obtained by heating an ethanol solution of the uretedione and two molecular proportions of the required amine on a steam-bath for fifteen to thirty minutes, although the tritolyl derivative was prepared in 1,4-dioxane solution and refluxing was continued for twenty-four hours. Also, in at least one case heat was not required. When unsubstituted diphenyluretedione was mixed with methylamine solution, reaction took place spontaneously with the evolution of heat. Molecular weight measurements were made by the freezing point method in 1,4-dioxane which had been purified as directed by Oxford (24).

1,3-Di-(2-naphthyl)-5-n-butylbiuret. A 1,4-dioxane solution of 10 g. of the required uretedione was heated on a steam-bath with two molecular proportions of *n*-butylamine. The product that separated on cooling was purified by repeated crystallization from ethanol and was obtained in colorless needles that melted at 117–118°.

Anal. Calc'd for $C_{26}H_{25}N_3O_2$: N, 10.21; Mol. wt, 411.

Found: N, 10.31; Mol. wt. (freezing point in dioxane) 423.

Data for other biurets are given in Table II.

SUMMARY

1. The effect of nuclear substituents on the stability of aryl isocyanates obtained by the action of phosgene on aromatic primary amines was tested. The isocyanate obtained from 3-methyl-5-bromo-6-(4-tolylsulfonyloxy)aniline could not be isolated. It dimerized at once into 1,3-di-(3-methyl-5-bromo-6-*p*-tolylsulfonyloxyphenyl)uretedione. When the starting amine contained an exposed hydroxyl group in the ortho position, the isocyanate formed rearranged immediately, by ring closure, into 5-methyl-7-bromobenzoxazolone.

2. Several new uretediones have been obtained by polymerization of the required isocyanates in the presence of triethylphosphine as catalyst. A mixture of two different isocyanates treated in this way gave an unsymmetrical uretedione.

3. Many of these compounds are but little soluble in the usual organic solvents. They react with primary aliphatic amines to form 1,3,5-trisubstituted biurets.

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THE NIEMENTOWSKI REACTION. THE USE OF METHYL ANTHRANILATE OR ISATOIC ANHYDRIDE WITH SUBSTITUTED AMIDES OR AMIDINES IN THE FORMATION OF 3-SUBSTITUTED-4-KETO-3,4-DIHYDROQUINAZOLINES. THE COURSE OF THE REACTION

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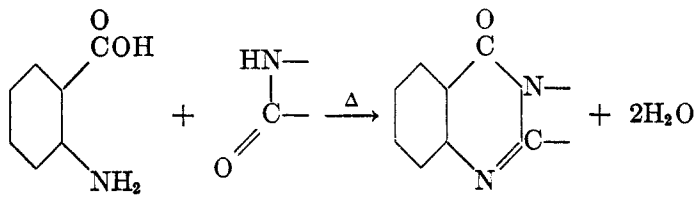
The formation of substituted 4-keto-3,4-dihydroquinazolines by interaction of anthranilic acid or substituted anthranilic acids and amides may be designated as the Niementowski reaction:

1. 

Numerous variants of the essential synthesis have been described, using *o*-acylaminobenzamides (1), ammonium *o*-acylaminobenzoates (2), anthranilic acid and nitriles in the presence of acetic anhydride (3), *o*-acetaminobenzonitrile in the presence of acetic anhydride or alkaline hydrogen peroxide (4), and acetanthranils and primary amines (5). The Niementowski procedure (using anthranilic acid and amides) has been found applicable to amides of the lower fatty acids, which show rapidly decreasing reactivities in this respect as the molecular weights increase. The usefulness of amides of acids of higher molecular weights has not been systematically studied, but is probably restricted by the fact that temperatures required for the ring closures cannot be attained or maintained without decarboxylation of anthranilic acid.

The experiments described below were undertaken to test several modifications and extensions of the Niementowski synthesis, *viz.*, (a) the use of methyl anthranilate instead of anthranilic acid, in order to permit higher reaction temperatures, (b) the use of substituted amidines instead of amides, and (c) the use of isatoic anhydride and amidines instead of anthranilic acid and amides. All these new procedures yielded the corresponding 4-keto-3,4-dihydroquinazolines. The last two procedures were designed respectively to take advantage of the relatively high reactivities of certain diarylamidines in ring closures similar to that involved in the Niementowski reaction (6), and of the notably high reactivity of isatoic anhydride as an agent which yields anthranoyl compounds by interaction with substances containing amino hydrogen.

[1] This paper is constructed from the thesis submitted by John F. Meyer to the Graduate School of the University of Pennsylvania in partial satisfaction of the requirements for the degree of Doctor of Philosophy, September 1942.

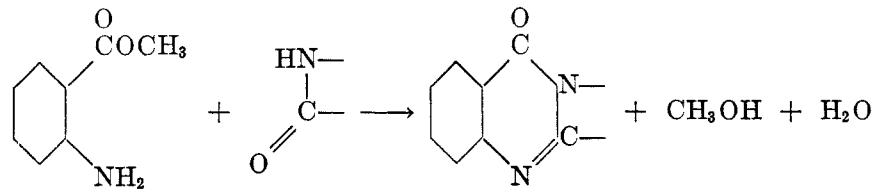
[2] Present address: Clarkson College of Technology, Potsdam, New York.

I. *Salt formation during the Niementowski reaction.* A preliminary study of the formation of quinazolone salts was necessitated by the observation that in the preparation of 3-phenyl-3,4-dihydroquinazolone-4 from anthranilic acid and formanilide the product was present in the reaction mixture in the form of its anthranilate. When the reaction mixture was extracted with aqueous alkali prior to isolation of the quinazolone no complication was encountered, but when the reaction mixture was at once dissolved in alcohol the crystallized product was not the expected quinazolone but its anthranilate. The salt character of this compound was established by tests outlined in the experimental section. There were prepared also the formate, benzoate, phenylacetate, and salicylate of this quinazolone. It is probable that the conversion of quinazolone to stable anthranilate within the reaction mixture withdrew part of the anthranilic acid from participation in the intended ring closure and so decreased the yield. When two equivalents of anthranilic acid were used the yield of quinazolone was increased from 40% to 73%.

Further study of salt formation as a possible interference in the Niementowski synthesis indicated anthranilates of the other quinazolones tested to be not sufficiently stable to survive under reaction conditions. That this instability may be rather general is to be inferred from the facts that yields by the Niementowski reaction are in many cases satisfactorily high (7), and that salts of several quinazolones could be prepared only under special conditions (*e.g.*, in indifferent solvents, or by fusion of the mixed solids) and could not be crystallized from alcohol without partial or complete separation into the components.

The practical application of these findings is comprised in (a) a preliminary extraction of the reaction mixture with cold aqueous alkali or alkali carbonate,[3] to remove anthranilic acid whether uncombined or present as salt, and (b) the use of an excess (to two equivalents) of anthranilic acid in cases in which salt formation is suspected because yields are low and considerable anthranilic acid is recoverable from the alkaline extracts.

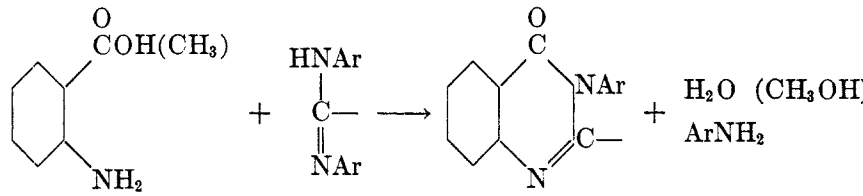
II. *The use of methyl anthranilate in the Niementowski synthesis.* The usefulness of the Niementowski synthesis is limited to some extent by the ease of thermal decarboxylation of anthranilic acid. Decarboxylation is rapid at 180°, and sustained heating at 150° or above may lead to extensive decarboxylation, followed by interaction of the resulting aniline with the amide or anilide by amide exchange. Thus, Niementowski (8) obtained acetanilide from anthranilic acid and acetamide. This difficulty is avoided if anthranilic ester is used instead of the acid. Methyl anthranilate is stable at temperatures approaching its boiling point (260°), and it was found to react with acetamide or with formanilide at about 200° to form the expected quinazolones:

2. 

[3] Ketodihydroquinazolines without substituents on nitrogen may be soluble in alkali.

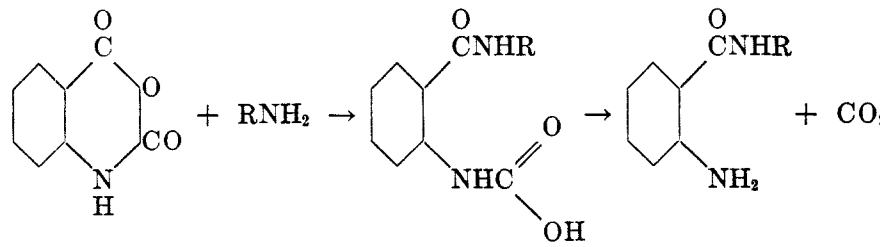
The yield from formanilide reached 49% at 225°. Acetamide and methyl anthranilate, heated together at 200°, gave small amounts of 2-methyl-3,4-dihydroquinazolone-4 and N-acetylanthranilic ester. Extension of this procedure to other amides showed that, while the aberrant reaction caused by decarboxylation of anthranilic acid was excluded, the synthesis was not improved with respect to yield or applicability. This must be due to the fact that in general the higher temperatures permitted by use of the ester do not compensate for its lower reactivity, the ring closure involving the aminolysis of an ester, which is relatively slower than the corresponding amide formation which is one step in the Niementowski reaction. The significance of the formation of N-acetylanthranilic ester is discussed in section V.

III. *The use of amidines in the Niementowski synthesis.* The previous demonstration (6) of a functional analogy between N,N′-disubstituted formamidines and acetamidines and carboxylic acids in certain ring closing reactions encouraged the belief that amidines could be used to replace amides (which are aquo-ammono acids) in the Niementowski reaction, and experimental trials showed this to be the case. Interaction of diaryl formamidines or acetamidines with anthranilic acid at 135–150° or with methyl anthranilate at 200–230° yielded the expected quinazolones with (respectively) amine and water or amine and methanol as by-products:

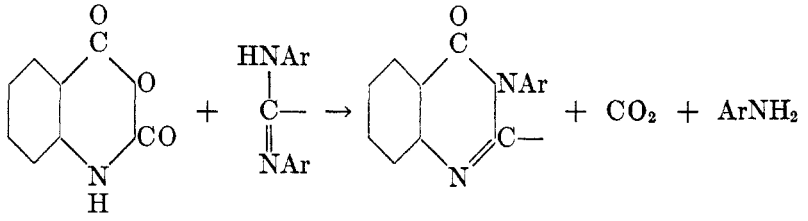
3. 

With anthranilic acid the reactions were rapid but yields were relatively low. Methyl anthranilate and disubstituted formamidines gave satisfactory yields of quinazolones, which were better than yields obtainable by the Niementowski reaction. Disubstituted acetamidines were found to react less readily than formamidines, a result consistent with previous findings (6). Results of these experiments appear in Table II.

IV. *The use of isatoic anhydride in the Niementowski synthesis.* In its most characteristic reactions (with ammonia or primary amines) isatoic anhydride serves essentially as an active agent for introduction of the anthranoyl group, probably thus:

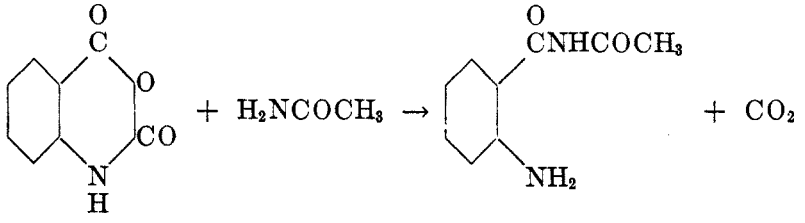
4. 

The similarity of the contribution of isatoic anhydride in such reactions and that of anthranilic acid in the Niementowski reaction suggested that the former might be useful as an active reagent in an extension of the synthesis. The use of isatoic anhydride with amides is excluded, because their interaction yields unidentified amorphous products (9). In contrast with this behavior of amides it was found that interaction of N,N′-diaryl formamidines and acetamidines with isatoic anhydride occurred smoothly at moderate temperatures (120–140°), with evolution of carbon dioxide and formation of 3-aryl-4-keto-3,4-dihydroquinazolines, the over-all reactions being:

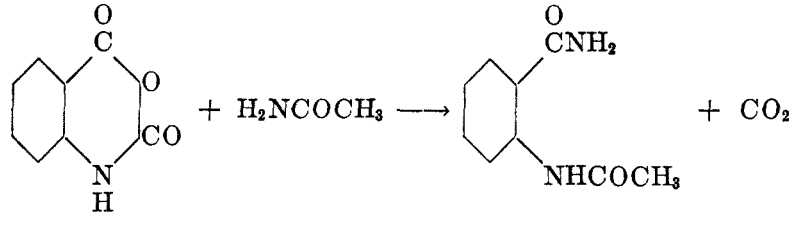
5. 

This result is apparently inconsistent with the structural and functional analogies between amides and amidines (considered respectively as aquo-ammono-acids and ammono-acids) and requires explanation.

The interaction of isatoic anhydride and primary amines yields substituted anthranilamides (equation 4). Interaction of isatoic anhydride and amides, *e.g.*, acetamide, is perhaps initially similar, the amide functioning as a weak base:

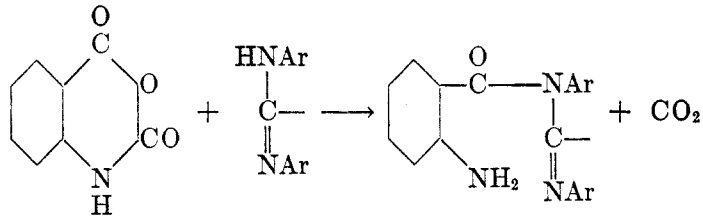
6. 

The product shown, though capable of ring closure to yield a quinazolone, probably reacts more readily (as a primary amine) with isatoic anhydride, for the reaction yields no quinazolone, but only amorphous material. The alternative initial condensation, with the amide functioning as an aquo-ammono-acid, *viz.*,

7. 

is an acylation, and it must be dismissed, for Weddige (1) found that *o*-acetaminobenzamide is readily convertible into 2-methyl-3,4-dihydroquinazolone-4, and it seems unlikely that it would react with isatoic anhydride more readily than

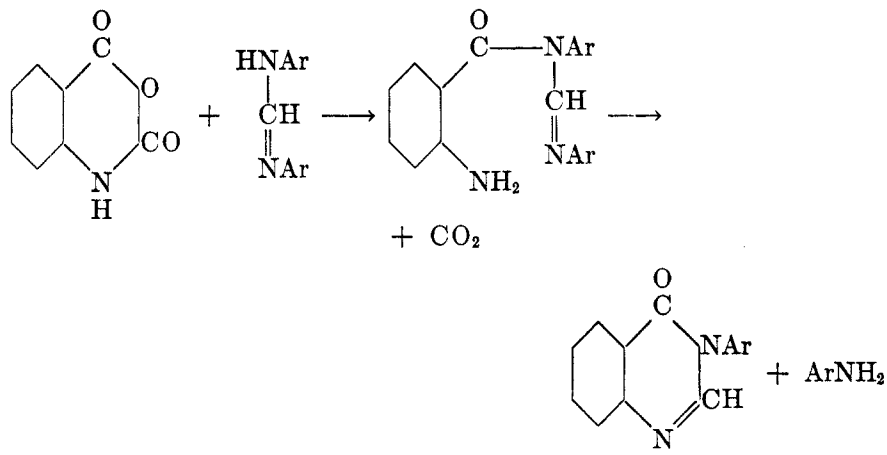
does acetamide and so escape conversion to the quinazolone. Equation 6 may therefore be accepted provisionally as representing the initial step when acetamide and isatoic anhydride react. By analogy the reaction of isatoic anhydride and an amidine may be represented by equation 8 (which may be considered as the first step in the synthesis represented by 5):

8. 

The apparently "normal" reaction of isatoic anhydride with diaryl formamidines and acetamidines to yield quinazolones (equation 5) is actually more complicated than is obvious, since it has been found that formamidines may yield quinazolones by two distinct series of reactions, as is to be inferred from the following experimental results.

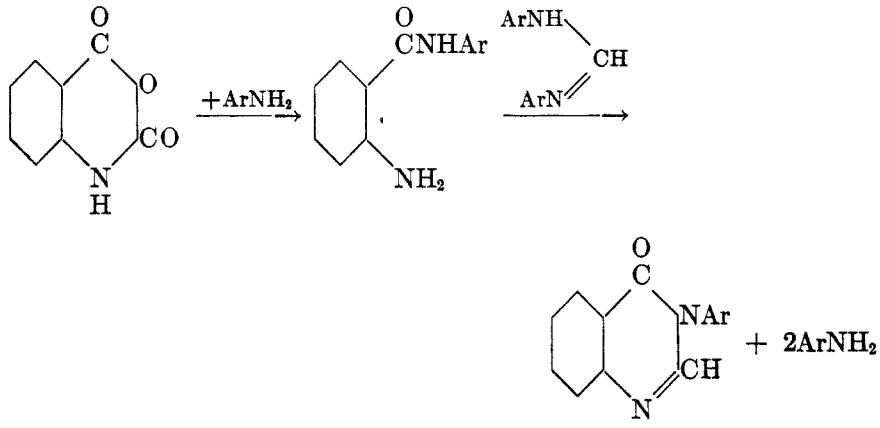
When equivalent amounts of isatoic anhydride and diaryl *formamidine* were heated together (120–130°) the yields of 4-keto-3,4-dihydroquinazoline were high (80–90%), and a corresponding quantity of amine (liberated in the reaction) was recoverable. Similar experiments in which diaryl *acetamidines* were used gave yields always less than 50%, and the reaction mixtures contained *no free amine*. These results were found to be explicable as follows.

Interaction of isatoic anhydride and diarylformamidines yields 3-aryl-4-keto-dihydroquinazolines by a reaction course not yet determined, but involving probably reactions 5 and 8, *viz.*,

9. 

The liberated amine reacts rapidly with more isatoic anhydride (this reaction occurs at or below water-bath temperature, equation 10) to form the corresponding anthranilanilide, and this then reacts with diaryl formamidine, as shown

previously (6), to yield the quinazolone with liberation of two equivalents of amine. This amine reacts with more isatoic anhydride, and these operations are repeated until no isatoic anhydride remains:

10. 

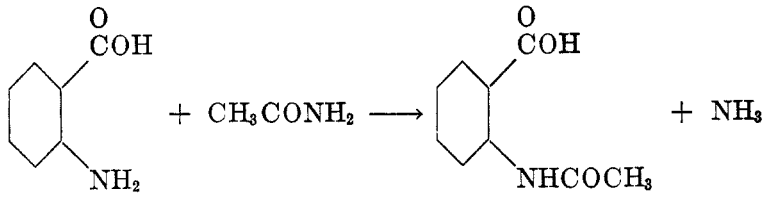
The net result is involvement of equivalent amounts of isatoic anhydride and diaryl formamidine, with formation of the quinazolone and liberation of an equivalent amount of amine. There are thus two paths which lead to the final products. To what extent the quinazolone is formed by each of these paths cannot be stated. The liberation of even a trace of amine by reaction 9 might start a reaction chain which could run to completion as shown in 10.

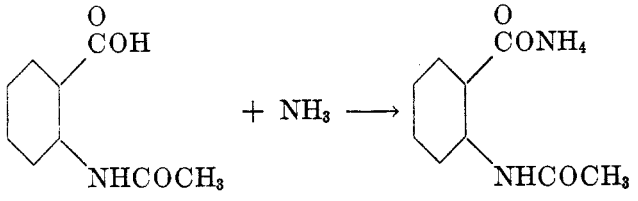
The reality of reaction 9 is thus far inferential. Evidence that quinazolones can be formed in this way is afforded by the results obtained with diaryl acetamidines: less than 50% yields of quinazolone and no free amine. In this case no quinazolone is to be expected by reaction 10, for it was shown previously (6) that diphenylacetamidine and anthranilanilide do not react even at 190°. It may be concluded that the quinazolone obtained from isatoic anhydride and diaryl acetamidines must have been formed by reaction 9. Only half the isatoic anhydride is convertible to quinazolone, and no free amine persists, conclusions in full agreement with the experimental results.

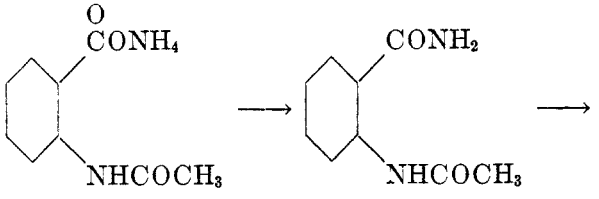
The secondary formation of anthranilanilide (equation 10) was demonstrated in an experiment in which isatoic anhydride and only one-half an equivalent of diphenylformamidine were heated at 125°. The evolved carbon dioxide was collected and weighed, its amount indicating that all of the isatoic anhydride had reacted. The reaction mixture yielded 3-phenyl-3,4-dihydroquinazolone-4 (72.7 % based on formamidine) and also anthranilanilide (53% based on isatoic anhydride).

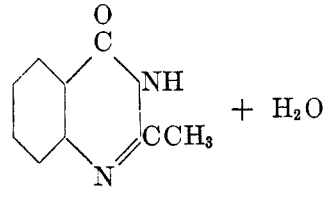
The formation of 4-keto-3,4-dihydroquinazolines from isatoic anhydride and amidines is to be regarded as a new quinazoline synthesis rather than as modification of the Niementowski synthesis.

V. *The course of the Niementowski reaction.* The only "mechanism" hitherto proposed is that of Bogert and Gotthelf (3):

11. (a) 

(b) 

(c) 

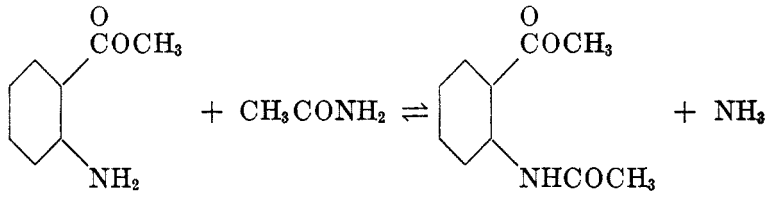


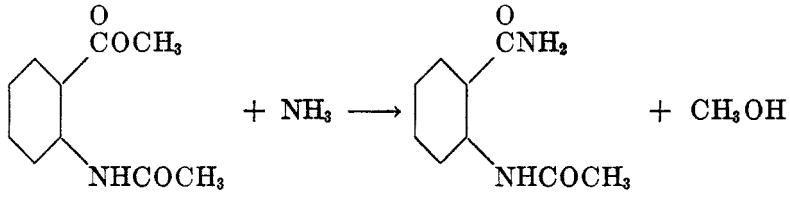
Reaction 11 (a) is an amide-exchange (or an ammonia-system acetylation), similar to the conversion of aniline to acetanilide by heating with acetamide (10). The conversion of ammonium-N-acetylanthranilate to 2-methyl-3,4-dihydroquinazolone-4 [reaction 11 (c)] was reported by Bischler and Burkart (2). Equations 11 (a) and 11 (b) lack experimental support. The present study yielded experimental evidence which directly or collaterally supports the reaction sequence suggested by Bogert and Gotthelf.

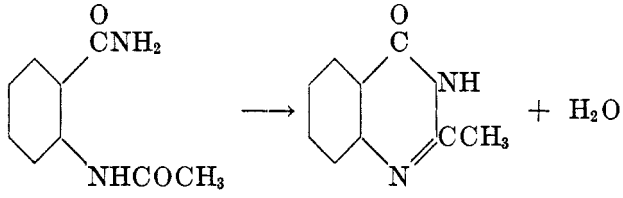
An effort was made to demonstrate the intermediate formation of N-acetylanthranilic acid or of N-acetylanthranilamide [equations 11 (a) (c)] by heating anthranilic acid with acetamide at minimal temperature for incipient reaction, but these experiments either yielded no reaction products or gave the quinazolone which is the final product. It appeared that this difficulty might be overcome by use of anthranilic ester instead of the acid, since the reaction corresponding to equation 11 (b) would be expected to proceed more slowly with anthranilic ester than with the acid,[4] thus favoring the survival of some of the N-acetyl-

[4] Methyl anthranilate in methanol, treated with excess strong ammonium hydroxide, showed no evidence of reaction at room temperature or on heating at 100° in a pressure-bottle.

anthranilic ester, a surmise which proved to be correct. When methyl anthranilate and acetamide were heated together the first evidence of reaction was the slow evolution of a little ammonia near 170°. After three hours at 200° the mixture was worked up, yielding sufficient N-acetylanthranilic ester for identification. A similar experiment run for seven hours yielded 9.6% of N-acetylanthranilic ester and 9.8% of 2-methyl-3,4-dihydroquinazolone-4. In both experiments most of the anthranilic ester was recovered unchanged. The evolution of ammonia, the formation of N-acetylanthranilic ester and the appearance of the quinazolone when the reaction period was prolonged, are results which are consistent with reactions 11 (a) (b) (c), extended to anthranilic ester, *viz.*,

12. (a) 

(b) 

(c) 

Reaction 12 (a) is the acetylation of anthranilic ester by acetamide (aquo-ammono-acetic acid); it is obviously slow. Reaction 12 (b) (c), the conversion of N-acetylanthranilic ester to 2-methyl-3,4-dihydroquinazolone-4 by action of ammonia and heat, was reported by Weddige (1). Reaction 12 (b) is the ammonolysis of an ester, for which the conditions cannot be considered favorable (11), and which is in part excluded by escape of ammonia from the mixture. Inferential support for this interpretation is provided by experiments using anthranilic ester and formanilide (section II), which compounds reacted to form the quinazolone in yields reaching 49%, a result considerably better than was obtained using acetamide. The greater effectiveness of formanilide may be attributed to its definitely acidic character, which probably favors the initial formylation, and to the fact that the aniline set free during the formylation does not escape from the reaction mixture, so that any N-formylanthranilic ester which forms will eventually react with aniline and undergo conversion to quinaz-

olone. The reaction of aniline with N-formylanthranilic ester to yield N-formylanthranilanilide (aminolysis of an ester) may be assumed to be slow, so that aniline produced in the initial reaction may accumulate in the mixture, its presence retarding the first reaction, which is the reversible formylation of an amine by an aquo-ammono-acid. In any case the final ring closure [12 (c)] may safely be regarded as fairly rapid, as has been observed in similar closures of pyrimidine and imidazole rings.

These considerations appear to account for the results with anthranilic ester and acetamide, and for those with anthranilic ester and formanilide, in a manner consistent with the series of reactions 12 (a) (b) (c), which is the counterpart of that suggested by Bogert and Gotthelf, the two principal steps having been realized separately. The extension of the indicated reaction course to the case of anthranilic acid (*i.e.*, to the Niementowski reaction) appears to involve no doubtful assumption. The principal obvious difference is that reaction 11 (b) (interaction of acid and ammonia) would occur much more rapidly than reaction 12 (b) (the ammonolysis of an ester), a conclusion in accord with the fact that in general the yields of quinazolones obtained from anthranilic acid and amides were higher than those from anthranilic ester and amides.

EXPERIMENTAL

Diaryl formamidines were prepared from arylamines and ethyl orthoformate (12). Diaryl acetamidines were prepared from arylamines, acetylarylamines, and phosphorus pentachloride (13). Isatoic anhydride was prepared from anthranilic acid and phosgene (14). Other organic compounds were used (after identification) as supplied by the Eastman Kodak Company.

I. Salt formation during the Niementowski reaction

3-Phenyl-3,4-dihydroquinazolone-4 anthranilate. A mixture of 18.7 g. (0.1 mole) of anthranilic acid and 12.1 g. (0.1 mole) of formanilide was heated at 140° for ninety minutes. The cooled mixture was dissolved in hot alcohol. Dilution with water caused the separation of 7.5 g. (41.4%) of the crude salt, m.p. 120–124° obs. After two recrystallizations from dilute alcohol the product was pure, and melted at 132.2° cor.

The same compound resulted when 4.48 g. (0.02 mole) of 3-phenyl-3,4-dihydroquinazolone-4 and 2.76 g. (0.02 mole) of anthranilic acid were dissolved together in the minimal hot alcohol. The total yield of salt, obtained in two crops (4.24 g., m.p. 131° obs., and 2.57 g., m.p. 130° obs.) was 94%. After recrystallization the salt was colorless, highly crystalline, and melted at 132.2° cor.

Anal. Calc'd for $C_{21}H_{17}N_3O_3$: N, 11.7; neut. equiv., 359; sap. equiv., 120.
Found: N, 11.36, 11.40; neut. equiv., 364, 365; sap. equiv., 129, 122.

The salt character of this compound was shown by the following results. (a) Cleavage by 5% aqueous sodium hydroxide solution, or by pyridine added to the solution in hot dilute alcohol, yielded 3-phenyl-3,4-dihydroquinazolone-4, m.p. 139° cor. The filtrate yielded anthranilic acid, m.p. 144°. Both compounds were identified by mixed melting point tests. (b) Cleavage by picric acid, of which an alcohol solution was added to one of the salt, yielded the crystalline quinazolone picrate, m.p. 179°.

Other quinazolone salts. These were made by the second method outlined above. In several cases dissociation occurred in alcohol, and the salts were obtained by using inert solvents (ligroin, benzene). Results are presented in Table I.

II. The use of methyl anthranilate in the Niementowski reaction

3-Phenyl-3,4-dihydroquinazolone-4. A mixture of 6.05 g. (0.05 mole) of formanilide and 7.60 g. (0.05 mole) of methyl anthranilate was heated at 200° in an oil-bath for three hours. The oily mass was dissolved in hot 50% alcohol and the solution decolorized with charcoal. Upon chilling the filtered liquid the product separated; it was recrystallized from 50% alcohol. The pure compound weighed 4.75 g. (42.8%), melted at 137–138°, and by mixed melting point test was shown to be identical with a specimen of 3-phenyl-3,4-dihydroquinazolone-4 made by the Niementowski reaction (4). A similar experiment at higher temperature (225° for one hour) yielded 5.23 g. (49.0%) of 3-phenyldihydroquinazolone.

TABLE I

SALTS OF 3-ARYL-4-KETO-3,4-DIHYDROQUINAZOLINES

SALT	SOLVENT	YIELD, %	M.P., °C.	FORMULA	ANALYSIS NITROGEN	
					Calc'd, %	Found, %
3-Phenyl-3,4-dihydroquinazolone-4 anthranilate	ethanol	94	132.2	$C_{21}H_{17}N_3O_3$	11.7	11.4 11.4
3-Phenyl-3,4-dihydroquinazolone-4 benzoate	"	—	131–132	$C_{21}H_{16}N_2O_3$	8.14	7.87 7.97
3-Phenyl-3,4-dihydroquinazolone-4 salicylate	"	—	168–169	$C_{21}H_{16}N_2O_4$	7.69	7.59 7.55
3-Phenyl-3,4-dihydroquinazolone-4 phenylacetate	"	—	113–114	$C_{22}H_{18}N_2O_3$	7.82	7.71 7.75
3-Phenyl-3,4-dihydroquinazolone-4 formate	ligroin[a]	—	119–120	$C_{15}H_{12}N_2O_3$	10.45	10.61 10.51
3-*m*-Tolyl-3,4-dihydroquinazolone-4 anthranilate	benzene-ligroin[a] 1:1	92	111–113	$C_{22}H_{19}N_3O_3$	11.23	11.15 11.10
3-*p*-Tolyl-3,4-dihydroquinazolone-4 anthranilate	benzene-ligroin[a] 1:1	69	119–121	$C_{22}H_{19}N_3O_3$	11.23	11.03 11.12

[a] Not isolable from alcohol.

III. The use of N,N'-diaryl amidines in the Niementowski reaction

A. Formation of 3-aryl-4-keto-3,4-dihydroquinazolines from anthranilic acid and diaryl formamidines or acetamidines. General procedure. A mixture of equivalent amounts (usually 0.01 mole) of anthranilic acid and diaryl formamidine or acetamidine was heated under air-reflux for fifteen to forty-five minutes in an oil-bath at 135–155°. Reaction occurred upon complete fusion of the mixture, a condensate appearing in the upper part of the flask. Free amine was removed by steam distillation, and in some experiments was recovered from the distillate as hydrochloride, which was dried at 100° and weighed. The residue in the distillation flask was made slightly alkaline by addition of 2 *N* sodium hydroxide solution. The brown solid product, washed with water and air-dried, was crystallized from alcohol or dilute alcohol, and was identified by mixed melting point test, using a specimen of the quinazolone made either by the Niementowski synthesis or by interaction of isatoic anhydride and diaryl formamidine (section IV). In some experiments the mother liquor from the crystallization was treated with a saturated alcohol solution of picric acid to recover additional quinazolone as picrate, which was identified by mixed melting point test. Results by this procedure are collected in Table II, A.

B. Formation of 3-aryl-4-keto-3,4-dihydroquinazolines from methyl anthranilate and amidines. General procedure. A mixture of equivalent amounts of methyl anthranilate and diaryl formamidine or acetamidine, in a flask provided with an air condenser, was heated in an oil-bath at 200–230° for three hours. Liberated amine was removed by steam distillation, and was recovered and weighed as hydrochloride. The residue not volatile with steam was heated and treated with alcohol until completely dissolved. The solution was digested with decolorizing carbon, the mixture was filtered, and the filtrate was chilled. The product was collected, washed with dilute alcohol, and dried in the air. One recrystallization from dilute alcohol was in most cases sufficient to yield a pure product. Results by this procedure appear in Table II, B.

TABLE II

FORMATION OF 3-ARYL-4-KETO-3,4-DIHYDROQUINAZOLINES FROM ANTHRANILIC ACID OR ESTER AND N,N'-DIARYLFORMAMIDINES OR N,N'-DIARYLACETAMIDINES

REACTANTS (0.01 MOLE OF EACH UNLESS STATED)	TEMP. °C.	TIME, MIN.	YIELD,[a] %	QUINAZOLONE M.P., °C.	AMINE, %
A. Anthranilic acid and:					
diphenylformamidine[e]	155	15	38.8[b]	138–139	—
di-*p*-tolylformamidine	130–135	30	38.1[c]	144–146	—
di-*m*-tolylformamidine	134–137	30	42.4[d]	129	—
diphenylacetamidine	150	45	29.6	141–145	80.7
di-*p*-tolylacetamidine	150	45	38.2	148–150	58.2
B. Methyl anthranilate and:					
diphenylformamidine	200	90	88.7	136–138	98[f]
di-*m*-tolylformamidine	197	180	80.5	128–130	88
di-*p*-tolylformamidine	200	180	85.7	145–147[g]	71
diphenylacetamidine	220–230	180	48.5	148–149	43

[a] The crude yields were in most cases much higher, *viz.*, 63.5 to 92%.

[b] Yield includes 8.2% recovered as picrate, m.p. 181°.

[c] Yield includes 8.5% recovered as picrate, m.p. 212–214°.

[d] Yield includes 11.9% recovered as picrate, m.p. 215–217°.

[e] Two equivalents of anthranilic acid. Yields were not improved by use of reactants in equivalent amounts or by longer periods of heating.

[f] The methanol recovered was 71% of the theoretical.

[g] Paal and Busch, *Ber.*, **22,** 2697 (1889).

In one experiment the mixture of anthranilic ester and diphenylformamidine was heated in a flask provided with a small Vigreux distillation column. During the heating a colorless liquid distilled at 66°: 1.91 g. was collected. It was identified as methanol by conversion to the 3,5-dinitrobenzoate, m.p. 106° obs. The hold-up of the column and flask was found to be 0.37 g. of methanol, making the indicated weight of the methanol disengaged 2.27 g., or 71% of the theoretical.

*3-*m*-Tolyl-3,4-dihydroquinazolone-4.*

Anal. Calc'd for $C_{15}H_{12}N_2O$: C, 76.22; H, 5.08; N, 11.86.
Found: C, 76.36, 76.46; H, 5.28, 5.29; N, 11.87, 11.87.

IV. The use of isatoic anhydride and amidines in the formation of 3-aryl-4-keto-3,4-dihydroquinazolines

3-Phenyl-3,4-dihydroquinazolone-4. A mixture of 9.8 g. (0.05 mole) of diphenylformamidine and 8.15 g. (0.05 mole) of isatoic anhydride was heated at 136° for thirty minutes.

Steam distillation removed aniline, which was recovered and weighed as hydrochloride (5.20 g.; 81% of the theoretical). The residue in the flask (11.3 g.) was crystallized from alcohol, yielding 7.0 g. of 3-phenyl-3,4-dihydroquinazolone-4, m.p. 137–139° cor. From the mother liquor there were obtained 1.96 g. more of the quinazolone and then 1.1 g. of the picrate (m.p. 174–177°). The total indicated yield was 9.49 g. (86.3%).

3-m-Tolyl-3,4-dihydroquinazolone-4. A mixture of 1.63 g. (0.01 mole) of isatoic anhydride and 2.24 g. (0.01 mole) of di-*m*-tolylformamidine, heated for one hour at 150°, yielded 2.63 g. of crude quinazolone, decreased to 1.67 g. (70.7%) after recrystallization from 30 cc. of 50% alcohol. The colorless needles melted at 123.5-125°.

3-p-Tolyl-3,4-dihydroquinazolone-4. A mixture of 4.08 g. (0.025 mole) of isatoic anhydride and 5.6 g. (0.025 mole) of di-*p*-tolylformamidine, heated for an hour at 160°, yielded 6.0 g. of crude quinazolone and 69.2% of the calculated *p*-toluidine. The pure quinazolone, obtained by recrystallization from 50% alcohol, weighed 5.0 g. (84.4%), and melted at 143–145° cor.

Formation of anthranilanilide during interaction of isatoic anhydride and diphenylformamidine (equations 9 and 10). A mixture of 8.15 g. (0.05 mole) of isatoic anhydride and 4.9 g. (0.025 mole; one-half equivalent) of diphenylformamidine was heated for one hour at 120–125° in a two-necked flask provided with an inlet tube to permit introduction of a stream of nitrogen, and with a reflux condenser the top of which was connected with an absorption train comprising a tube charged with dehydrite and one charged with ascarite. The increase in weight of the ascarite tube was 2.20 g. (0.05 mole of carbon dioxide),showing that all the isatoic anhydride had reacted. The reaction mixture was extracted with 50 cc. of ether. The residue insoluble in ether weighed 4.82 g. and melted at 115–130°; after crystallization from 50% alcohol the weight was 4.0 g., and the compound was identified as 3-phenyl-3,4-dihydroquinazolone-4, m.p. 134–136° obs. The yield was 72.7%, calculated on the weight of diphenyl formamidine taken. The ether extract, on evaporation of the solvent, left a brown semisolid residue, which was taken up in hot benzene. The solution was filtered hot and then chilled, yielding 1.60 g. of anthranilanilide (m.p. 126–130°), and 1.15 g. more upon working up the mother liquor; the total yield was 2.75 g., or 53%. The anthranilanilide was identified by mixed melting point test (126–130°) using a specimen of the same m.p., prepared from isatoic anhydride and aniline (10).

2-Methyl-3-phenyl-3,4-dihydroquinazolone-4. A mixture of 8.15 g. (0.05 mole) of isatoic anhydride and 9.80 g. (0.05 mole) of diphenylacetamidine was heated for two hours at 130°. Steam distillation of the reaction mixture yielded no trace of aniline. The residue in the flask remained oily after cooling. The oil was separated and extracted with 50 cc. of ether, leaving undissolved a white solid which was separated by filtration, washed with cold ether, and air-dried. Crystallization from 50% alcohol yielded 4.55 g. (38.5%) of 2-methyl-3-phenyl-3,4-dihydroquinazolone-4, m.p. 145–147° cor. It was identified by mixed melting point test using a specimen (m.p. 143–145° cor.) prepared from acetanilide and anthranilic acid; mixed m.p. 144–147° cor.

V. Formation of methyl N-acetylanthranilate and 2-methyl-3,4-dihydroquinazolone-4 from methyl anthranilate and acetamide (equation 12,a)

A mixture of 1.48 g. (0.025 mole) of acetamide and 3.77 g. (0.025 mole) of methyl anthranilate in a large test tube was heated in an oil-bath at 195–200° for seven hours. Near 170° a slow evolution of ammonia was detected. The reaction mixture was extracted with 6 *N* hydrochloric acid, and the undissolved material was separated, washed with water and dried in the air. The m.p. was 89–95°, changed to 95–97° after crystallization from ligroin. This compound was identified as methyl N-acetylanthranilate by its failure to depress the melting point of a specimen (m.p. 99–100°) prepared by action of acetic anhydride upon methyl anthranilate (15). The yield of acetylanthranilic ester was 0.33 g. (9.6%). The acid extract and the washings were combined, made alkaline with dilute ammonium hydroxide, and the mixture was extracted with two 35-cc. portions of ether.

The dried ether extract yielded a small amount of 2-methyl-3,4-dihydroquinazolone-4; the greater part of this product was deposited from the ammoniacal water layer upon standing for twelve hours cold. The yield was 0.60 g. (9.8%). The m.p. 229–233° was raised to 235–236° by recrystallization from water. Identification was made by mixed melting point test, using a specimen (m.p. 234–235°) made from anthranilic acid and acetamide (8).

A similar experiment, heated for only three hours, yielded N-acetylanthranilic ester sufficient for identification, but no isolable quinazolone, and 76% of the anthranilic ester was recovered unchanged.

SUMMARY

A study of the Niementowski quinazolone synthesis and of several new extensions disclosed the following facts:

1. In the preparation of 4-keto-3,4-dihydroquinazolones the yields may be decreased by the formation of stable quinazolone anthranilates in the reaction mixture, thus making part of the anthranilic acid unavailable for the synthesis. This behavior (observed in the preparation of 3-phenyl-3,4-dihydroquinazolone-4) seems to be not general, and its interference can be minimized by use of more than one equivalent of anthranilic acid. A number of quinazolone salts of organic acids were prepared.

2. Methyl anthranilate can be used instead of anthranilic acid in the Niementowski reaction, permitting (and requiring) higher reaction temperatures than can be maintained with anthranilic acid. With respect to yield and applicability this modification of the Niementowski synthesis is without advantage.

3. Diaryl formamidines and acetamidines can be used instead of amides in the Niementowski reaction, with either anthranilic acid or ester. Yields are good when anthranilic ester and formamidines react. This reaction shows a functional analogy between amides and amidines considered respectively as aquo-ammono-acids and ammono-acids.

4. A new quinazolone synthesis is described, involving interaction of isatoic anhydride and diarylamidines. By use of diaryl formamidines high yields of quinazolones are obtainable. The synthesis was found to follow two divergent courses, each leading to the same product. By use of acetamidines only one reaction course leading to the quinazolone is open (the other terminating with the formation of the anthranilanilide), with the result that yields are relatively lower.

5. The interaction of methyl anthranilate and acetamide was found to yield methyl N-acetylanthranilate, 2-methyl-3,4-dihydroquinazolone-4, and traces of ammonia. This result indicates the sequence of reactions by which anthranilic ester and amides yield quinazolones, and provides collateral experimental support for the two assumed steps in the reaction course proposed by Bogert and Gotthelf for the Niementowski synthesis.

PHILADELPHIA, PA.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

STUDIES IN DEHYDROGENATION. III. THE DEHYDROGENATION OF A METHYL SPIRAN

MEYER LEVITZ[1] AND MARSTON TAYLOR BOGERT

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In their recent studies on the inactive perhydrodiphenic acids, Linstead and Doering (1) were confronted with the problem of having available a greater number of isomeric acids than the six called for by classical stereochemical theory. One of these acids, labeled Linstead and Walpole acid, m.p. 203°, was made from the product of the cyclization of *dl*-$\Delta^{1,1'}$-cyclohexenylacetylene with formic acid. This cyclization product was first prepared by Marvel and co-workers (2) and was considered by them to be 9-dodecahydrophenanthrene, since reduction by the Clemmensen method followed by dehydrogenation over platinum-charcoal in the vapor phase yielded phenanthrene (3).

Studies by our laboratories on the compound spirocyclohexane-1,1′-indane (4) isomeric with octahydrophenanthrene led us to suggest that the compound prepared by Marvel and co-workers had a spiran structure rather than a hydophenanthrene structure. This suggestion was based partly on the fact that the spiran studied readily yielded phenanthrene when passed over palladium-charcoal in the vapor phase. Another isomeric spiran, spirocyclopentane-1,1′-tetralin has also been found to yield phenanthrene under the same conditions (5). The proposed spiran skeleton was accepted by Linstead and Doering (1). Consequently they decided that the excess acid, m.p. 203°, was actually dicyclohexyl-1,2′-dicarboxylic acid which would be derived from a spiran structure.

One reaction studied by Marvel and co-workers (6) may still point to a hydrophenanthrene structure. They condensed the supposed 9-dodecahydrophenanthrone (I) with methylmagnesium chloride, dehydrated the carbinol (II), and subjected the hydrocarbon (III) to dehydrogenation over platinum-charcoal at 320° for three hours. They obtained 9-methylphenanthrene (IV). This was offered as evidence for the hydrophenanthrene structure, since they considered it unlikely that an alkyl group would retain its position in the rearrangement of a spiran to a phenanthrene under dehydrogenation conditions.

To test the validity of this conclusion, similar reactions with a typical tricyclic spiran were carried out in these laboratories. Spirocyclopentane-1,1′-tetralin (V) was oxidized to the tetralone (VI) and condensed with methylmagnesium iodide. The carbinol (VII) was dehydrated and the resulting hydrocarbon (VIII) was continuously recirculated over palladium-charcoal in the vapor phase at 330–340° for five hours. The methyl spiran readily rearranged and dehydrogenated to 9-methylphenanthrene. The methyl group retained its position.

Acknowledgment. The authors wish to thank Mr. Saul Gottlieb for the microanalyses reported in this paper.

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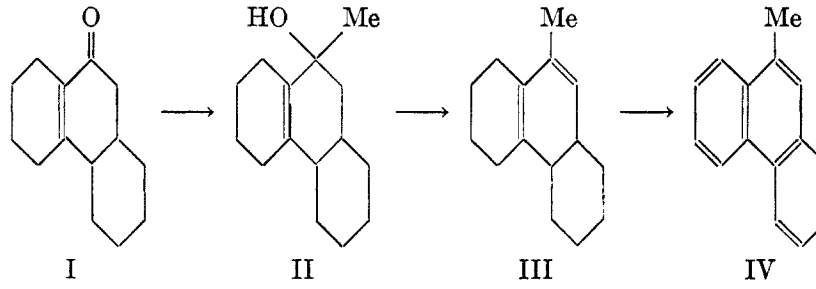
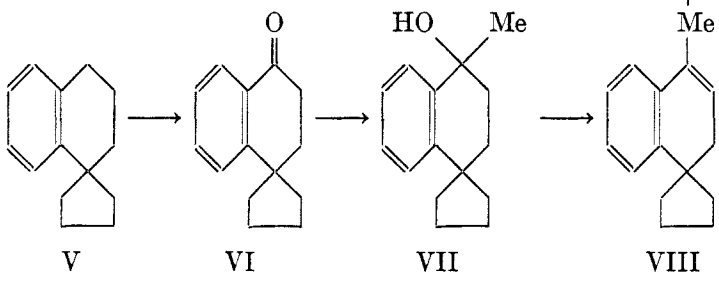
FLOW-SHEET

Marvel *et al.*:



Levitz and Bogert:



EXPERIMENTAL

Spirocyclopentane-1,1′-tetralin (V) was prepared according to the method of Perlman, Davidson, and Bogert (7). Thirteen grams dissolved in 75 ml. of glacial acetic acid was oxidized with chromic acid in acetic acid at room temperature as previously described (4). Yield of spirocyclopentane-1,1′-tetralone-4′ (VI), 7.8 g. or 56%; b.p. 140–142°/3 mm.; n_D^{25} 1.5716.

The semicarbazone was prepared by refluxing the ketone with semicarbazide hydrochloride and sodium acetate in ethyl alcohol for two hours, and was recrystallized from hot ethyl alcohol, m.p. 204.5–205.5° (corr.).

Anal. Calc'd for $C_{15}H_{19}N_3O$: C, 70.0; H, 7.4.
Found: C, 70.0; H, 7.5.

By the usual procedure, 6.3 g. of the ketone in 10 ml. of ether was brought into reaction with the methylmagnesium iodide made from 2.4 g. of magnesium and 14.2 g. of methyl iodide. The resulting carbinol (VII) was heated for 40 minutes with an equal weight of fused potassium bisulfate under 18 mm. pressure at 150–160°. The hydrocarbon (VIII) was extracted with petroleum ether and distilled. A yield of 4.4 g. or 70% was secured; b.p. 109–110°/2 mm.; n_D^{25} 1.5737.

Anal. Calc'd for $C_{15}H_{18}$: C, 90.9; H, 9.2.
Found: C, 90.9; H, 9.2.

Dehydrogenation was carried out in a continuous recirculation apparatus similar to the one previously described (5), but designed for smaller quantities. The heating furnace was 48 cm. long with an internal diameter of 11 mm. The apparatus was charged with 3.7 g. of the methyl spiran (VIII) and the temperature was raised to 330°. Dehydrogenation started as soon as the hydrocarbon was passed over the palladium-charcoal catalyst, as evidenced by the rapid flow of hydrogen through the bubble-counter. The operation was continued for five hours at 330–340°. The solid then removed from the apparatus weighed

3 g. Recrystallization from ethyl alcohol gave 2.4 g. of 9-methylphenanthrene, m.p. 90–91° (corr.). The picrate made by heating with an alcoholic solution of picric acid melted at 156° (corr.). Previously reported for 9-methylphenanthrene, m.p. 91–92° and for the picrate m.p. 154–155° (6).

SUMMARY

Marvel, Pearson, and White (6) have synthesized a ketone which they believe to be a 9-dodecahydrophenanthrone, and in support of this structure cite the preparation therefrom of 9-methylphenanthrene by a series of reactions involving a final dehydrogenation over platinized charcoal for 3 hrs. at 320°. They conclude that their initial ketone (I) could not have been the isomeric spiran (VI) because "it would be unlikely that an alkyl group would retain its position in the rearrangement of a spiran to a phenanthrene under dehydrogenation conditions." The present paper shows that this particular spiran, when carried through a similar series of reactions, does yield 9-methylphenanthrene, without any shift in the initial position of the methyl group.

NEW YORK, N. Y.

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[CONTRIBUTION NO. 27 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, FORDHAM UNIVERSITY]

ESSENTIAL STEPS IN THE CATALYTIC CONDENSATION OF ALDEHYDES; NEW SYNTHESIS OF GLYCOL ESTERS[1,2]

MARTIN S. KULPINSKI AND F. F. NORD[3]

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Claisen (1) observed that benzaldehyde when treated with sodium alkoxides yields benzyl benzoate. Tischtschenko *et al.* in 1906 (2) discovered that aluminum alkoxides are able to condense smoothly aliphatic and aromatic aldehydes to form simple esters. Hence, with the aid of these catalysts, Claisen's original observation received an important extension and generalization.

Nord and his co-workers (3) showed for the first time that two *dissimilar* aldehydes in the presence of aluminum alkoxides react through an oxidation-reduction interchange and form mixed esters. The reaction of this type proved to be of a rather general nature, as was shown by the study of numerous pairs of aldehydes. Many other investigators continued the research following similar lines (4).

In view of the diverse examples, it was deemed suitable to condense an aliphatic saturated aldehyde, such as, butyraldehyde with an aliphatic unsaturated aldehyde, such as crotonaldehyde. Condensation of crotonaldehyde alone (2) and acrylic aldehyde alone (5), with the aid of aluminum ethoxide resulted in failure, due to the extensive polymerization of these substances.

Since polymerization seemed to be the main reaction to overcome, it was thought that with an appropriate control of conditions, as for example, temperature, solvents, time of reaction, exclusion of oxygen, use of polymerization inhibitors, and variation of alkoxides, the mixed condensation could be realized. In spite of all these variants, the mixed unsaturated esters, *i.e.*, butyl crotonate and crotonyl butyrate, in accordance with the usual course of the reaction, could not be isolated.

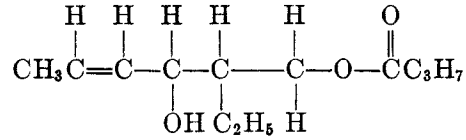
Bearing in mind the sensitiveness of crotonaldehyde to alkali, a milder form of the catalyst could possibly bring about the desired result. A catalyst hitherto unapplied to this type of reaction was resorted to, *i.e.*, magnesium-aluminum ethoxide. In contradistinction to the simple aluminum alkoxide, it is a co-ordination compound (6) of the formula: $Mg[Al(OC_2H_5)_4]_2$. The complex catalyst did not lead to the mixed esters when crotonaldehyde was condensed with butyraldehyde. On the other hand, examination of the higher-boiling product

[1] Abridged from the dissertation of M.S.K., submitted in partial fulfillment of the requirements of Doctor of Philosophy to the Graduate School of Fordham University, June, 1943.

[2] Presented before the Fall meeting of the American Chemical Society, Buffalo, N. Y., September, 1942.

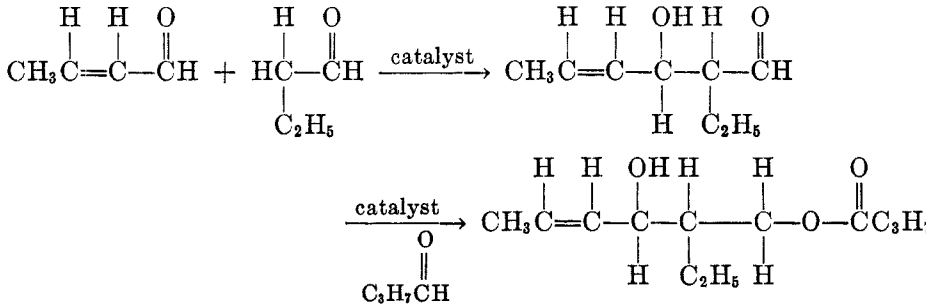
[3] For a preliminary communication see Kulpinski and Nord, *Nature*, **151**, 363 (1943).

obtained, revealed that the main reaction took a different course. The higher condensate proved to have the following structure:

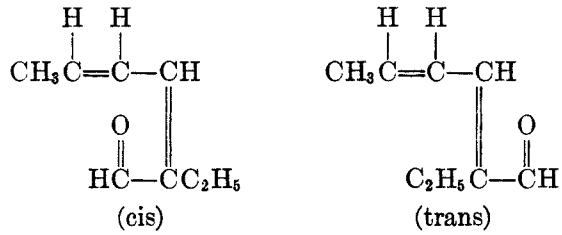


The formulation of the above was deduced from the following determinations: C and H analysis, molecular weight obtained from the saponification equivalent, absorption of one molecule of hydrogen, formation of a monoacetylated derivative, catalytic hydrogenation to the corresponding saturated glycol ester, saponification, which yielded butyric acid and an unsaturated glycol which was converted to the corresponding saturated glycol.

Hence, a condensation occurred, whereby two molecules of butyraldehyde and one of crotonaldehyde reacted to form an unsaturated glycol ester. From a consideration of its structure, it is indicated that the compound is formed in two stages. First, the formation of a mixed unsaturated aldol between one molecule of crotonaldehyde and one of butyraldehyde, and then an esterification between the aldol and a second molecule of butyraldehyde:



Additional evidence for such a formulation was derived from the isolation of the cis and trans isomeric forms of the conjugated aldehydes, which can result from the dehydration of the mixed aldol during the course of the condensation:



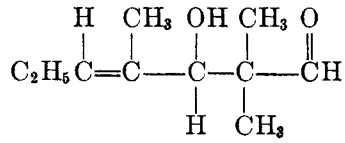
(cis) (trans)

2-Ethyl-2, 4-hexadiene-1-al

The latter were shown to have the same empirical formula, but different physical constants, *i.e.*, density and refractive index. They both took up hydrogen equivalent to two double bonds. The 2,4-dinitrophenylhydrazones and the

semicarbazones have different melting points. On hydrogenation they yielded the same saturated aldehyde derivative of 2,4-dinitrophenylhydrazine, namely that of *alpha*-ethylhexaldehyde. The position isomer, 2-ethyl-2,5-hexadiene-1-al, which could arise from the rearrangement of the double bond in the original crotonaldehyde from the 2 position to the 3, and which on hydrogenation could yield the same derivative as mentioned above, can be discounted. Young (7) who studied the composition of crotonaldehyde, states that such a rearrangement is very unlikely, since there is no substitution in position 3.

Morawetz (8) attempted to effect a trimolecular condensation between α-methyl-β-ethylacrolein (a homolog of crotonaldehyde) and isobutyraldehyde in the presence of alcoholic potassium hydroxide, but obtained only the following mixed unsaturated aldol:



Although no mixed aldol was isolated in our work, its formation was indirectly confirmed by the isolation of its dehydration products. However, Morawetz's condensate, being entirely analogous to the aldol, which is assumed to be the intermediary stage of the condensation described herein, supports the correctness of the structural formulation given for it.

Since the condensation with the aid of the complex catalyst is trimolecular, butyraldehyde alone would be expected to condense in the same way and yield the corresponding saturated glycol ester. This view proved to be correct.

Accordingly, the condensation of butyraldehyde with crotonaldehyde in the presence of the coordination alkoxide represents another type of the "crossed" Cannizzaro reaction, in which the condensation of the dissimilar aldehydes proceeds *via* a mixed aldol and another molecule of the saturated aldehyde, through the bifunctional agency of the catalyst.

In view of this behavior of the catalyst, it was deemed justifiable to test its general applicability in the aliphatic series of saturated aldehydes, both for preparative purposes, as well as from the possibility of a closer study of its manner of action. Magnesium-aluminum isopropoxide and aluminum-magnesium butoxide were also employed in order to investigate any qualitative or quantitative differences in this type of catalyst. Comparison was also made of the action of these coordination alkoxides with the simple aluminum alkoxides under the same conditions.

The results of the experiments have shown that coordination catalysts of the magnesium-aluminum alkoxide type are generally applicable to the α-CH_2 saturated aldehydes, enabling a trimeric condensation to take place to form glycol esters.

In Table I are presented the percentage yields of the glycol esters obtained with such aldehydes under the influence of the various catalysts. The low yield of the glycol ester from the self-condensation of acetaldehyde is attributed to side-polymerization reactions, *i.e.*, formation of metaldehyde and paraldehyde.

Search of the literature showed that workers of the Lieben school (9) had obtained glycol esters in the presence of alkali, only from the condensation of α-alkyl aldehydes, namely, isobutyraldehyde and methylethylacetaldehyde. Rosinger's claim to have obtained a glycol ester from isovaleraldehyde, prepared from fermentation amyl alcohol, was disproved by Cihlar, who, using the synthetic product, obtained under the original conditions only the aldol and the unsaturated aldehyde.

TABLE I

α-CH_2-ALDEHYDES	CATALYST	GLYCOL ESTER, %	
Acetaldehyde	MgAlEt MgAlIsopr MgAlBut	24.4 23.5 24.0	monoacetate of 1,3-butanediol
Propionaldehyde	MgAlEt MgAlIsopr	65 61	monopropionate of 2-methyl-1,3-pentanediol
n-Butyraldehyde	MgAlEt MgAlIsopr MgAlBut AlIsopr AlEt	54.5 44.5 42 — —	monobutyrate of 2-ethyl-1,3-hexanediol
Isovaleraldehyde	MgAlEt	52.0	monoisovalerate of 2-isopropyl-6-methyl-1,3-hexanediol
n-Valeraldehyde	MgAlEt MgAlIsopr	62.5 57.1	monovalerate of 2-propyl-1,3-heptanediol
n-Hexaldehyde	MgAlEt MgAlEt MgAlIsopr AlIsopr	61 63 61 —	monohexanoate of 2-butyl-1,3-octanediol
n-Heptaldehyde	MgAlEt MgAlBut AlIsopr	51 51 —	monoheptanoate of 2-amyl-1,3-nonanediol

The Lieben school also proved the structure of the glycol esters, which was later confirmed by v. Braun and Manz (10). However, α-CH_2 aldehydes exhibited a much different behavior, leading solely to aldolization and crotonization.

Grignard and Fluchaire (11), doing esterification studies with catalysts of the general formula, ROMgI, isolated the glycol ester of butyraldehyde as a by-product of the condensation of the aldehyde with C_2H_5OMgI.

It is evident that the action of the complex alkoxides is essentially different from that of the simple alkoxides. Under the conditions employed, the latter give only simple esters and no higher distillable products arise. On the other hand, with the coordination compounds, the formation of the simple esters

occurred as a side reaction, which proceeded to a very small extent. Moreover, the trimolecular condensation yielded in small amounts α,β-unsaturated aldehydes, the dehydration products of the aldols. Their isolation gave an indication of the probable course of the reaction.

In contradistinction to the α-CH_2 aldehydes, the α-alkyl substituted aldehydes exhibited a surprisingly different behavior. With simple alkoxides, both types of aldehydes can be condensed in an identical manner and with similar ease to give simple esters.

α-CH_2		α-ALKYL	
Butyraldehyde	80% yield	Isobutyraldehyde	75% yield
n-Hexaldehyde	60% yield	α-Ethylbutyraldehyde	60% yield

Aluminum isopropoxide was used as a catalyst in the above cases.

TABLE II

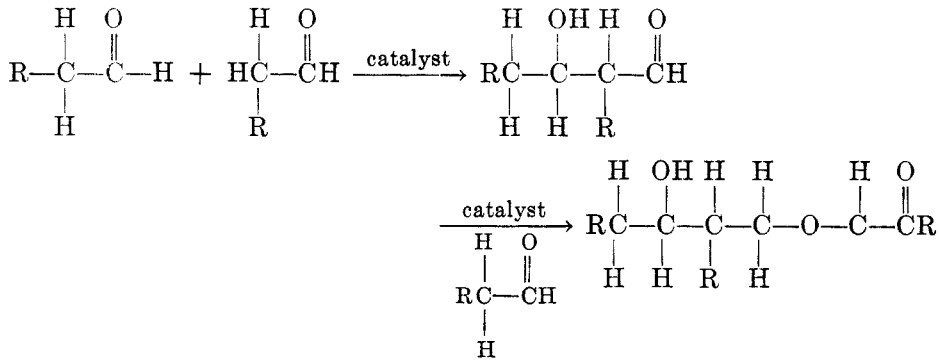
α-ALKYL ALDEHYDES	CATALYST	GLYCOL ESTER, %	SIMPLE ESTER, %	
Isobutyraldehyde	MgAlEt	10.9[a]	56.5	Isobutylisobutyrate
	MgAlIsopr	12.8[a]	56.3	
	MgAlBut	20.6[a]	50.1	
	AlIsopr	—	75.0	
α-Ethylbutyraldehyde	MgAlEt	6.0[b]	57.4	2-ethyl-butyl-2-ethyl-butyrate
	MgAlIsopr	4.0[b]	59	
	MgAlBut	4.0[b]	58	
	AlIsopr	—	60	
α-Ethylhexaldehyde	MgAlEt	—	75	2-ethylhexyl-2-ethyl-hexanoate
	MgAlIsopr	—	69	
	MgAlBut	—	75	
	AlIsopr	—	75	

[a] Monoisobutyrate of 2,2,4-trimethyl-1,3-pentanediol.
[b] Monoethylbutyrate of 2,2,4-triethyl-1,3-hexanediol.

This lack of distinction no longer exists when the complex alkoxides are employed. As was mentioned previously, with α-CH_2 aldehydes, the main products of the reaction are the glycol esters. On the other hand, the α-alkyl aldehydes condense to give mainly the simple esters, the trimeric condensation occupying a secondary place. In the last case mentioned, the complex catalysts, therefore, behave like the simple alkoxides. Moreover, with the increase in the length of the chain in the α-alkyl aldehydes, the yield of the glycol ester is considerably lowered in the following order: isobutyraldehyde, α-ethylbutyraldehyde, α-ethylhexaldehyde (Table II). The last one gives no glycol ester at all.

Such a sharply contrasting behavior can readily be explained on the basis of the primary stage of aldolization. The important role that the aldol plays in the intermediary stage is brought out as follows: In practically all of the cases where the α-CH_2 aldehydes had been condensed, unsaturated aldehydes, *i.e.*, dehydration products of the aldols, were obtained under the influence of the complex catalysts. Ordinarily, with alkali, aldolization, which is a reversible

process, is carried to completion through dehydration to the α,β-unsaturated aldehydes. Such a dehydration can be prevented if the aldol is "trapped," as it were, by another molecule of the reactant. Accordingly, the formation of the glycol esters can be embraced in such a concept: Two molecules of the aldehyde react to form the aldol, and then, instead of the expected dehydration, under the strong esterifying influence of the coordination catalyst, the aldol is trapped by another molecule of the original aldehyde, thus producing the glycol ester:



This being the case, we should expect the over-all yield of the higher ester to be dependent on conditions favorable toward intermediary aldolization. Such conditions are evidently not present for the trimolecular condensation of α-alkyl aldehydes. One factor would be, for example, the ease of aldolization. Apparently, the aldol takes a longer time to form in the case of these aldehydes, and the equilibrium would be greatly on the side of the unreacted aldehyde. The variance in the yields of the glycol esters with the lengthening of the chain can be understood on the basis that such an increase impedes aldolization.

Support for this view can be found in the work of Usherwood (12), who made studies of the equilibration of α-alkyl aldehydes and their aldols. In the isobutyraldehyde-aldol system the equilibrium conditions greatly favor the aldehyde. A still more pronounced effect is observed in the next higher homolog, α-methylbutyraldehyde. Furthermore, under the conditions of the experiment, only very small amounts of the α-methylbutyraldol were isolated and only by cold treatment for several weeks, could moderate amounts be obtained.

For the observation of temperature effects, an experiment was performed with isobutyraldehyde wherein the spontaneous evolution of heat was allowed to continue without external cooling as was usual in the general procedure. Comparison of the yield with and without external cooling shows that the yield of the glycol ester is reduced by approximately half, and at the same time the quantity of the simple ester is noticeably increased:

ISOBUTYRALDEHYDE AND MAGNESIUM-ALUMINUM-ISOPROPOXIDE

	GLYCOL ESTER	SIMPLE ESTER
Without cooling	6.5%	65%
With cooling	12.8%	56.3%

Because of the apparent greater difficulty of aldol formation with α-alkyl aldehydes, the esterification role of the catalyst is brought to the fore, and consequently the main part of the aldehyde is converted to the simple ester.

From the above considerations we may conclude that one of the conditions for the formation of glycol esters with coordination catalysts in satisfactory yields is that the aldehyde must have a CH_2 group in the α position. Alkyl substitution brings in structural limitations which appear to diminish the rate of aldolization, which is requisite as one of the intermediary stages in the synthesis of glycol esters.

There are no qualitative differences among the complex alkoxides. Quantitatively magnesium-aluminum ethoxide is a somewhat better condensing agent but its difficulty of preparation and its low yield must be borne in mind.

Trimolecular condensations of the type described of acetaldehyde, propionaldehyde, *n*-valeraldehyde, isovaleraldehyde, *n*-hexaldehyde, and α-ethylbutyraldehyde are not reported in the literature.

EXPERIMENTAL[4, 5]

Materials. Acetaldehyde obtained from Eastman Kodak Co. (E.K.), b.p. 20–22°. Propionaldehyde, from E.K., dried with sodium sulfate and fractionated, b.p. 49–50°. Isobutyraldehyde (E.K.), redistilled, b.p. 63.5°. *n*-Butyraldehyde (E.K.), redistilled, b.p. 74–75°. *n*-Valeraldehyde (E.K.), redistilled, b.p. 102–103°. Isovaleraldehyde, from the potassium dichromate oxidation of refined isoamyl alcohol, obtained from U.S. Industrial Chemicals, Inc. The alcohol was carefully fractionated in an electrically jacketed glass-helice-packed column and the portion boiling at 130–130.5° (n^{26} 1.3882) was used for the oxidation; boiling point of the aldehyde, 92.5°. *n*-Heptaldehyde (E.K.), redistilled, b.p. 40–42° (10 mm.). α-Ethylbutyraldehyde, obtained from the Carbide and Carbon Chemicals Corp. (C. and C.). Dried with sodium sulfate and fractionated, b.p. 115–116°. *n*-Hexaldehyde (C. and C.), dried and fractionated, b.p. 66.5–67.5° (93 mm.). α-Ethylhexaldehyde (C. and C.), dried and fractionated, b.p. 71–71.5° (28 mm.). Crotonaldehyde (C. and C.), dried and fractionated, b.p. 102–103°.

Preparation of catalysts. For the preparation of the simple alkoxides, *i.e.* aluminum ethoxide and aluminum isopropoxide, the customary procedure was essentially followed.

Coordination catalysts. Magnesium-aluminum butoxide $[Al(OC_4H_9)_4]_2Mg$. Magnesium (9.6 g.) and 21.6 g. of aluminum were added to a large excess of dry *n*-butyl alcohol, in a one liter r.b. flask attached to a reflux condenser provided at the top with a drying tube. A few crystals of iodine and 2 g. of mercuric chloride were then introduced. A moderate evolution of hydrogen ensued which became more vigorous as the contents became warmer from the heat of reaction. After the self-reaction subsided, the contents were refluxed for several hours.

The blackish, viscous mass was then transferred to a large Claisen flask with a low, wide side-arm, and the excess alcohol distilled off by suction. At lower pressure the complex alkoxide came over at 290–295° (2 mm.) as a viscous liquid which solidified in the receiver as a milky-white, glass-like solid. It could be readily broken up with a porcelain spatula. The amount totalled 231 g.; yield 88%.

Magnesium-aluminum isopropoxide: $[Al(OC_3H_7)_4]_2Mg$. Four and eight-tenths grams of magnesium and 10.8 g. of aluminum were added to an excess of anhydrous isopropyl alcohol.

[4] The microanalyses here reported were performed by Mr. Joseph Alicino of this laboratory.

[5] The authors' indebtedness for certain starting materials used in this investigation is expressed to Carbide and Carbon Chemicals Corporation, New York, N. Y., and to the U.S. Industrial Chemicals, Inc., Baltimore, Md.

Upon addition of small quantities of iodine and mercuric chloride, immediate evolution of hydrogen set in. When the initial reaction subsided, the contents were refluxed for several hours. The excess alcohol was then driven off by suction from the blackish-gray mass. The complex alkoxide came over as a clear white, viscous liquid at 225–226° (6 mm.). It began to crystallize in clumpy white needles. However, only a small part solidified, the main portion retaining a sirupy consistency; yield 92 g. (85%).

Magnesium-aluminum ethoxide: $[Al(OC_2H_5)_4]_2Mg$. This was the most difficult to prepare and the yields were rather low. Because it solidified very rapidly when distilled, difficulties were encountered when it choked up the side-arm of the distilling flask. The procedure was followed out as above. From 2.5 g. of magnesium and 4.8 g. of aluminum in excess ethyl alcohol, 25 g. of the coordination compound was obtained; yield 56%. On distillation it came over at 235–237° (1 mm.). It rapidly solidified into a transparent crystalline mass.

General procedure for the condensation. A definite quantity of the aldehyde was weighed into an Erlenmeyer flask and a weighed amount (5%) of the catalyst was then added and the flask quickly stoppered. Warming took place and the temperature began to rise rapidly. Consequently, the contents were cooled under the tap from time to time. The rise in temperature usually stopped within an hour, and the flask was allowed to stand overnight. During the condensation the contents attained a color varying from yellowish to greenish amber to amber red, depending on the nature of the reactant. Moreover, in most cases a fluorescence appeared. The simple alkoxides dissolved very slowly as the reaction proceeded, whereas the complex catalysts readily went into solution. In the instance where the trimolecular condensation took place, the completion of the reaction was indicated upon shaking of the reactants by formation of a foam on the surface of the liquid, which lasted for a few minutes.

Without further treatment, the condensate was transferred to a flask provided with an electrically jacketed fractionating column of the Vigreux type. The lower-boiling components were distilled off by suction and the pressure gradually lowered. The higher condensates, *i.e.*, the glycol esters were separated at the vacuum of an oil-pump.

The glycol ester fractions were treated with a dilute solution of potassium carbonate and taken up with ether. The ethereal layer was dried with sodium sulfate, evaporated off, and the remainder slowly rectified. The products treated in this manner were used for further analytical determinations. Refractometer readings were frequently employed, either to establish the identity of fractions in the various runs, or as an indication of the completeness of separation of the various components.

General analytical procedures. Acetylation. About 3 to 4 cc. of the glycol ester was mixed with twice the amount of acetic anhydride and gently refluxed for several hours. When the reaction mixture no longer gave a positive test for the hydroxyl group with the ceric nitrate reagent, it was poured into 100 cc. of cold water. The excess anhydride was then treated with sodium carbonate. The oily layer was taken up with ether, well shaken, and separated. After drying with sodium sulfate, the ethereal extract was evaporated and the residue distilled in a vacuum.

Saponification. A definite amount of the ester was added to a large excess of alcoholic alkali. The contents were gently refluxed for several hours. Most of the solvent was then removed by ordinary distillation. Water was subsequently added for the separation of the glycol layer. The latter was extracted twice with ether and separated from the aqueous layer. The ethereal solution was thoroughly dried with anhydrous sodium sulfate, evaporated, and the remainder distilled in a small Claisen flask.

The water layer was acidified with sulfuric acid to Congo red, extracted with ether, and upon separation was treated in the same way as the glycol extract.

Hydrogenation. The apparatus and procedure as described by Rampino and Nord (13), and palladium-polyvinyl alcohol catalyst were employed. One- to two-gram samples of the unsaturated compound were taken for the hydrogenation. For isolation of the hydrogenated derivative, the contents were transferred to an Erlenmeyer flask and saturated

with sodium sulfate to flocculate the colloidal catalyst. After filtration, the saturated substance was extracted twice with ether and separated. The ether solution was evaporated after having been dried with sodium sulfate. The residue was then distilled in a vacuum.

Miscellaneous derivatives. For the preparation of these the customary directions were essentially utilized (14). The *p*-bromophenacyl esters of the acids and the 3,5-dinitrobenzoates of the alcohols were mixed with authentic specimens for further identification.

Condensation of butyraldehyde with crotonaldehyde. Seventy grams (1 mole) of freshly distilled crotonaldehyde and 72 g. (1 mole) of butyraldehyde were treated with 7 g. of magnesium-aluminum ethoxide. The condensate was a somewhat viscous amber fluid. Four such runs were made and submitted to separate fractionations in a D. M. Smith glass-helice, electrically jacketed column. It will be unnecessary to record the data of all the components obtained in all the four runs, since we are merely concerned with the higher-boiling portions. However, complete data of the first run (A) will be given.

FRACTIONATION OF CONDENSATE

RUN	FRACTION	B. P. °C	PRESS. MM.		YIELD
A	1	40–45	(120)	17 g.	crotonaldehyde
	2	45–46	(62)	10 g.	"
	3	30–35	(62)	6 g.	"
	4	28–35	(6)	3 g.	butyl butyrate
	5	45–50	(6)	19 g.	
	6	50–58	(6)	16 g.	
	7	58–75	(6)	10 g.	
B	5	46–60	(3)	25.5 g.	
	6	65–70	(3)	21 g.	
C	5	40–60	(1)	20 g.	
	6	60–75	(1)	14 g.	
D	5	35–45	(5)	14 g.	
	6	45–58	(5)	15 g.	
	7	60–80	(4)	10 gr.	

All the fractions numbered 5 were combined and shaken twice with 5% potassium carbonate, extracted with ether, dried and again fractionated. The same procedure was carried out for the combined remaining fractions, *i.e.*, A 6 and 7, B 6, C 6, D 6 and 7.

Rectification of the combined fractions numbered 5:

1.	32–34°	(2 mm.)	12 g.	n^{24}	1.4848
2.	35–40°	(2 mm.)	12 g.		1.5032
3.	42–50°	(2 mm.)	14 g.		1.4682

At this point the combined higher-boiling portion was added and fractionation resumed:

4.	35–42°	(2 mm.)	9 g.	n^{23}	1.4817
5.	42–50°	(2 mm.)	7 g.		1.4668
6.	53–58°	(2 mm.)	22 g.		1.4580
7.	62–70°	(2 mm.)	16 g.		1.4540
8.	68–71°	(2 mm.)	15 g.		1.4552

As indicated by the refractive indices, all the fractions with the exception of 1, 2, and 4, are mainly composed of the same substance, as was subsequently found out by distillation in a Claisen flask. Moreover, the boiling points observed were much higher than those above. The difference in the value of the boiling points and their wide range is due to the unavoidable cooling and flooding which occurred at the top of the fractionating column in the vacuum employed. Rectification in a Claisen flask:

3rd fraction	103–105°	(2 mm.)	10 g. n^{24}	1.4510
5th fraction	103–105°	(2 mm.)	6 g.	1.4512
6th fraction	104.5–105.5°	(2 mm.)	22 g.	1.4530
7th fraction	103–105°	(2 mm.)	15 g.	1.4512
8th fraction	105–106°	(2 mm.)	14.5 g.	1.4538

The above were combined and redistilled. Final boiling point 104.5–105.5° (2 mm.) n^{22} 1.4530. This component was identified as the condensation product between two molecules of butyraldehyde and one of crotonaldehyde, *i.e.*, monobutyrate of 2-ethyl-4-hexene-1,3-diol; d^{22} 0.9541; n^{22} 1.4530.

Anal. Calc'd for $C_{12}H_{22}O_3$: C, 67.24; H, 10.36; Sapon. equiv. (mol. wt.), 214.3.
Found: C, 66.72; H, 10.33; Sapon. equiv. (mol. wt.), 227.5, 224.1.

It took up hydrogen equivalent to one double bond.

Monoacetyl derivative: b.p. 89–90° (1 mm.); d^{23} 0.9462; n^{23} 1.4412.

Anal. Calc'd for $C_{14}H_{24}O_4$: C, 65.58; H, 9.44.
Found: C, 65.06; H, 9.63.

Conversion to the saturated glycol ester. Catalytic hydrogenation of the double bond yielded a somewhat viscous, water-white liquid, b.p. 100–102° (0.5 mm.). This proved to be identical with the glycol ester obtained from the condensation of butyraldehyde (see later) alone, *i.e.*, the monobutyrate of 2-ethyl-1,3-hexanediol; d^{21} 0.9492; n^{21} 1.4462.

Anal. Calc'd for $C_{12}H_{24}O_3$: C, 66.62; H, 11.19.
Found: C, 66.67; H, 10.79.

Saponification. The hydroxy compound was a viscous, almost colorless liquid, boiling at 92–98° (3 mm.). Upon redistillation it passed over at 88–90° (1 mm.); n^{23} 1.4600. Hydrogenation converted it to the corresponding saturated dihydroxy compound, *i.e.*, 2-ethyl-1,3-hexanediol (see later); n^{25} 1.4515.

Anal. Calc'd for $C_8H_{18}O_2$: C, 65.73; H, 12.38.
Found: C, 65.27; H, 12.36.

The acid portion yielded butyric acid. The *p*-bromophenacyl ester melted at 62°.

2-Ethyl-2,4-hexadiene-1-al (cis and trans). The fractions 1, 2, and 4 previously mentioned were combined and rectified. They yielded two close-boiling components which proved to be cis and trans isomeric conjugated aldehydes: I, b.p. 42–43° (2 mm.); II, b.p. 44–45° (2 mm.). Both were yellow, readily flowing liquids with a pungent odor. I, $d^{21.5}$ 0.8857; $n^{21.5}$ 1.4780; II, $d^{21.5}$ 0.9112; $n^{21.5}$ 1.5040.

Anal. Calc'd for $C_8H_{12}O$: C, 77.36; H, 9.74.
Found: (I), C, 77.15; H, 9.68; (II), C, 77.10; H, 9.76.

Semicarbazones. Twice recrystallized from 50% alcohol, white, flaky, flat, shiny plates, (I) m.p. 185–186°; (II) m.p. 201–202°.

Anal. Calc'd for $C_9H_{15}N_3O$: N, 23.18.
Found: (I), N, 23.15; (II), N, 23.19.

2,4-Dinitrophenylhydrazones. Twice recrystallized from alcohol, (I) small, red crystals, m.p. 136–137°. (II) Crimson red, fine fluffy needles, m.p. 187.5–188.5°.

Anal. Calc'd for $C_{14}H_{16}N_4O_4$: N, 18.42.
Found: (I), N, 18.46. (II), N, 18.34.

Hydrogenation. Hydrogen calculated for two double bonds was taken up. The aldehydic product derived therefrom yielded the same 2,4-dinitrophenylhydrazones in both cases; (I), m.p. 114°; (II), m.p. 114°.

Anal. Calc'd for $C_{14}H_{20}N_4O_4$: N, 18.18.
Found: (I), N, 18.10; (II), N, 17.91.

When the two were mixed, the melting point was not depressed. When each was separately mixed with the 2,4-dinitrophenylhydrazine derivative of 2-ethylhexaldehyde, no depression of the melting point was observed.

Condensation of butyraldehyde: (monobutyrate of 2-ethyl-1,3-hexanediol). Forty-eight grams of the freshly distilled aldehyde was treated with 2.4 g. of the alkoxides. Magnesium-aluminum butoxide: The glycol ester portion boiled at 114–120° (2 mm.); 18 g., yield (based on the reacted aldehyde) 42%. All subsequent yields will be calculated on this basis. Magnesium-aluminum isopropoxide: The main fraction boiled at 105–109° (1 mm.); yield 20 g. (44.5%). Magnesium-aluminum ethoxide: Glycol ester portion boiled at 105–107° (0.5 mm.); yield 23.2 g. (54.5%). Aluminum isopropoxide: Only the simple ester, butyl butyrate was obtained, b.p. 59–61° (14 mm.); yield 38 g. (80%). Aluminum ethoxide: Only the simple ester was obtained, b.p. 52–54° (13 mm.); yield 40 g. (83%).

Identification of the glycol ester. The higher condensate was shaken with dilute potassium carbonate and redistilled, b.p. 103–104° (0.5 mm.); d^{21} 0.9433; n^{21} 1.4438.

Anal. Calc'd for $C_{12}H_{24}O_3$: C, 66.62; H, 11.19; Sapon. equiv. (mol. wt), 216.3.
Found: C, 66.37; H, 11.13; Sapon. equiv. (mol. wt.), 209.1, 208.9.

Monoacetyl derivative, b.p. 86–88° (0.5 mm.); d^{25} 0.9570; n^{25} 1.4368.

Anal. Calc'd for $C_{14}H_{26}O_4$: C, 65.10; H, 10.14.
Found: C, 65.20; H, 10.06.

Saponification. The dihydroxy compound, which was a viscous, colorless liquid, boiled at 94–96° (0.5 mm.) (2-ethyl-1,3-hexanediol); d^{22} 0.9325; n^{22} 1.4530.

Anal. Calc'd for $C_8H_{18}O_2$: C, 65.72; H, 12.40.
Found: C, 65.79; H, 12.12.

The acidified part was identified as butyric acid, m.p. of the *p*-bromophenacyl ester 63°.

Diacetyl derivative of the glycol, b.p. 87–88° (1 mm.); d^{23} 0.9759; n^{23} 1.4328.

Anal. Calc'd for $C_{12}H_{22}O_4$: C, 62.60; H, 9.60.
Found: C, 62.88; H, 9.88.

Just before the glycol ester fraction, small amounts of α-ethyl-β-isopropylacrolein distilled over. Redistillation gave the b.p. 173–175.° The 2,4-dinitrophenylhydrazone melted at 123–124°. The melting point was not lowered when the derivative was mixed with a known sample.

The butyl butyrate was identified by conversion into butyric acid (*p*-bromophenacyl ester m.p. 63°) and butyl alcohol (3,4-dinitrobenzoate, m.p. 63–63.5°).

Condensation of acetaldehyde: (monoacetate of 1,3-butanediol). Magnesium-aluminum butoxide: 4 g. of the aldehyde was treated with 2.2 g. of the catalyst; high-boiling portion, 80–90° (13 mm.), 10.5 g., yield 24%. Magnesium-aluminum ethoxide: 55 g. of the aldehyde and 2.5 g. of the alkoxide; higher condensate, b.p. 80–90° (13 mm.) 13.4 g., yield 24.4%. Magnesium-aluminum isopropoxide: 52 g. of the aldehyde and 2.5 g. of the catalyst; higher fraction: b.p. 80–92° (13 mm.), 13.4 g., yield 23.5%. Other products which formed in the course of the condensation were ethyl acetate, crotonaldehyde (identified through the 2,4-dinitrophenylhydrazone, m.p. 189–190°), paraldehyde and metaldehyde (decomposed with dilute sulfuric acid to acetaldehyde).

Identification of the glycol ester. After treatment with dilute potassium carbonate it was rectified, b.p. 87–89° (13 mm.), as a colorless, somewhat mobile liquid; d^{25} 1.005; n^{25} 1.4182.

Anal. Calc'd for $C_6H_{12}O_3$: C, 54.55; H, 9.09; Sapon. equiv. (mol. wt.), 132.2.
Found: C, 54.50; H, 8.89; Sapon. equiv. (mol. wt.), 128.5.

Acetylation. The final distillate boiled at 92–94° (13 mm.), *i.e.*, the diacetate of 1,3-butanediol; d^{25} 1.028; n^{25} 1.4145.

Anal. Calc'd for $C_8H_{14}O_4$: C, 55.15; H, 8.09; Sapon. equiv. (87.1 × 2 mol. wt.); 174.2.
Found: C, 55.14; H, 8.16; Sapon. equiv. (87.48 × 2 mol. wt.), 175.

Saponification of the diacetate. Numerous extractions of the reaction mixture after saponification with ether-ethyl acetate mixture gave a very small quantity of a viscous liquid boiling at 203–205° from the unacidified portion of the saponified ester. It was extremely hygroscopic, and as a result did not give a satisfactory analysis: 1,3-butanediol.

Anal. Calc'd for $C_4H_{10}O_2$: C, 53.27; H, 11.11.
Found: C, 51.27; H, 11.18.

The acidified portion readily yielded acetic acid, *p*-bromophenacyl ester, m.p. 85°.

Condensation of propionaldehyde: monopropionate of 2-methyl-1,3-pentanediol. Magnesium-aluminum isopropoxide: 64 g. of the aldehyde was treated with 2.5 g. of the alkoxide; main fraction 86–90° (2 mm.), 37.6 g., yield 61%. Magnesium-aluminum ethoxide: 48.8 g. of the aldehyde and 2.5 g. of the catalyst; main component 89–92° (3 mm.), 29.4 g.; yield 65%.

In the course of the condensation a small amount of α-methyl-β-ethylacrolein was formed. The 2,4-dinitrophenylhydrazone melted at 159.5°. Mixing with a known sample produced no depression of the melting point.

Identification of the glycol ester. The higher-boiling condensate was redistilled after

shaking with dilute potassium carbonate, final boiling point 92–94° (2 mm.); d^{20} 0.9788; n^{20} 1.4369.

Anal. Calc'd for $C_9H_{18}O_3$: C, 62.06; H, 10.44.
Found: C, 61.76; H, 10.50.

Monoacetyl derivative, b.p. 71–72° (0.5 mm.); $d^{18.5}$ 0.9985; $n^{18.5}$ 1.4302.

Anal. Calc'd for $C_{11}H_{20}O_4$: C, 61.07; H, 9.33.
Found: C, 60.77; H, 9.20

Saponification. Glycol: 2-methyl-1,3-pentanediol, b.p. 85–86° (1 mm.); d^{22} 0.9737; n^{22} 1.4486.

Anal. Calc'd for $C_6H_{14}O_2$: C, 60.96; H, 11.94.
Found: C, 60.86; H, 11.88.

Acid: Propionic acid, *p*-bromophenacyl ester, m.p. 63°.

Condensation of isovaleraldehyde: monoisovalerate of 2-isopropyl-6-methyl-1,3-hexanediol. Magnesium-aluminum ethoxide: 42 g. of the aldehyde was treated with 2 g. of the catalyst; high-boiling fraction, b.p. 142–149° (2 mm.), 22 g.; yield 52%. After the usual treatment it boiled at 137–139° (1 mm.); d^{32} 0.9242; n^{32} 1.4421.

Anal. Calc'd for $C_{15}H_{30}O_3$: C, 69.74; H, 11.70.
Found: C, 69.60; H, 11.44.

Monoacetylated product: b.p. 126–128° (1 mm.); d^{28} 0.9386; n^{28} 1.4381.

Anal. Calc'd for $C_{17}H_{32}O_4$: C, 67.96; H, 10.75.
Found: C, 67.87; H, 10.64.

Saponification. Glycol: 2-isopropyl-6-methyl-1,3-hexanediol, b.p. 105–106° (1 mm.). In spite of repeated fractionation the glycol could not be obtained analytically pure; d^{23} 0.9161; n^{23} 1.4528. Acid: Isovaleric acid, *p*-bromophenacyl ester, m.p. 67.5°.

Condensation of n*-valeraldehyde: the monovalerate of 2-propyl-1,3-heptanediol.* Magnesium-aluminum ethoxide: 40 g. of the aldehyde and 2 g. of the catalyst yielded a high-boiling liquid, b.p. 145–160° (2 mm.); yield 26.2 g. (62.5%). Magnesium-aluminum isopropoxide: 35 g. of the aldehyde and 2 g. of the alkoxide; main fraction b.p. 144–155° (2 mm.); yield 20.2 g. (57.1%).

Identification of the glycol ester: After the usual treatment and redistillation, b.p. 138–139° (1 mm.); d^{28} 0.9203; n^{28} 1.4442.

Anal. Calc'd for $C_{15}H_{30}O_3$: C, 69.74; H, 11.70.
Found: C, 70.03; H, 11.82.

Monoacetylated product, b.p. 135–137° (1 mm.); d^{23} 0.9344; n^{28} 1.4365.

Anal. Calc'd for $C_{17}H_{32}O_4$: C, 67.96; H, 10.75.
Found: C, 68.00; H, 10.60.

Saponification: Glycol, 2-propyl-1,3-heptanediol, b.p. 107–108° (1 mm.); d^{28} 0.9155; n^{28} 1.4513.

Anal. Calc'd for $C_{10}H_{22}O_2$: C, 68.90; H, 12.74.
Found: C, 68.81; H, 12.45.

Acid: *n*-valeric acid, *p*-bromophenacylester, m.p. 74.5°.

Condensation of n*-hexaldehyde: monohexanoate of 2-butyl-1,3-octanediol.* (About 50% of it remained unreacted with the complex catalysts.). Magnesium-aluminum ethoxide: 50 g. of the aldehyde was treated with 2.5 g. of the alkoxide. First run: Main fraction, b.p. 145–160° (1 mm.), 15 g. yield (61%). Second run: b.p. 135–150° (0.5 mm.), 16 g., yield (63%). Magnesium-aluminum isopropoxide: Amounts same as above; main fraction b.p. 150–165° (1 mm.), 17.2 g. yield (61%). Identification of the ester: After the usual treatment and rectification, the high condensate boiled at 150–152° (1 mm.); d^{24} 0.9240; n^{24} 1.4500.

Anal. Calc'd for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08.
Found: C, 71.85; H, 11.92.

Monoacetyl derivative: b.p. 132–134° (0.5 mm.); d^{21} 0.9388; n^{21} 1.4462.

Anal. Calc'd for $C_{20}H_{38}O_4$: C, 70.13; H, 12.95.
Found: C, 70.36; H, 12.84.

Saponification: Glycol, 2-butyl-1,3-octanediol, b.p. 128–129° (1 mm.); d^{25} 0.9184; n^{25} 1.4570.

Anal. Calc'd for $C_{12}H_{26}O_2$: C, 71.23; H, 12.95.
Found: C, 71.17; H, 12.84.

Acid: *n*-hexanoic acid, *p*-bromophenacyl ester, m.p. 72°. With aluminum isopropoxide (2.5 g.) and 50 g. of the aldehyde, the main component was the simple ester, hexyl hexanoate, b.p. 105–108° (10 mm.); yield 30 g. (60%). There were no higher-boiling fractions. Saponification of the simple ester: Alcohol: *n*-hexanol, 3,5-dinitrobenzoate, m.p. 58–59°. Acid: *n*-hexanoic, *p*-bromophenacyl ester, m.p. 72°.

Condensation of n-*heptaldehyde: monoheptanoate of 2-amyl-1,3-nonanediol.* Fifty grams of the aldehyde and 2.5 g. of the catalyst were used. Magnesium-aluminum butoxide: main fraction: b.p. 165–180° (0.5 mm.); yield 22 g. (51%). Magnesium-aluminum ethoxide: main fraction: b.p. 165–183° (0.5 mm.); yield 23 g. (51%). Aluminum isopropoxide: 34 g. of the simple ester, heptyl heptanoate, b.p. 135–137° (8 mm.); yield 74%. The latter was identified by its saponification products, *n*-heptyl alcohol, 3,5-dinitrobenzoate, m.p. 46–47°; *n*-heptanoic acid, *p*-bromophenacyl ester, m.p. 72°.

Identification of the glycol ester. After the usual procedure, and a very slow and careful distillation the high condensate boiled at 167–170° (0.5 mm.); d^{21} 0.9065; n^{21} 1.4510.

Anal. Calc'd for $C_{21}H_{42}O_3$: C, 73.64; H, 12.35.
Found: C, 73.69; H, 12.29.

Monoacetyl derivative, b.p. 160–164° (1 mm.); $d^{18.5}$ 0.9184; $n^{18.5}$ 1.4484.

Anal. Calc'd for $C_{23}H_{44}O_4$: C, 71.83; H, 11.52.
Found: C, 71.97; H, 11.41.

Saponification: Glycol, 2-amyl-1,3-nonanediol, b.p. 125–127° (0.5 mm.); d^{23} 0.8984; n^{23} 1.4545.

Anal. Calc'd for $C_{14}H_{30}O_2$: C, 72.98; H, 13.12.
Found: C, 73.15; H, 13.34.

Acid, *n*-heptanoic acid, *p*-bromophenacyl ester, m.p. 71–72°.

Condensation of isobutyraldehyde: monoisobutyrate of 2,2,4-trimethyl-1,3-pentanediol. Forty-eight grams of the aldehyde and 2.5 g. of the alkoxides were used. The complex alkoxides gave as the main product the simple ester, isobutyl isobutyrate, and in smaller amounts, the glycol ester. Magnesium-aluminum ethoxide: simple ester, b.p. 53–55° (18 mm.), 26 g. (56.5%), and the glycol ester, b.p. 105–110° (2 mm.), 5.0 g. (10.9%). Magnesium-aluminum isopropoxide: simple ester, b.p. 35–38° (13 mm.), 25.5 g. (56.3%), and glycol ester, b.p. 105–110° (2 mm.), 5.8 g. (12.8%). Magnesium-aluminum butoxide: simple ester, b.p. 56–58° (26 mm.), 23.4 g. (50.1%), and glycol ester, b.p. 96–100° (0.5 mm.), 9.5 g. (20.6%). Aluminum isopropoxide: only the simple ester was obtained, b.p. 55–56° (24 mm.), 36 g. (75%).

The isobutyl isobutyrate was identified by conversion into isobutanol, 3,5-dinitrobenzoate, m.p. 86°, and isobutyric acid, *p*-bromophenacyl ester, m.p. 77°.

Identification of the glycol ester. All the higher-boiling fractions were combined and submitted to the usual procedure. Redistillation, b.p. 85–86° (0.5 mm.); d^{23} 0.9507; n^{23} 1.4390.

Anal. Calc'd for $C_{12}H_{24}O_3$: C, 66.62; H, 11.19.
Found: C, 66.63; H, 11.02.

Monoacetylated derivative, b.p. 91–93° (2 mm.); d^{23} 0.9660; n^{23} 1.4352.

Anal. Calc'd for $C_{14}H_{26}O_4$: C, 65.10; H, 10.14.
Found: C, 65.33; H, 10.29.

Saponification: Glycol, 2,2,4-trimethyl-1,3-pentanediol, b.p. 81–82° (1 mm.). It could not be obtained in an analytically pure state; d^{23} 0.9619; n^{23} 1.4518.

Condensation without cooling. Forty grams of the aldehyde was treated with 2.0 g. of magnesium-aluminum isopropoxide. The temperature rose to 85°, and after 20 minutes it gradually fell off. The cessation of ebullition indicated the completion of the reaction. A 26 g. yield of the simple ester was obtained (65%). The yield of the glycol ester amounted to only 2.6 g. (5.8%).

Condensation of 2-ethylbutyraldehyde: monoethylbutyrate of 2,2,4-triethyl-1,3-hexanediol. Fifty grams of the aldehyde was condensed with 2.5 g. of the alkoxides. The main fraction

consisted of the simple ester, 2-ethybutyl 2-ethybutyrate and only very small amounts of the higher condensation product. Magnesium-aluminum butoxide: simple ester, b.p. 95–105° (15 mm.), 28.7 g. (57.4%), 3 g. up to 175° (15 mm.) (6%). Magnesium-aluminum isopropoxide: simple ester, b.p. 98–105° (15 mm.), 29.5 g. (59%), 2 g. up to 170° (15 mm.) (4%). Aluminum isopropoxide: only the simple ester was obtained, b.p. 95–100° (12 mm.), 30 g. (60%).

Identification of 2-ethylbutyl 2-ethybutyrate. The ester was shaken with potassium carbonate solution and redistilled, b.p. 100–102° (14 mm); d^{25} 0.8628; n^{25} 1.4200.

Anal. Calc'd for $C_{12}H_{24}O_2$: C, 71.94; H, 12.08.
Found: C, 72.12; H, 12.18.

The ester was finally identified by conversion with excess alcoholic alkali to 2-ethylbutanol, b.p. 147–148.5°, 3,5-dinitrobenzoate, m.p. 50°, and to 2-ethylbutyric acid b.p. 89–90° (14 mm.), amide, m.p. 125°.

Identification of the glycol ester. All the fractions from the various runs were combined, treated in the usual way and redistilled, b.p. 127–130° (1 mm.); d^{28} 0.9327; n^{28} 1.4425. The product could not be purified. Acetylation gave definite indication that one acetyl group was introduced, but the original impurity remained.

Saponification. Because of the small amount available for saponification only a few drops of a viscous liquid were obtained from the alcoholic portion; n^{28} 1.4565. Its analysis agreed with the formula of 2,2,4-triethyl-1,3-hexanediol.

Anal. Calc'd for $C_{12}H_{26}O_2$: C, 71.23; H, 12.95.
Found: C, 71.10, 71.10; H, 12.71, 12.64.

The acid was identified as 2-ethylbutyric acid, through its amide, m.p. 124°.

Condensation of 2-ethylhexaldehyde. Only the simple ester, 2-ethylhexyl 2-ethylhexanoate was obtained in all cases. There were no higher distillable products. Fifty grams of the aldehyde and 2.5 g. of the alkoxides were employed. Magnesium-aluminum butoxide: simple ester, b.p. 110–116° (1 mm.), 37.4 g. (75%). Magnesium-aluminum ethoxide: simple ester, b.p. 100–108° (0.5 mm.), 37.4 g. (75%). Magnesium-aluminum isopropoxide: simple ester, b.p. 110–116° (1 mm.), 34.5 g. (69%). Aluminum isopropoxide: b.p. 110–116° (1 mm.), 36.7 g. (73%).

Identification. The simple ester was shaken with dilute potassium carbonate and redistilled, b.p. 112–116° (1 mm.); d^{23} 0.8591; n^{28} 1.4315.

Anal. Calc'd for $C_{16}H_{32}O_2$: C, 74.93; H, 12.60.
Found: C, 74.89; H, 12.55.

The ester was converted by excess alcoholic alkali to 2-ethylhexanol, α-naphthylurethan, m.p. 59–60°, and 2-ethyl-hexanoic acid, amide, m.p. 102° (15).

SUMMARY

1. The catalytic condensation of the dissimilar aldehydes, butyraldehyde and crotonaldehyde to yield an unsaturated glycol ester represents a second form of the "crossed" Cannizzaro reaction.

2. The cis and trans conjugated aldehydes obtained from the condensation of butyraldehyde and crotonaldehyde represent an interesting example of such isomers.

3. The coordination catalysts, *i.e.*, the magnesium-aluminum alkoxides, enable a trimeric self-condensation of saturated aldehydes to occur. This condensation is generally applicable to the α-CH_2 aldehydes, and it provides a convenient method for the synthesis of glycol esters of this series.

4. The simple alkoxides, *i.e.*, aluminum alkoxides lead only to dimeric products, that is, the simple esters, whereas the complex catalysts can bring about trimerization, *i.e.*, form glycol esters.

5. The failure to obtain glycol esters as the main products in the case of

α-alkyl aldehydes with the coordination catalysts has been explained as due to the limiting factors imposed on the primary stage of the condensation, that is, aldolization. The similarity of behavior in this instance between the simple and the complex alkoxides originates from the bifunctional nature of the latter.

6. The complex alkoxides do not differ qualitatively in their action. Magnesium-aluminum ethoxide appears to be a better condensing agent, although it is most difficult to prepare and with low yield.

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. XIII. STEROLS FROM VARIOUS MARINE INVERTEBRATES

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Comparative studies on the occurrence and constitution of invertebrate sterols have now been extended to a number of marine invertebrates, which had not yet been subjected to a careful analysis of their sterol content. The investigations were carried out in order to obtain additional data proving or disproving a previously formulated working hypothesis (1), which suggests the existence of relations between the body and food sterols of marine invertebrates, or a dependency on exogenous sterols on the part of such animals. It was also hoped to find among the extraordinarily diverse sterols of marine invertebrates some, which, for reasons of abundance and constitution, might become starting material for the preparation of steroid hormones.

The animals available for the present investigation were either fresh, preserved in formalin, or air-dried. In most cases the sterols were isolated from the unsaponifiable matter of the animals in the form of their digitonides, from which they were recovered by means of the modified Schoenheimer method (2). The amount of 7-dehydrosterols present in the crude sterol mixture was determined spectrographically. In comparing the data obtained with those reported in the literature, account should be taken of the possibility that significant quantities of 7-dehydrosterols might have undergone decomposition during the air-drying process. The homogeneity of the crude sterol was tested by recrystallization and preparation of derivatives. Wherever the presence of a mixture was indicated, attempts were made to bring about a separation of the components by means of solubility differences of their bromides.

COELENTERATA

This phylum includes polyps, solitary and colonial, corals, gorgonias, jellyfish and sea anemones. As yet the sterol content of only a few representatives of this phylum has been investigated. It has been stated by Haurowitz (3) that the tropical jellyfish, *Vellella spirans*, contains cholesterol. The identification, however, was based only on the melting point of the sterol and a common sterol color reaction, and it is therefore not conclusive. Dorée (4) found cholesterol and no other sterols in two sea anemones, but Klenk and Diebold (5) have described the presence of a new sterol, actiniasterol, in another sea anemone. The sterol, which melts at 145–146° and which gives an acetate melting at 126°, is regarded by the authors as a dehydrocholesterol, $C_{27}H_{44}O$. The homogeneity of the sterol, however, must remain questionable, until it has been demonstrated by methods other than recrystallization. Nevertheless, the melting point of

actiniasteryl acetate, while not proving the absence of cholesteryl acetate, definitely demonstrates the presence of significant quantities of acetates of one or more sterols other than cholesterol. Of subordinate interest are the determinations of the "provitamin-D" content of several coelenterata sterols by Heilbron (6), and Bock and Wetter (7); they deal with spectographic, rather than chemical evidence.

In the present investigation corals and gorgonias were selected as representatives of coelenterata because of their abundance and the ease with which they can be preserved and stored for a long time. The only lipoid constituents which have so far been isolated from these animals are cetyl palmitate and the alcohols described in previous communications of this series (8, 9).

STEROLS OF CORALS

Sterols of Madrepora cervicornis, *the staghorn coral.* This coral contained 0.3–0.4% of unsaponifiable matter and 0.0015–0.002% of sterol. A total of one-half gram of sterol was available for investigation; it contained less than one per cent of 7-dehydrosterol. The lack of homogeneity of the sterol was indicated by the fact that in a series of recrystallizations the melting point of its acetate rose from 145° to 176.5°, when it remained constant. Paucity of available material prevented further study of this compound. The acetates recovered from the mother liquors of the high-melting product melted between 130° and 150°. Incomplete as they are, these results indicate the presence in the sterol mixture, of some as yet unknown sterol, which gives an uncommonly high-melting acetate, and also show that the amount of cholesterol, if at all present, is rather small.

Sterols of Meandra areolata. This coral differs from the staghorn coral in its habitat, which is not that of a true reef-building animal. Unlike most corals it lacks a firm basal attachment and lives on smooth, sandy sea bottom (10). The coral contained 0.25–0.3% of unsaponifiable matter and 0.035–0.04% of sterol. The crude sterol was a mixture of at least two components. One of them was positively identified as cholesterol by the physical properties and analyses of a number of characteristic derivatives. A second sterol, characterized by an acetate of m.p. 141°, $[\alpha]_D^{26}$ − 49°, closely resembled sponge sterols (11).

STEROLS OF GORGONIAS

Sterols of Xiphogorgia *sp.* The crude sterol showed considerable similarity to the sterol mixture from *Meandra.* Like the latter it contained cholesterol, which was identified by a number of derivatives. In addition a second sterol, m.p. 139–141°, was isolated, which gave an acetate of m.p. 140–141°, $[\alpha]_D^{26}$ −48.3°; a propionate of m.p. 114–115°, $[\alpha]_D^{26}$ −45.6°, and a *m*-dinitrobenzoate of m.p. 214–216°, $[\alpha]_D^{26}$ −15.3°. The analysis of the last derivative indicated a molecular formula of $C_{29}H_{50}O$ for the sterol. The sterol showed close resemblance to the sponge sterols, and its derivatives when mixed with the corresponding derivatives of clionasterol (11) gave no depression of the melting point.

Sterols of Plexaura flexuosa. Preliminary experiments showed that the bulk of the lipoid material of this gorgonia is concentrated on its calcareous, outer

layers (9). They were found to contain as much as three per cent of acetone-ether-soluble material, and 0.25% sterol. In contrast, the horny skeletons contained only 0.16–0.17% of lipoids and 0.07–0.08% of sterol. The 7-dehydrosterol content of a number of samples of crude sterols, m.p. 120–131°, was zero to one per cent. After several recrystallizations, the acetate of the crude sterol melted at 143–144°; $[\alpha]_D^{26}$ −52.4°; it appeared to be fairly homogenous. Quantitative saponification of the acetate showed it to have the unexpectedly high molecular weight of 474, a value indicating a molecular formula of $C_{30}H_{50-52}O$ or $C_{31}H_{52-54}O$ for the sterol. The analyses of the acetate, propionate, m.p. 125.5–127.5°, and particularly of the *m*-dinitrobenzoate, m.p. 195–200°, corroborated the probability that the sterol was of the order C_{30} or C_{31} rather than C_{27}–C_{29}.

The lack of uniformity of the sterol became apparent when perbenzoic acid titrations gave values which were persistently higher than those calculated for a mono-unsaturated sterol. The acetate of the sterol was therefore subjected to a separation by means of the bromides, a process which entailed conspicuous

TABLE I

COMPARISON OF SPONGE STEROLS AND XIPHOGORGIA STEROL

NAME	STEROL		ACETATE		PROPIONATE		*m*-DINITRO-BENZOATE	
	m.p.°C	α_D	m.p.°C	α_D	m.p.°C	α_D	m.p.°C	α_D
Clionasterol	138	−37	140	−42	118	−42	203	−14
Poriferasterol	156	−49	147	−53	125	−48	227	−22
Xiphogorgia sterol	139	−40	141	−48	115	−45	214	−15

loss of material. An insoluble dibromide was obtained which corresponded to forty-five per cent of the total acetate. By debromination with zinc in glacial acetic acid it gave an acetate of m.p. 137–146°, which showed an unusual change of its melting point upon numerous recrystallizations. When pure, the acetate melts at 140° to an opalescent liquid, which on further heating turns clear and colorless sharply at 152°, $[\alpha]_D^{26}$ −56°. This behavior is reminiscent of that of a number of steryl benzoates, particularly of cholesteryl benzoate. Titration of the acetate with perbenzoic acid showed the presence of one double bond, and quantitative saponification indicated a molecular formula $C_{30}H_{52}O$ or $C_{31}H_{54}O$ for the sterol. These formulas found support in the analyses of the *m*-dinitrobenzoate of the sterol, m.p. 227–228°, $[\alpha]_D^{26}$ −20°. The pure sterol crystallizes from methanol in long needles; its melting point is 184–185°, $[\alpha]_D^{26}$ −45°. Since the rather unusual properties of the sterol and its derivatives demonstrate its dissimilarity from all as yet reported naturally occurring sterols, it is proposed to name it gorgosterol.

Debromination of the mother liquor from the insoluble acetate bromide yielded an acetate, m.p. 133–135°, or a mono-unsaturated sterol. Lack of material prevented further studies of this compound.

ECHINODERMATA

In a previous paper of this series (12) it has been shown that starfish contain some as yet ill-defined sterols, the most characteristic properties of which are their low positive optical rotations and their green color reactions with bromine. So far no positive evidence for the presence of cholesterol in starfish has been discovered. Since up to the present no definite information has become available on the nature of sterols from other classes of echinoderms, it remained uncertain, whether or not starfish sterols were typical constituents of all classes of the phylum.

STEROLS OF SEA URCHINS

Although the sea urchins of the class of *Echinoidea* have long been the subject of numerous biological and biochemical investigations, their sterols have never been properly identified. Several investigators like Smith (13), Mathews (14), Myers (15), and Page (16) have commented upon the presence of a sterol in the eggs and adults of a variety of sea urchins, and have assumed that it was cholesterol. In the present investigation sterols of three varieties of sea urchins have been isolated and analyzed.

Sterols of Lytechinus variegatus. The crude sterol melted at 144–145° and appeared to be cholesterol. The melting point of its acetate, however, indicated the presence of material other than cholesteryl acetate. Fractionation by means of the bromides was therefore carried out, which led to the isolation of a quantity of cholesterol representing 70–80% of the crude sterol. A second sterol, m.p. 137–139°, $[\alpha]_D$ −42°, was obtained by refractionation of the debromination product. It gave an acetate of m.p. 131–132°, $[\alpha]_D^{26}$ −44°, and a *m*-dinitrobenzoate of 198–200°. The analysis of the last derivative showed the sterol to be of the type of plant sterols of clionasterol.

Analogous results were obtained with the sterols from *Centrichinus antillarum* and *Tripneustes esculentus*, except that in the latter case the amount of cholesterol appeared to be smaller than in the others. The 7-dehydrosterol content of crude *Centrichinus* sterol was 0.83%.

STEROLS OF SEA CUCUMBER

Up to the present no available information existed on the lipoids of *Holothuridae*, with the exception of the statement by Liu (17) that dried Chinese sea cucumbers contain 0.8% of fat.

Sterols of Holothuria princepo. About fifty pounds of formalin-preserved sea cucumbers gave only twenty-four grams of acetone-ether-soluble oil, and 0.35 g. of sterol. The crude sterol showed considerable resemblance to the sterol mixture of starfish. Like the latter it melted at 135–145°, $[\alpha]_D^{26}$ +4° and gave a green color reaction with bromine. Its content of 7-dehydrosterol was 0.8%.

STEROLS OF *Limulus polyphemus*, HORSESHOE CRAB

There has existed up to now very little information on the sterol of this animal. Shope (18) has reported the blood serum of the crabs to be free from

sterols and sterol esters, and the blood cells to contain about 70 mg. per cent of sterol which he assumed to be cholesterol. In the present investigation the sterol was isolated from freshly killed crabs. It contained about 0.4% of 7-dehydrosterol. Application of the previously discussed methods of separation proved the crude sterol to be a mixture of approximately 80% of cholesterol and 20% of a sterol of m.p. 137–140°, which gave an acetate of m.p. 127–129°, $[\alpha]_D^{26}$ −39°. The latter sterol appeared to be of the plant or clionasterol type.

STEROLS OF THE TUNICATE, *Styela plicata*

A search through the literature failed to reveal any previous reports on the sterols of tunicates. The crude *Styela* sterol obtained during the present investigation contained seven per cent of 7-dehydrosterol. The remainder consisted of cholesterol. Careful fractionation of all mother liquors obtained during an attempted separation by means of the bromides gave no evidence of the presence of sterols of the type of plant or sponge sterols.

DISCUSSION

The results of the investigations which have been outlined in the preceding paragraphs again demonstrate the diversity of sterols to be found in marine invertebrates. They show that certain corals and gorgonias contain sterols, the properties of which are quite different from known naturally occurring sterols, and they also foreshadow the possible existence of sterols, which like gorgosterol, are composed of more than twenty-nine carbon atoms. The evidence that gorgosterol is a sterol, rests as yet only on the ability of the compound to form an insoluble digitonide. It is therefore possible although not probable that like agnosterol, $C_{30}H_{48}O$, and lanosterol, $C_{30}H_{50}O$, it may prove to be a triterpene rather than a true sterol (19).

With the exception of the tunicate, all animals which have been dealt with in the present investigation were found to contain sterols which resembled plant or sponge sterols. The melting points of these sterols fall between 135° and 142°, and those of their acetates between 125° and 140°. The sterols are difficult to obtain in a pure state, particularly when they have been isolated from a sterol mixture containing large quantities of cholesterol. It appears certain that cholesteryl acetate is present as a contaminant in the lower-melting steryl acetates. There exist strong indications that once obtained in a pure state some of them will be shown to be identical with clionasterol. As shown in table I the physical properties of the sterol from *Xiphogorgia* already show the closest resemblance to a typical clionasterol preparation from which poriferasterol has not been completely removed (11).

It has been stated in the introductory chapter of this presentation, that one of the reasons for undertaking the present investigation was the desire to obtain data for testing the value of the hypothesis according to which there exist relations between the body and food sterols of marine invertebrates. On the basis of this hypothesis a marine invertebrate which feeds on plant material exclusively is expected to contain sterols of the order of C_{29} or plant sterols. The

observation that the herbivorous bivalves contained C_{29} sterols rather than cholesterol (1) was the basis of this hypothesis, and the discovery of C_{29} sterols in the herbivorous sponges seemed to substantiate it (11). Carnivorous invertebrates are expected to contain cholesterol or one of its derivatives if they feed on cholesterol-containing animals. Thus sea anemones which prey on fish and crustaceans should contain C_{27} sterols, which according to available information appears to be indeed the case (4, 5). A more complex situation will prevail in such carnivorous invertebrates as feed both on cholesterol-containing animals, and on herbivorous invertebrates containing C_{29} sterols. In these cases one might expect the presence of a mixture of C_{27} and C_{29} sterols, such as has been shown to occur in the gastropod *Fulgur*, which preys upon fish, crustaceans, and herbivorous bivalves (1). As has been stated before (11) application of the hypothesis is to be restricted to marine invertebrates. With one possible exception all non-marine invertebrates which have so far been studied contain cholesterol as their principal sterol, regardless of their feeding habits.

In applying the working hypothesis to the results of the present investigation some difficulties are at once encountered in the case of corals and gorgonias. Little is known about the feeding habits of these animals except the fact that they are wholly carnivorous. It is therefore as yet impossible to compare the nature of their body and food sterols. One might expect them to contain some cholesterol, and one coral and one gorgonia indeed meet this expectation. Feeding upon "clionasterol"-containing zooplancton-like minute sponges might account for the occurrence of C_{29} sterols in these animals. The staghorn coral and another gorgonia contain little if any cholesterol, and from the viewpoint of the hypothesis this might indicate a different selection of food material by these animals. The problem, however, will have to remain unsolved until more data have become available on the sterol content of zooplancton, and until more is known about the nature and occurrence of such unusual sterols as gorgosterol.

The studies on the sterols of echinoderms have brought out the fact that the starfish sterols are not typical constituents of all classes of the phylum. They have shown that sea urchins contain a mixture of cholesterol and C_{29} sterols in proportions of approximately three or four to one. This is rather surprising for the sea urchins which feed largely upon algae and decaying matter might be expected to contain considerable quantities of C_{29} sterols. It is conceivable, however, that as far as its sterol requirements are concerned, the sea urchin forms a link between marine invertebrates and vertebrates. Its position in this respect might be similar to the one it occupies on the evolutionary scale of the arginine-creatine distribution in the animal world. Here it stands on the borderline between invertebrates and vertebrates, being the only invertebrate which contains the typical vertebrate creatine phosphoric acid in addition to the typical invertebrate arginine phosphoric acid (20).

The fact that the sterol of the tunicate, *Styela*, has been shown to consist only of cholesterol and some 7-dehydrosterol, is of particular interest. This animal occupies a place on the evolutionary scale between invertebrates and vertebrates. Since it is principally herbivorous, its cholesterol content appears to indicate

that its sterol requirements are like those of vertebrates rather than invertebrates.

EXPERIMENTAL

All melting points are corrected. All optical rotations were taken in a 1 dm. tube, the sample being dissolved in 3.03 cc. of chloroform.

The following general procedure was used for the isolation of sterols from air-dried marine invertebrates. The material was broken up and extracted in a large Soxhlet apparatus for twenty-four hours each with acetone and ether. The extracts were evaporated, and the residues combined. They were then heated for thirty minutes on a steam-bath with a 20% solution of potassium hydroxide in 70% ethanol. The alkaline solution was diluted with three times its volume of water and thoroughly extracted with ether. The combined ether extracts were washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was then dissolved in hot 90% ethanol, and the sterol content of a representative sample determined by precipitation with digitonin. Sufficient digitonin was then added to the total to precipitate the entire amount of sterol. The digitonides were washed with alcohol and ether, and cleaved into their components by treatment with pyridine according to the method of Bergmann (2). In several cases part of the sterols was first isolated from the unsaponifiable fraction by crystallization from methanol, and the remainder then precipitated with digitonin.

Madrepora cervicornis

The extract of 2,850 g. of crushed corals gave 0.48 g. of sterol. It was at once acetylated, and the acetate, m.p. 145–146°, recrystallized from chloroform-methanol.

Anal. Calc'd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.3.
$C_{31}H_{52}O_2$: C, 81.5 ; H, 11.5.
Found: C, 81.6 ; H, 11.7.

After eight recrystallizations the melting point of the acetate remained constant at 176.5°. Concentration of the mother liquors gave fractions of m.p. 124–154°. From the lowest-melting fraction an acetate of m.p. 119° was obtained. It probably contained some cholesteryl acetate, but the available material was too scanty to permit further separation and identification.

Meandra areolata

The unsaponifiable matter of 12 kg. of this coral weighed 32.3 g. (0.27%). When treated with hot methanol it yielded 0.57 g. of a sterol crystallizing in nice, long prisms, m.p. 132–134° (Fraction A). The remainder of the sterol isolated by means of the digitonide weighed 4 g., m.p. 132–136° (Fraction B).

Fraction A. It was acetylated, and the acetate, m.p. 139.5°, recrystallized four times from chloroform-methanol, m.p. 141.5°. An ether solution of the acetate was treated with a 5% solution of bromine in glacial acetic acid until 1.2 moles of bromine had been added. A minute quantity of an insoluble bromide was obtained. The filtrate was debrominated with zinc, the acetate precipitated with water and recrystallized from chloroform-methanol, m.p. 141° $[\alpha]_D^{28}$ −49° (48.9 mg., α −0.79°).

Anal. Calc'd for $C_{29}H_{52}O_2$: C, 81.5; H, 11.5.
$C_{29}H_{50}O_2$: C, 82.0; H, 11.1.
Found: C, 81.8; H, 11.2.

The molecular weight determined by quantitative saponification was 448. The sterol obtained from the purified acetate melted at 137–138°.

Fraction B. The sterol was acetylated, and the acetate (3.5 g., m.p. 124–127°) was treated with bromine in ether-glacial acetic acid. On standing overnight at 5° there had separated 1.9 g. of a crystalline precipitate (Fraction C). Slight concentration of the

filtrate gave 1.2 g. of a second precipitate (Fraction D). The remaining filtrate contained fraction E.

Fraction C. Debromination of this fraction with zinc in glacial acetic acid gave an acetate of m.p. 127–128°, which was rebrominated. An insoluble bromide was obtained, m.p. 117°, which on debromination gave an acetate of m.p. 114°. It gave no melting point depression with cholesteryl acetate.

Debromination of the filtrate from cholesteryl acetate dibromide gave an acetate of m.p. 132°, $[\alpha]_D^{26}$ −45.5°, which upon saponification gave a sterol of m.p. 131°, $[\alpha]_D^{26}$ −41.6°. It appeared to be a mixture of cholesterol and a di-unsaturated sterol. Because of lack of material it was not further investigated.

Fraction D (Cholesterol). Debromination of this fraction with zinc in glacial acetic acid gave 690 mg. of an acetate of m.p. 115°. It gave no melting point depression with cholesteryl acetate. Hydrolysis of the acetate gave cholesterol, m.p. 148.5°, $[\alpha]_D^{26}$ −39.8°. The benzoate melted to an opalescent liquid at 145.5°, which turned clear at 178°. It gave no melting point depression with cholesteryl benzoate. The *m*-dinitrobenzoate, m.p. 195–195.5°, gave no melting point depression with cholesteryl *m*-dinitrobenzoate.

Anal. Calc'd for $C_{34}H_{48}N_2O_6$: C, 70.3; H, 8.3.
Found: C, 70.4; H, 8.4.

Fraction E. This fraction showed signs of considerable decomposition. Two debrominations were required to obtain a bromine-free product. Upon repeated treatment of the oily material with methanol an acetate of m.p. 143° was obtained. It was not further investigated.

Xiphogorgia sp.

Treatment of the unsaponifiable material with methanol gave a sterol of m.p. 130–135°, which crystallized in form of nice colorless prisms (Fraction A). The remainder of the sterol, m.p. 120–125°, was isolated by way of the digitonide (Fraction B).

Fraction A. The acetate of this fraction melted at 139.5–140.5° after four recrystallizations from chloroform-methanol. It gave no depression of the melting point when mixed with the acetate of fraction A from *Meandra areolata*, m.p. 141°, with clionasteryl acetate, m.p. 140°, and the acetate of the *Xiphogorgia* fraction D, m.p. 140–141°, which is described below.

Fraction B. This fraction was separated by means of the sterol bromides. In a sample experiment a solution of 2 g. of sterol in 20 cc. of anhydrous ether was mixed with 18 cc. of a 5% solution of bromine in glacial acetic acid and 4 cc. of glacial acetic acid. On cooling, 1.5 g. of a precipitate was obtained, m.p. 99–103° (Fraction C). The filtrate contained fraction D.

Fraction C (Cholesterol). The sterol bromide was debrominated by Schoenheimer's method (21) with sodium iodide in alcohol. A sterol was obtained (0.8 g.) which after four recrystallizations from ethanol melted at 147°, $[\alpha]_D^{26}$ −39.3°. It gave no melting point depression with cholesterol. The acetate melted at 117°, and gave no melting point depression with cholesteryl acetate.

Anal. Calc'd for $C_{29}H_{48}O_2$: C, 81.3; H, 11.3.
Found: C, 81.4; H, 11.5.

The benzoate melted to an opalescent liquid at 146° which turned clear at 176°. The *m*-dinitrobenzoate melted at 194.5–195.5°. Neither derivative gave a melting point depression with the corresponding derivatives from cholesterol.

Anal. Calc'd for $C_{34}H_{48}N_2O_6$: C, 70.3; H, 8.3.
Found: C, 70.25; H, 8.4.

Fraction D. The filtrate from fraction C was debrominated with zinc, and the bromine-free product precipitated with water. It was at once acetylated giving 0.3 g. of an acetate of m.p. 133–135°. An accumulation of this acetate was recrystallized from chloroform-methanol until the melting point remained constant at 140–141°, $[\alpha]_D^{26}$ −48.3° (31.5 mg., α −0.50°). It gave no melting point depression with clionasteryl acetate.

Hydrolysis of the acetate gave a sterol which melted at 139–141° after four recrystallizations from ethanol.

The sterol was refluxed with propionic anhydride, giving a propionate which after three recrystallizations from ether-methanol melted at 114–115.5°, $[\alpha]_D^{26}$ −45.6° (46.6 mg., α −0.70°). It gave no melting point depression with clionasteryl propionate, m.p. 116–117°.

Anal. Calc'd for $C_{32}H_{54}O_2$: C, 81.6; H, 11.6.
Found: C, 81.6; H, 11.6.

The *m*-dinitrobenzoate melted at 214–216°, $[\alpha]_D^{26}$ −15.3° (21.8 mg., α −0.11).

Anal. Calc'd for $C_{36}H_{52}N_2O_6$: C, 71.0; H, 8.6.
Found: C, 71.3; H, 8.4.

Plexaura flexuosa

Three thousand grams of external layers of this gorgonia gave a total of 8.4 g. of sterol, m.p. 138–139°, $[\alpha]_D^{26}$ −42.8°. It was acetylated, and the acetate, m.p. 135–138°, recrystallized six times from ether-methanol and once from absolute alcohol m.p. 143–145°, $[\alpha]_D^{26}$ −52.4° (42.2 mg., α −0.73°).

Anal. Calc'd for $C_{34}H_{54}O_2$: C, 81.62; H, 11.56.
$C_{35}H_{56}O_2$: C, 81.77; H, 11.64.
Found: C, 81.73; H, 11.88.

The average of three determinations of the molecular weight by quantitative saponification was 474.4. Calc'd for $C_{32}H_{54}O_2$: 470.7; $C_{33}H_{56}O_2$: 484.8.

The sterol obtained by saponification of the recrystallized acetate melted at 139–146°.

After five recrystallizations from ether-methanol and absolute ethanol the propionate melted to a turbid liquid at 125.5–127.5°, which turned clear at 143°.

Anal. Calc'd for $C_{33}H_{56}O_2$: C, 81.77; H, 11.64.
$C_{34}H_{58}O_2$: C, 81.87; H, 11.72.
Found: C, 82.07; H, 11.57.

The *m*-dinitrobenzoate melted at 195–200°.

Anal. Calc'd for $C_{37}H_{54}N_2O_6$: C, 71.35; H, 8.73.
$C_{38}H_{56}N_2O_6$: C, 71.68; H, 8.86.
Found: C, 71.60; H, 8.62.

Perbenzoic acid titrations of the acetate gave values corresponding to the presence of 1–1.5 double bonds.

Separation of the acetate. In a sample experiment 4 g. of the acetate of m.p. 135–140°, was dissolved in 40 cc. of anhydrous ether, and 50 cc. of a 5% solution of bromine in glacial acetic acid was added. After six hours at 5°, 2.5 g. of a crystalline precipitate had appeared, m.p. 135–138°, bromine content: 26–27% (Fraction A). By removal of the ether from the filtrate 1.5 g. of a second precipitate, m.p. 115–117°, was obtained (Fraction B). The final filtrate gave no crystalline material.

Fraction A. Preparation of gorgosteryl acetate. Debromination of fraction A with zinc in glacial acetic acid gave an acetate, m.p. 137–146°, which after three recrystallizations from absolute ethanol melted to an opalescent liquid at 140°, which turned clear sharply at 152.6°, $[\alpha]_D^{26}$ −56.3° (34.7 mg., α −0.65°). Further recrystallizations did not change the melting point.

Anal. Calc'd for $C_{32}H_{54}O_2$: C, 81.62; H, 11.56.
$C_{33}H_{56}O_2$: C, 81.77; H, 11.64.
Found: C, 81.45; H, 11.80.

The average of six determinations of the molecular weight by quantitative saponification was 478.6. Calc'd for $C_{32}H_{54}O_2$: 470.7; $C_{33}H_{56}O_2$: 484.8.

Gorgosterol. Saponification of the acetate gave a sterol which after five recrystallizations from alcohol melted at 184–185°, $[\alpha]_D^{26}$ −45° (28.3 mg., α −0.42°). It crystallized from methanol in the form of long needles.

Anal. Calc'd for $C_{30}H_{52}O$: C, 84.06; H, 12.23.
$C_{31}H_{54}O$: C, 84.10; H, 12.30.
Found: C, 84.20; H, 12.50.

Titration with perbenzoic acid. A sample of sterol weighing 0.1196 g. consumed 4.59 mg. of oxygen corresponding to 1.04 double bonds.

Gorgosteryl m-*dinitrobenzoate.* It was prepared in the usual manner. After three recrystallizations from ethyl acetate it melted at 227.5–228.5°, $[\alpha]_D^{26}$ −20.3° (27.1 mg. in 3.03 cc. pyridine, α −0.18°).

Anal. Calc'd for $C_{37}H_{54}N_2O_6$: C, 71.35; 8.73.
$C_{38}H_{56}N_2O_6$: C, 71.68; 8.86.
Found: C, 71.44; 8.42.

Fraction B. Debromination of this fraction with zinc in glacial acetic acid gave an acetate which melted at 134–136° after three recrystallizations from ether-methanol. Titration with perbenzoic acid gave a value corresponding to 1.09 double bonds.

Lytechinus variegatus

The sterol was obtained by treating the unsaponifiable matter with hot methanol. The crude, slightly brown product was at once acetylated, and the acetate recrystallized from absolute ethanol. A solution of 6.7 g. of acetate in 67 cc. of ether was treated with 83 cc. of a 5% solution of bromine in glacial acetic acid, and the mixture kept at 5° overnight. A precipitate appeared which weighed 5.95 g. (Fraction A). It corresponded to 67% of the acetate mixture. The filtrate contained fraction B.

Fraction A (Cholesterol). A sample of the bromide was recrystallized from ethyl acetate and ethanol, m.p. 109.5–111.5°.

Anal. Calc'd for $C_{29}H_{48}Br_2O_2$: C, 59.2; H, 8.2.
Found: C, 58.9; H, 8.3.

Debromination of the acetate bromide with zinc in glacial acetic acid gave an acetate of m.p. 115°, which gave no melting point depression with cholesteryl acetate.

Anal. Calc'd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.3.
Found: C, 81.20; H, 11.3.

Hydrolysis of the acetate gave cholesterol of m.p. 147°. The benzoate melted to a turbid liquid at 146° which turned clear at 176°. It gave no melting point depression with cholesteryl benzoate.

Anal. Calc'd for $C_{35}H_{52}O_2$: C, 83.3; H, 10.4.
Found: C, 83.3; H, 10.6.

Fraction B. Debromination of the filtrate from fraction A gave an acetate of m.p. 120–125°. Upon rebromination it gave 0.24 g. of cholesteryl acetate dibromide. The filtrate was debrominated and the acetate recrystallized four times from absolute ethanol, m.p. 131–132°, $[\alpha]_D^{26}$ −44°.

Saponification of the acetate gave a sterol of m.p. 137–139°, $[\alpha]_D^{26}$ −42°. Its *m*-dinitrobenzoate melted at 198–200°.

Anal. Calc'd for $C_{36}H_{52}N_2O_6$: C, 71.3; H, 8.3.
Found: C, 71.1; H, 8.5.

Centrichinus antillarum

The acetone-ether extract from 3 kg. of air-dried sea urchins weighed 30 g. Saponification, which was accompanied by evolution of ammonia and amines, gave 6 g. of unsaponifiable matter. The sterol isolated by means of the digitonide weighed 3.3 g., m.p. 144–145°. Separation of the steryl acetates by way of the bromides gave results similar to those described above. Cholesteryl acetate was obtained and an acetate of m.p. 132–133°, $[\alpha]_D^{27}$ −46.3°.

Tripneustes esculentus

The acetone-ether extract of 2 kg. of air-dried material weighed 23 g. It gave 6 g. of unsaponifiable matter, which yielded 4.2 g. of sterol. Analysis of the sterol mixture by the method described above showed the presence in about equal amounts of cholesterol and a sterol giving a high-melting acetate.

Holothuria princepo

About 50 pounds of wet, formalin-preserved sea cucumbers was passed through a meat grinder. The pulp was dehydrated with acetone and extracted with ether. Upon evaporation of the combined acetone-ether extract 24 g. of oil was obtained. Saponification of the oil gave 3.6 g. of unsaponifiable matter from which 0.35 g. of sterol was obtained by means of the digitonide. The sterol was at once acetylated, giving an acetate of m.p. 130–142°, $[\alpha]_D^{26}$ +2°. Hydrolysis of the acetate gave a sterol of m.p. 135–145°, $[\alpha]_D^{26}$ +4°. Because of the small amount of material available no separation was carried out.

Limulus polyphemus

Freshly killed horseshoe crabs were sliced into small pieces and digested with 20% aqueous potassium hydroxide for 24 hours at 80°. The alkaline liquid was decanted from the insoluble material, and thoroughly extracted with ether. The residue from the ether extract was then resaponified with alcoholic potassium hydroxide. A slightly yellow, crystalline material was obtained which after one recrystallization from alcohol melted at 144–147°. The acetate of the sterol, m.p. 112–117°, was treated with bromine in the usual manner. An insoluble bromide was obtained which represented 70% of the original acetate. Upon debromination with zinc in glacial acetic acid it gave an acetate of m.p. 114°, $[\alpha]_D^{25}$ −43°, which gave no melting point depression with cholesteryl acetate. Hydrolysis of the acetate gave cholesterol, m.p. 147–148°. The benzoate melted to a turbid liquid at 146° which turned clear at 176°. It gave no melting point depression with cholesteryl benzoate.

Debromination of the filtrate from the cholesteryl acetate dibromide gave an acetate which melted at 127–129°, $[\alpha]_D^{25}$ −39°. The sterol obtained from the acetate melted at 137–140°.

Styela plicata

The air-dried tunicates were digested with 20% aqueous potassium hydroxide for 24 hours at 80°. The insoluble cellulose was removed by filtration over glass wool, and the alkaline extract extracted with ether. The sterol was obtained from the residue by way of the digitonide. After one recrystallization from ethanol it melted at 147–148°, $[\alpha]_D^{26}$ −40°. The acetate melted at 114°, $[\alpha]_D^{25}$ −43°, and the benzoate at 146° to a turbid liquid which turned clear at 176°. Both compounds gave no melting point depressions with the corresponding derivatives of cholesterol.

By treatment of the acetate with bromine an insoluble bromide, m.p. 117° was obtained, which represented 80% of the total acetate. Debromination gave cholesteryl acetate of m.p. 114°. Slight concentration of the filtrate from the first bromide gave a second precipitate which upon debromination also gave cholesteryl acetate of m.p. 114°. Debromination of the final filtrate from the bromination gave cholesteryl acetate of m.p. 113–115°.

SUMMARY

The sterols of a number of marine invertebrates have been isolated and investigated. The 7-dehydrosterol content of the crude sterols has been determined spectrographically.

The staghorn coral, *Madrepora cervicornis*, contains a mixture of sterols which are difficult to separate. One of the components gives an acetate of m.p. 176°. The sterols of *Meandra areolata* consist of a mixture of cholesterol and a sterol showing considerable similarity to clionasterol.

The gorgonia, *Xiphogorgia* sp., contains a mixture of sterols similar to the one present in *Meandra areolata*. *Plexaura flexuosa* contains among other unidentified sterols a mono-unsaturated compound of the order C_{30} or C_{31}, for which the name gorgosterol has been proposed

The crude sterols of three varieties of sea urchins consist of a mixture of cholesterol and a sterol of the order C_{29}, which is similar to sterols of the sitosterol or clionasterol type. The sea cucumber, *Holothurio princepo*, contains a mixture of sterols similar to the one found in starfish.

The horseshoe crab, *Limulus polyphemus*, contains a mixture of cholesterol and a sterol similar to plant sterols or clionasterol. The sterol mixture from the tunicate, *Styela plicata*, contains only cholesterol and some 7-dehydrosterol.

The significance of these results has been discussed.

NEW HAVEN, CONN.

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. XIV. ASTROL

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The name astrol was assigned in 1915 by Kossel and Edlbacher (1) to an alcohol of m.p. 71° and probable formula $C_{23}H_{48}O_3$, which occurs together with the as yet ill-defined stellasterol in the unsaponifiable fraction of the fat of the starfish *Asterias rubens*. Page (2), in 1923 announced the presence of a sterol-like compound of m.p. 71° in *Asterias forbesi*, the common starfish of the New England coast. Believing this compound to be different from previously described sterols, the author named it asteriasterol. As has already been pointed out in a previous communication (3), however, asteriasterol is not a single compound, but a mixture of one or more sterols of the type of stellasterol and an alcohol similar to or identical with astrol.

A comparison of the properties and the molecular formula of astrol with those of the naturally occurring glyceryl ethers at once suggested to the present authors the identity of astrol with either batyl alcohol or the as yet unknown α-eicosyl-glyceryl ether. An opportunity to investigate this question presented itself when, during a study of the starfish sterols, there became available several grams of a non-steroid alcohol which showed close similarity to astrol and batyl alcohol. The compound melted at 70–71°, analyzed for $C_{21}H_{44}O_3$, and showed a slight positive optical rotation, the magnitude of which was significantly influenced by the concentration of the solution. The identity of this substance with batyl alcohol was demonstrated by its behavior towards lead tetraacetate (4), its conversion to the bis-phenylurethan of m.p. 100.5–101°, and by direct comparison with the synthetic *d*-α-(*n*-octadecyl)glycerol ether[1] of Baer and Fischer (5). While it is true that the results of Kossel's analyses of astrol are in closer agreement with a formula $C_{23}H_{48}O_3$ rather than one of $C_{21}H_{44}O_3$, there exists a strong possibility that the higher carbon values were caused by the presence of some sterol, which was indicated by a slight reaction of astrol with digitonin. The present investigation leaves little doubt as to the identity of astrol and batyl alcohol, the presence of which in marine invertebrates has already been indicated in a previous communication (6). It is of interest to note in this connection that Kossel and Edlbacher must be regarded as the discoverers of this interesting compound, since their description of astrol predates by seven years the report of Tsujimoto and Toyama (7) on the isolation of batyl alcohol from sharkliver oil.

[1] The authors express their gratitude to Drs. H. O. L. Fisher and E. Baer for a sample of synthetic batyl alcohol.

EXPERIMENTAL

All melting points are corrected.

The unsaponifiable matter of the oil from the starfish *Asterias forbesi*[2] was dissolved in the minimum amount of hot methanol, and the sterols which separated on cooling were removed by filtration. The mother liquor was evaporated to dryness *in vacuo*, and the residue again dissolved in hot methanol. After several repetitions of this process the bulk of the sterols had been removed from the unsaponifiable matter. The remaining material was then dissolved in the minimum amount of hot benzene. Upon cooling, a copious precipitate of small needles separated. It was recrystallized three times from ethyl acetate and once from dilute acetone. It melted at 70–70.5°; when mixed with synthetic *d*-α-(*n*-octadecyl)glycerol ether of m.p. 71–71.5° it melted at 70.5–71°. Rotation: 30.6, 110.3 and 254.4 mg. dissolved in chloroform and made up to 3 cc. gave rotations in a 2 dm. tube of +0.08°, 0.16°, and 0.13°; hence $[\alpha]_D^{25}$ + 3.9°, 2.2°, and 0.8°. The values given by Baer and Fischer (5)for corresponding concentrations of synthetic material were $[\alpha]_D$ + 4.0°, + 1.70°, and +0.8° respectively.

Titration with lead tetraacetate. Samples weighing 56.0 and 49.0 mg. were treated with an excess of 0.1 *N* lead tetraacetate solution for 24 hours at room temperature. Titration of the solution indicated a consumption of 1.06 and 1.04 moles of lead tetraacetate per mole of alcohol.

Anal. Calc'd for $C_{21}H_{44}O_3$: C, 73.25; H, 12.8.
Found: C, 73.5; H, 13.0.

Octadecyl iodide. A 100-mg. sample of the alcohol was converted into octadecyl iodide by the method previously described (6). The iodide melted at 32.5°, and when mixed with an authentic sample of octadecyl iodide at 32.5–33.5°.

Anal. Calc'd for $C_{18}H_{37}I$: C, 56.8; H, 9.8.
Found: C, 57.0; H, 9.6.

Batyl bis-phenylurethan. This derivative was prepared as previously reported. It melted at 100.5–101°, and gave no depression of the melting point with authentic batyl bis-phenylurethan.

CONCLUSIONS

It has been demonstrated that the alcohol astrol, first isolated by Kossel and Edlbacher from the starfish *Asterias rubens* is identical with batyl alcohol.

NEW HAVEN, CONN.

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[2] The authors are greatly indebted to Mr. Chas. F. Lee, Fish and Wildlife Service, College Park, Md. for his generous gift of a large quantity of starfish oil.

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

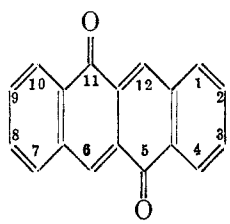
EXPERIMENTS IN THE ARYL NAPHTHACENE SERIES. PART III

A. WEIZMANN

Received March 11, 1943

In Part I (1) experiments with 6,11-diphenylnaphthacene-5,12-quinone have been described which contribute to our knowledge of the rubrenes proper, the 5,6,11,12-tetraaryl naphthacenes (4). In order to make the 5,11-diaryl naphthacenes equally available by synthesis, it was necessary to find a suitable 5,11-dicarbonyl derivative of naphthacene, which was to be treated with organometallic compounds. In view of the observation that the ana-quinone (I) of naphthacene (naphthacene-5,11-quinone) does not react "normally" with organometallic compounds, its hydrogenation products have been investigated. A preliminary report has been given in Part II (2) on the experiments with the dihydro derivative (II) of (I), the 5,11-diketo-5,11,11a,12-tetrahydronaphthacene. These experiments have been continued, but neither phenyl- nor *p*-tolyllithium have given with (II) the expected reaction: in neither case, could more than one aryl group be introduced into the naphthacene system by means of the aryl lithium compounds.

On interaction with phenyllithium, (II) gave a compound $C_{24}H_{16}O$ (m.p. 255°), which could be transformed with acetyl chloride into a yellow substance of the formula $C_{26}H_{18}O_2$ and of m.p. 268°. This composition and the color support the previously suggested formula of 11-phenyl-5-acetoxynaphthacene (IV); the substance $C_{24}H_{16}O$, therefore, is 11-phenyl-5-hydroxynaphthacene (III a) or its ketonic form, 11-phenyl-5-keto-5,12-dihydronaphthacene (III b). The mechanism of the reaction appears to be the following: The saturated carbonyl group at C_{11} reacts normally, and subsequently splits off water between C_{11} and C_{11a}. The resulting dihydronaphthacene derivative (III b) may stabilize itself by enolization.



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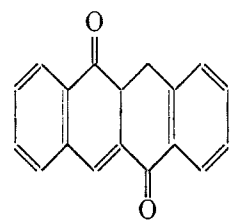

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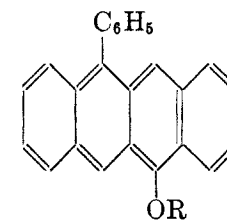
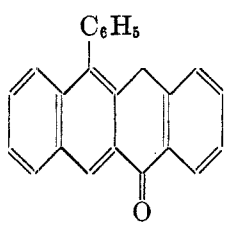


IIIa: R=H IV: R=CH_3CO



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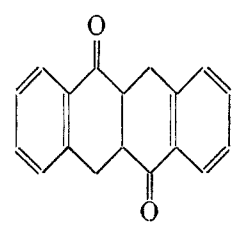

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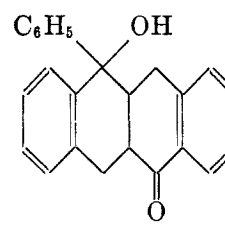

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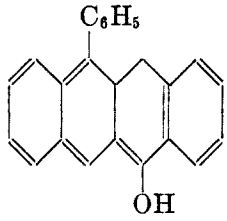

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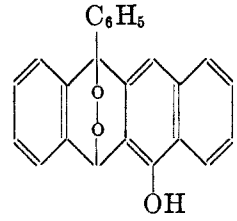

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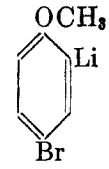

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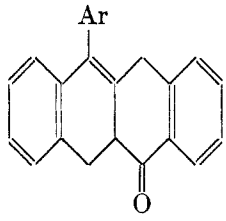

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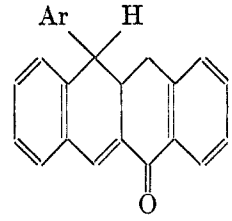

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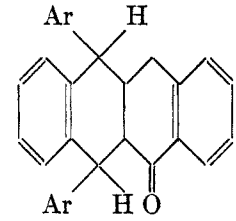

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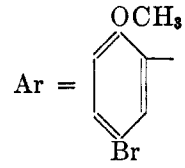

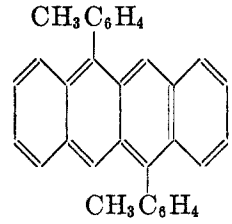

XIII

With *p*-tolyllithium, the reaction of (II) proceeded analogously. A substance $C_{25}H_{18}O$, m.p. 248°, was formed, which could be acetylated to give a compound $C_{27}H_{20}O_2$; evidently, these are the analogs of (III) and (IV), respectively.

In view of the possible desmotropy between (III a) and (III b), the observation should be recorded that in one of the reactions of (II) with phenyllithium, instead of the substance of m.p. 255°, a brown isomer, m.p. 230°, has been obtained in small quantities, which may be the desmotropic form.

All these experiments tend to show that carbonyl derivatives of the naphthacene series which contain a double bond in α,β-position to the carbonyl group, do not react "normally" with organometallic reagents. Recourse was therefore taken to the tetrahydro derivative (V) of (I), the 5,5a,6,11,11a,12-hexahydro-5,11-diketonaphthacene. This substance, m.p. 220–222°, was made available

from *sym.* dibenzylsuccinic acid; its interaction with a number of aryl lithium compounds proved rather complex.

With phenyllithium, again only one phenyl group could be introduced into the molecule. The well-crystallized product of m.p. 295–298° had the curious formula $C_{24}H_{16}O_3$. Two of the three oxygen atoms are of peroxydic nature, as the liberation of iodine from potassium iodide solution shows. As a possible formula (VIII) is suggested, which would be understandable if the following mechanism of reaction is assumed: one carbonyl group in (V) reacts with phenyllithium in the expected manner; the product (VI) loses one molecule of water and is subsequently enolized to (VII), which in contact with air is dehydrogenated and converted into the peroxide (VIII) in the same way as most naphthacenes are.

Still more complicated was the reaction with the organometallic compound derived from *p*-bromoanisole and lithium. This compound was the 2-lithio-4-bromoanisole (IX), in analogy with the recent observations of Wittig and his co-workers (7). Its crystalline reaction product with (V) had the formula $C_{32}H_{26}Br_2O_3$, showing that two aromatic nuclei had entered the molecule; two of the oxygen atoms are accounted for by the two methoxyl groups, the third is not hydroxylic in nature, as the substance is resistant to boiling acetyl chloride. Its formula is assumed to be (XII), 6,11-di-(2′-methoxy-5′-bromophenyl)-5-keto-5,5a,6,11,11a,12-hexahydronaphthacene; such a substance would be formed by the following successive steps: normal reaction at C_{11} and dehydration to (X), which, however, rearranges to (XI), possessing an α,β-unsaturated carbonyl system. This reacts by the usual 1,4-addition process with a second molecule of the lithium compound (IX) and gives, by hydrolysis and simultaneous ketonization, (XII).

Only with *p*-tolyllithium, could the desired reaction be achieved. From (V) a deep yellow hydrocarbon $C_{32}H_{24}$ was obtained, which according to its formula, its color, and the high melting point (335–336°) is regarded as the desired 5,11-di-*p*-tolylnaphthacene (XIII).

EXPERIMENTAL

Benzylsuccinic acid was prepared according to Cordier (3). An alcoholic solution of sodium ethoxide (from 7.5 g. of sodium and 100 cc. of anhydrous alcohol) was treated in quick succession with ethyl benzylmalonate (75 g.) (5) and ethyl bromoacetate (51 g.). After 6–8 hours on the water-bath, the reaction was complete. The alcohol was evaporated, the residue treated with a little dilute sulfuric acid and extracted with ether. The crude triethyl 1-phenylpropane-2,2,3-tricarboxylate (96 g.) was hydrolyzed by heating for 4 hours with alcoholic potash (75 g. of KOH in 300 cc. of alcohol). The product was diluted with water (200 cc.), acidified, and extracted with boiling ether. The tricarboxylic acid was thus obtained as an oil (89 g.), which crystallized partly on standing. Decarboxylation was effected by heating at 165–170° for 1 hour. Twenty grams of the tricarboxylic acid gave 15 g. of benzylsuccinic acid, m.p. 160–161°, after recrystallization from benzene.

Dimethyl benzylsuccinate was obtained in good yield from the acid (53 g.) and methanol (90 cc.), saturated with gaseous hydrochloric acid, on the water-bath for one hour; boiling point 128–135°/1.5 mm.

Anal. Calc'd for $C_{13}H_{16}O_4$: C, 66.1; H, 6.8.
Found: C, 65.8; H, 7.0.

Benzylidenebenzylsuccinic acid. To a mixture of dimethyl benzylsuccinate (28 g.), benzaldehyde (13.4 g.) and ether (60 cc.), 2.8 g. of sodium powder was added. The initial reaction was violent; it was completed by heating on the water-bath for 3 hours. Water (100 cc.), and after 1 hour 33% sodium hydroxide solution (20 cc.), were added, and the hydrolysis was completed on the water-bath, for 1.5 hours. After cooling, hydrochloric acid (75 cc. of concentrated acid and 75 cc. of water) was added, and the oily product isolated after 12 hours standing at 0°, and triturated with isopropyl ether. The crystals had, after recrystallization from 50% acetic acid, the expected m.p. 160–162°; yield 10 g.

sym. *Dibenzylsuccinic acid.* The two diastereomerides of this acid have already been observed by Stobbe and von Vigier (6); our experience is that catalytic hydrogenation of benzylidenebenzylsuccinic acid gives sometimes the high-melting isomer (m.p. 210°; Stobbe 204°), sometimes a low-melting product (m.p. 170°), which, however does not depress markedly the melting point of the 210° substance. No attempt has been made to find whether these two products represent two distinct and pure isomers (Stobbe's second isomer had the m.p. 203°), and whether and how their formation depends on the conditions of hydrogenation (speed of hydrogen absorption, etc.), as it was observed that both cyclize to the same diketone (V). The hydrogenations were carried out in propyl or isopropyl alcohol as solvent, with palladium on barium sulfate as catalyst, at the boiling point of the solvent. The 210° product is best recrystallized from benzene, the 170° product from isopropyl alcohol.

5,5a,6,11,11a,12-Hexahydro-5,11-diketonaphthacene (*V*). Dibenzylsuccinic acid (1 g.) and concentrated sulfuric acid (50 cc.) were heated on the water-bath for 1 hour; the mixture was then poured onto ice and the solid product collected (yield, 0.6 g.). From butyl alcohol, fine, white needles, m.p. 220–222°.

Anal. Calc'd for $C_{18}H_{14}O_2$: C, 82.5; H, 5.3.
Found: C, 82.5; H, 5.3.

Peroxide (*VIII*). The foregoing diketone (V, 1 g.) was added to an ethereal solution of phenyllithium (from 6 g. of bromobenzene and 0.6 g. of lithium shavings) in a Schlenk-tube under nitrogen in the usual manner. After 48 hours, the tube was opened and the reaction mixture decomposed with ice-cold dilute sulfuric acid. The ether residue was triturated with methyl alcohol and recrystallized from butyl alcohol; reddish, long needles, m.p. 295–298°, which liberate iodine from a solution of potassium iodide in glacial acetic acid.

Anal. Calc'd for $C_{24}H_{16}O_3$: C, 81.8; H, 4.5.
Found: C, 81.9, 82.0; H, 4.1, 4.3.

6,11-Di-(2'-methoxy-5'-bromophenyl)-5-keto-5,5a,6,11,11a,12-hexahydronaphthacene (*XII*). To the filtered organometallic solution (from 0.26 g. of lithium metal and 6.7 g. of *p*-bromoanisole in anhydrous ether), the diketone (V, 0.5 g.) was added. The color turned to a fluorescent green, then to brown-red, while the diketone dissolved. After one day in the sealed Schlenk-tube, the reaction product was treated with dilute sulfuric acid and the ether dried and evaporated. The residue was triturated with methyl alcohol and recrystallized from benzene; colorless, hexagonal prisms, m.p. 278°; yield, 0.33 g.

Anal. Calc'd for $C_{32}H_{26}Br_2O_3$: C, 62.1; H, 4.2; Br, 25.9.
Found: C, 62.5; H, 4.3; Br, 25.3.

The substance contains methoxyl and is resistant to prolonged treatment with boiling acetyl chloride.

5,11-Di-p-tolylnaphthacene (*XIII*). In the analogous reaction of (V) with *p*-tolyllithium, the reaction mixture turned first red, then brown. The reaction product was triturated with methyl alcohol and recrystallized from pyridine; deep yellow, rhombic crystals, m.p. 335–336°. The analysis (Found: C, 93.6; H, 6.4) is perhaps in better accord with the formula $C_{32}H_{26}$ than with the expected $C_{32}H_{24}$ (Calc'd: C, 94.1; H, 5.9), but $C_{32}H_{26}$ appears to be unlikely, all the properties of the material pointing to a purely naphthacenic structure. In addition, the analysis of hydrocarbons of this series is not always easy.

REHOVOTH, PALESTINE.

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[CONTRIBUTION NO. 73 FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

CONSTITUENTS OF *ARTEMISIA TRIDENTATA* (AMERICAN SAGE BRUSH). II

CORLISS R. KINNEY AND JAMES SUGIHARA

Received April 3, 1943

Artemisia tridentata, the common western sage brush, furnishes browse for countless numbers of cattle, sheep, deer, and many smaller animals as well. This is particularly true in winter when most desert plants have dropped their leaves or are covered with snow. Since sage brush retains its leaves through freezing weather and is tall enough to extend above the snow, desert range animals survive on sage brush. In summer, even though an abundance of feed is available, range animals continue to eat some sage. Consequently, the plant is economically of very great importance.

The shrub is characterized by the grey-green color of its leaves, their aromatic odor, and their bitter taste. The latter properties are quite marked and probably discourage a greater utilization of the plant by animals. In fact, another closely related member of the species, *A. nova*, is found more palatable by range animals and is consequently much over-grazed.

In addition to the utilization of sage by animals, the pioneers of the West made use of it in several ways. An infusion of the leaves in hot water, called sage tea, was used as a "blood purifier," "stomach tonic," "spring tonic," etc. The very bitter taste of the extract probably was responsible for these uses, as are the statements that sage contains quinine. Sage was also used for washing the hair, as a poultice, a cure for goiter, etc. In view of these uses of sage by both men and animals an investigation was made on some of the main constituents of the plant. For determining the food values, the official methods of the Association of Official Agricultural Chemists were used. For some of the other constituents the methods described below were used. The samples were taken from sage growing near the mouth of Big Cottonwood Canyon, about fifteen miles southeast of Salt Lake City, Utah. Samples of both leaves and flower stalks were collected on October 23, 1942. The leaf samples included stems three to five inches long while the flower stalks were four to six inches.

The moisture content of the green leaf was only 44.0% while that of the flower stalks was 46.6% (Table I). A low moisture content was to be expected because the green leaf must withstand drought conditions in summer and subzero temperatures in winter. This gives a more concentrated green feed than most cultivated plants. On drying the samples in the air of the laboratory, the moisture became constant at 6.7% and 8.7% for the leaves and flowers respectively. This compares well with many types of hay.

The three major foodstuffs were present in the two samples in favorable amounts. Particularly outstanding was the high per cent of fat, which will be found in Table II. The values given in the Table are the average of two or more checking determinations. A portion of the crude fat is, of course, essential oil

which is responsible for the aromatic odor of the shrub (1). This amount was determined separately and is listed under the crude fat. The per cent of glycerides was also determined independently. This was accomplished by hydrolyzing the fats and isolating the glycerol quantitatively. By assuming that the fats were tripalmitin the per cent of glyceride fat was calculated to be 6.7% in the leaves and 7.3% in the flowers. This is unusually high for this kind of

TABLE I

MOISTURE DETERMINATIONS

SAMPLES	LEAVES	FLOWER STALKS
Green (12 hours after collection)	44.0%	46.6%
Air-dry (14 days to constant weight)	6.7	8.7

TABLE II

ANALYSES

(On Dry Basis)

CONSTITUENT	LEAVES		FLOWER STALKS	
Crude Fat (ether-soluble)				
Volatile oils	2.2		2.0	
Glycerides (calc'd as tripalmitin)	6.7		6.8	
Difference (waxes, etc.)	1.6		1.9	
		10.5		10.7
Carbohydrates				
Soluble reducing sugars	3.1		1.7	
Sol. non-reducing sugars	8.2		2.0	
Starch	15.0		13.4	
		26.3		17.1
Crude Fiber		27.9		28.4
Protein		11.2		7.5
Tannins		4.5		3.6
Alkaloids		0.3		0.4
Ash		4.9		6.0
Difference (largely alkali soluble, see Table III)		14.4		26.3
		100.0		100.0

plant material. There is an unaccounted-for difference of 1.6% and 2.0% in the crude fat respectively, which is most likely waxes, free fatty acids, etc.

The carbohydrates are also very high, especially the water-soluble sugars. The reducing sugars in the cold water extract were determined volumetrically with Fehling's solution after removing the glucosides with lead acetate. The total soluble sugars were determined by first hydrolyzing with acid and then titrating with Fehling's reagent. The difference in the two titrations was calculated as sucrose. The starch was determined after removal of the water-soluble

sugars by acid hydrolysis and estimation of the glucose produced by Fehling's reagent. The leaves contained a much larger amount of soluble sugars than the flower stalks, particularly in the form of non-reducing sugar. This was to be expected because the flower stalks wither and die shortly after the time of collection.

The crude fiber was estimated by the official method after preparing the sample by an improved procedure. Sage brush leaves cannot be ground easily because of the high fat and sugar content which makes the material very gummy. However, by first extracting these constituents with ether and water then drying, the grinding is greatly facilitated and the results check much better. The amount of fiber in the leaves and flower stalks was 27.9% and 28.4% respectively. This amount of fiber would be expected in material of this sort.

Protein was determined by the official Kjeldahl method. The value of 11.2% found in the leaves makes sage a satisfactory feed from this requirement. A smaller quantity, 7.5%, was found in the flowers. Since a number of leaves grow along the flower stalk it is possible that a considerable portion of the food values occur in these tissues.

The bitter taste of sage and its blackening effect upon iron vessels indicates the presence of tannic acid. To determine the amount, preliminary analyses were made using the permanganate oxidation method with oxalic acid as the standard. This gave a total oxidizable content in the leaves of 109%, and 65.4% in the flowers. Using glue to remove the tannins, values of 78.0% and 34.1% were obtained for the tannins. Obviously these values are too high when compared with the percentages of constituents already determined. Upon using the official hide powder method, 4.5% and 3.6% were obtained for the leaves and flowers respectively. Without doubt these results are more reliable. To test the use of glue for the removal of tannins, a permanganate analysis was made on the flower sample using hide powder instead of glue. This gave 33.8% tannins instead of 34.1% which checks the value obtained with glue as well as could be expected. Apparently, the trouble lies in the use of permanganate, large quantities of which are reduced by the water-soluble extract.

The bitter taste of the sage was found to be largely independent of the tannins because the removal of these substances with lead salts or with hide powder did not diminish the bitter taste noticeably. The bitter principle was isolated by the following manipulations. A hot-water extract was evaporated to dryness and the residue extracted with alcohol. After evaporating the alcohol, the residue was dissolved in water and boiled with Norit. The tannins were removed with lead acetate and the excess lead precipitated with ammonium carbonate. The filtrate was evaporated to dryness, leaving a brown amorphous powder. Several attempts to obtain a crystalline compound failed. The substance is exceedingly bitter, even in a dilute solution. It is very soluble in water and alcohol, but much less in ether, chloroform, and benzene. The yield was very small and further attempts to purify the substance were discontinued. Upon boiling the compound with dilute hydrochloric acid for four hours the bitter taste was destroyed. The solution was treated with phenylhydrazine and an

osazone melting at 200–202° was obtained. A mixed melting point determination and a comparison of the crystalline form with known glucosazone proved that the bitter principle was a glucoside. No odor of hydrogen cyanide was observed during the hydrolysis, indicating that the glucoside is of the simple type. Attempts to isolate the second part of the glucoside failed. It was water-soluble and no pure substance could be obtained with the quantity at hand.

Claims have been made that sage brush contains quinine (2), which if true would make sage brush a valuable source of this drug. To determine this point, the alkaloids present in sage were investigated. The alkaloids were removed from both the leaves and the flowers by extracting with a mixture of one part chloroform to two parts ether after the sample had been heated for an hour with dilute hydrochloric acid and then neutralized with ammonia. The solvent was extracted with several portions of dilute hydrochloric acid. Upon neutralizing the acid with ammonia the alkaloids were extracted by several lots of chloroform. The chloroform was evaporated and the residue extracted with alcohol. The alcohol was evaporated to dryness and the residue weighed to determine the

TABLE III

DETERMINATION OF CRUDE FIBER

EXTRACT	PER CENT COMPOSITION ON DRY BASIS	
	Leaves	Flower Stalks
Dry Ether (Crude Fat)	10.5	10.7
Cold Water (Soluble Sugars)	17.5	16.9
Hot H_2SO_4 (1.25%)	22.0	21.1
Hot NaOH (1.25%)	22.3	22.9
Crude Fiber (By Difference)	27.2	28.4
	100.0	100.0

quantity. The crude alkaloid yields were 0.3% and 0.4% in the leaves and flowers respectively.

The alkaloids isolated were viscous oils with a bitter taste. The material did not give a blue fluorescence in dilute sulfuric acid solution and did not give the thalleioquine test. Consequently, in the absence of any indication of even a trace of quinine, it seems very unlikely that the plant produces this drug.

The possibilities of obtaining santonin from species of Artemisia native to North America has been explored by Viehoever and Capen (3). These investigators have found that *A. tridentata* obtained from California yielded no santonin. The Utah samples, also, failed to give positive sublimation, furfural, and phosphoric acid tests for this drug.

Although sage contains alkaloid extractives, no outstanding physiological responses have been reported. Certain conversations have given the impression that larger quantities of sage tea produce dizziness, but few actual data seem to be available. Consequently, nothing further was done with this material.

The percent of ash appears to be quite low for the type of plant, but probably

is adequate for animal feeding. The amount of ash may vary with the soil, rainfall, and other factors and should be determined on sage from other localities.

The remainder of the plant material is to be accounted for in the alkali-soluble fraction in the fiber determination. The different fractions in these analyses have been arranged in Table III. Presumably, the alkali-soluble is largely lignin in nature.

SUMMARY

The results of these investigations have shown that sage brush is an excellent feed for animals, particularly in winter, because of its high glyceride fat content. The available carbohydrates are also high and the protein and ash are adequate. Tannins are present, but in insufficient amounts to be a source of tanning material. The bitter taste of sage is due to the presence of a glucoside to a very great extent.

Sage brush contains small quantities of alkaloids, but neither quinine nor santonin could be detected. Nothing definite is known about the physiological effects of this material.

SALT LAKE CITY, UTAH.

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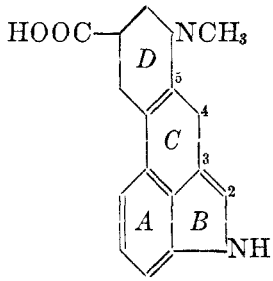
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

AN INDOLE SYNTHESIS FROM A *m*-CARBOXYPHENYLHYDRAZONE

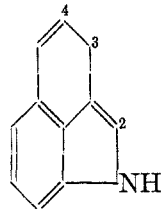
C. F. KOELSCH

Received January 31, 1940

Certain speculations which need not be detailed here indicate [contrast the data of Craig, Shedlovsky, Gould, and Jacobs (1)] that the conversion of derivatives of lysergic acid (I) into those of isolysergic acid may be explained by assuming that the change involves a shift of the 2,3-unsaturation of I into the 3,4-position. Particularly concerned in the assumed tautomerization are rings *A*, *B*, and *C* of I, rings which constitute the nucleus of the unknown 1,3-dihydrobenz[cd]indole (II; Ring Index 1681). The present paper describes an attempt to synthesize a derivative of this substance.

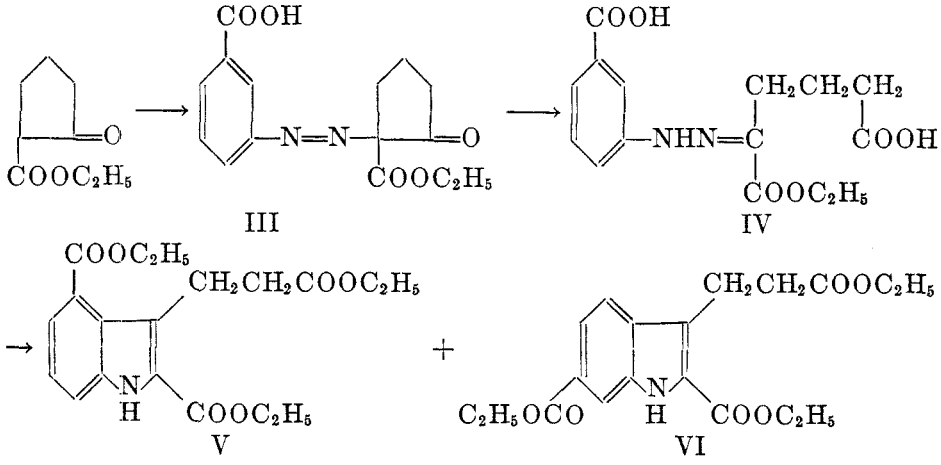


I

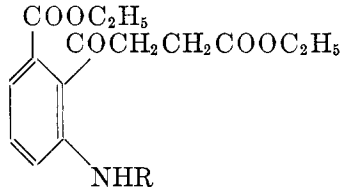


II

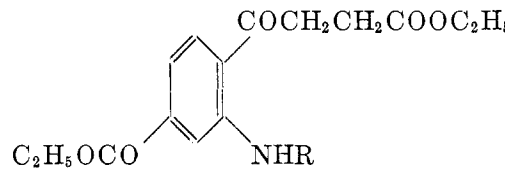
The proposed synthesis, illustrated in part in the accompanying chart, was carried out up to the final step. This step was to consist of a Dieckmann reaction with the ester V, but no conditions were found under which ring closure could be effected. The results are of interest, however, in that they show that the Fischer synthesis gives a mixture of a 4- and a 6-substituted indole when it is carried out using a *m*-carboxyphenylhydrazone. The formation of similar mixtures has been reported in several instances by Plant and his co-workers (2) but it was not noted in an early investigation on pyruvic acid *m*-carboxyphenylhydrazone (3).



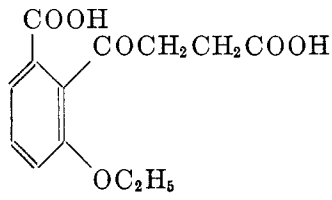
In order to determine the orientations of the two products from the Fischer reaction (V and VI), the substances were oxidized, yielding respectively VII and VIII, and these oxalo compounds were then alcoholyzed to the amino esters IX and X. It was planned to eliminate nitrogen from the amino esters and to oxidize the products to phthalic and terephthalic acids. But although the amino esters could be diazotized, in neither could the amino group be replaced by hydrogen, iodine, or methoxyl. When treated with alcohol the diazonium compound from IX gave a mixture from which the ethoxy compound XI was isolated in poor yield; with alcohol, the diazonium compound from X gave only the cinnoline XII.



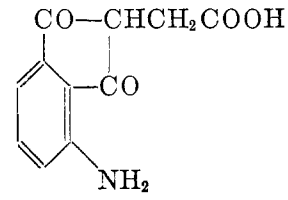
VII, R = $COCOOC_2H_5$
IX, R = H



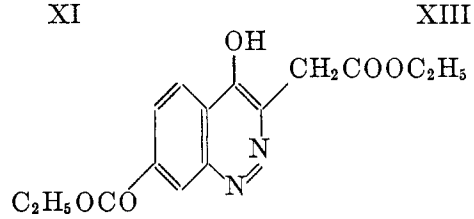
VIII, R = $COCOOC_2H_5$
X, R = H



XI



XIII



XII

The orientations of the esters IX and X were ultimately easily shown when it was found that hot aqueous sodium hydroxide saponified X, but converted IX into a mixture of its saponification product with the indandione XIII. The formation of the cyclic diketone established the *ortho*-relationship of the groups $—COOC_2H_5$ and $—COCH_2CH_2COOC_2H_5$ in IX, and hence the position of the carbethoxyl group in V. In agreement with the structures assigned on the basis of this reaction, IX and the corresponding acid are colorless, as are derivatives of 3-aminophthalic acid, whereas X and the acid corresponding to it are yellow, as are derivatives of aminoterephthalic acid.

EXPERIMENTAL

m-*Aminobenzoic acid.* This substance was prepared by the reduction of *m*-nitrobenzoic acid with ammonium sulfide (4) but none of the methods previously described for its isola-

tion was entirely satisfactory. The amino acid hydrochloride was difficultly soluble in excess hydrochloric acid, and it formed compact crystals much more easily handled than the bulky free acid; these properties made it possible to isolate the hydrochloride in nearly quantitative yields from the reduction mixture.

2-Carbethoxy-2-(m-carboxybenzeneazo)cyclopentanone (III), and the hydrazone IV. Treatment of a solution of ethyl cyclopentanone-2-carboxylate in sodium hydroxide with diazotized *m*-aminobenzoic acid according to the procedure of Manske and Robinson (5) gave mainly a dark red solid, probably a formazyl compound, and only small amounts of the desired hydrazone. A procedure analogous to that of Kalb, Schweizer, and Schimpf (6) gave satisfactory results.

A mixture of 17.3 g. of *m*-aminobenzoic acid hydrochloride, 10 ml. of conc'd hydrochloric acid and ice was treated with a solution of 7 g. of sodium nitrite; after solution was complete, sodium acetate (20 g. of the trihydrate) in water, and then 15.6 g. of ethyl cyclopentanone-2-carboxylate were added. The clear solution soon became turbid and deposited an oil which became crystalline on scratching. The azo compound, crystallized from ethanol, formed yellow needles that sintered at 105° and melted at 118–120° with decomposition.

The crude azo compound was dissolved in 100 ml. of 7% sodium carbonate, and the solution was boiled for two minutes. Acidification gave the hydrazone IV, which separated from 50% ethanol in the form of small orange-brown crystals which melted at 165–167°. The yields were usually better than 70% even in experiments several times the size of the one described.

Anal. Calc'd for $C_{15}H_{18}N_2O_6$: C, 55.8; H, 5.6.
Found: C, 55.5; H, 5.6.

Boiled for two hours with absolute ethanol (25 ml.) containing sulfuric acid (2.5 ml.) the hydrazone IV (5 g.) was simply esterified and not rearranged. The resulting m-*carbethoxyphenylhydrazone* of *diethyl α-ketoadipate* crystallized from ethanol in colorless needles that melted at 125–127°.

Anal. Calc'd for $C_{19}H_{26}N_2O_6$: C, 60.3; H, 6.9.
Found: C, 60.0; H, 6.7.

When the hydrazone IV (2 g.) was boiled for thirty minutes with 10% sodium hydroxide (20 ml.) and the resulting solution was then acidified, there was obtained the m-*carboxyphenylhydrazone* of *α-ketoadipic acid.* This substance was easily soluble in dilute sodium carbonate, but insoluble in organic solvents. After being washed with hot water, alcohol, and ether it formed a tan powder which melted at 215–218° with gas evolution.

Anal. Calc'd for $C_{13}H_{14}N_2O_6$: C, 53.0; H, 4.8.
Found: C, 52.7; H, 5.0.

2,4-Dicarbethoxy-3-(β-carbethoxyethyl)indole (V) and 2,6-dicarbethoxy-3-(β-carbethoxyethyl)indole (VI). A solution of the hydrazone IV (165 g.) in absolute ethanol (750 ml.) containing sulfuric acid (75 ml.) was boiled for two hours, then an additional 75 ml. of sulfuric acid was added and boiling was continued for three hours. The dark solution was cooled, giving the ester VI together with ammonium sulfate (15 g.). The latter was removed by washing with water. The alcoholic mother liquor was treated with water and ether, and the resulting ether solution was washed with dilute sodium carbonate, which removed partially esterified indole acids (13 g.). Concentration of the ether solution gave a second crop of ester VI; the residue was heated on a water-bath under reduced pressure to remove water and taken up in ether. The addition of ligroin (30–60°) and seeding caused the separation of the crude ester V.

The partially esterified indole acids (13 g.) were boiled for three hours with absolute ethanol (50 ml.) and sulfuric acid (5 ml.). The resulting ester mixture was composed almost entirely of ester V.

Ester VI was readily obtained pure by crystallization from ethanol. There was obtained a total of 40 g. of this substance, which formed colorless needles that melted at 113°.

Anal. Calc'd for $C_{19}H_{23}NO_6 + 0.5\ C_2H_5OH$: C, 62.5; H, 6.7.
Found: C, 62.4: H, 6.5.

Ester V was purified by crystallization from ether-ligroin, and by treatment in ether

solution with Merck's "Alumina nach Brockmann"; charcoal, ordinary alumina, and many other adsorbents tried were completely incapable of removing any of the colored impurities. There was obtained a total of 58 g. of ester V, which formed faintly tan needles that melted at 105–106°.

Anal. Calc'd for $C_{19}H_{23}NO_6$: C, 63.1; H, 6.3.
Found: C, 63.0; H, 6.6.

Esters V and VI were obtained in somewhat better yields in a number of smaller runs that were made.

Oxidation of esters V and VI. To a suspension of 5 g. of ester VI in acetic acid (25 ml.) was added slowly a solution of chromic anhydride (4 g.) in water (2 ml.) and acetic acid (13 ml.), while the reaction mixture was kept at 25–30° by external cooling. After the resulting solution had stood for twelve hours it was treated with enough water to cause turbidity. The product, *ethyl β-(4-carbethoxy-2-ethoxalylaminobenzoyl)propionate* (*VIII*) (4.6 g.) rapidly crystallized in an almost pure condition. Recrystallized from alcohol, it formed colorless plates that melted at 97–99°.

Anal. Calc'd for $C_{19}H_{23}NO_8$: C, 58.0; H, 5.8.
Found: C, 57.7; H, 5.9.

Similar treatment of ester V (5 g.) gave *ethyl β-(6-carbethoxy-2-ethoxalylaminobenzoyl) propionate* (*VII*) (4.3 g.), which crystallized from alcohol in the form of colorless needles that melted at 84–86°.

Anal. Calc'd for $C_{19}H_{23}NO_8$: C, 58.0; H, 5.8.
Found: C, 58.0; H, 6.0.

Alcoholysis of the ethoxalylamino compounds VII and VIII. When VIII was boiled with alkali, intramolecular condensation apparently accompanied hydrolysis of the ester groups, and a yellow substance which sintered and blackened above 225°, probably 2,7-dicarboxy-4-hydroxyquinolyl-3-acetic acid (7) was obtained.

When VIII (9.4 g.) was boiled for three hours with ethanol (50 ml.) containing sulfuric acid (5 ml.), the reaction involved only the ethoxyalylamino group. The product was isolated by adding aqueous sodium acetate and seeding. The resulting *ethyl β-(2-amino-4-carbethoxybenzoyl)propionate* (*X*) crystallized from ethanol in the form of bright yellow plates (5.4 g.) that melted at 87–88°.

Anal. Calc'd for $C_{15}H_{19}NO_5$: C, 61.4; H, 6.5.
Found: C, 61.5; H, 6.6.

On treatment with benzoyl chloride in aqueous sodium carbonate, the amino ester X gave a benzoyl derivative which formed colorless needles that melted at 86–88°, and when the latter was boiled with aqueous sodium hydroxide gave a white crystalline acid, probably (7) a quinoline derivative, that sintered and darkened at 210°.

The substance IX, prepared by the action of alcoholic sulfuric acid on VII, was a colorless basic oil. It was not analyzed.

Action of nitrous acid on the amino esters IX and X. Both of the amino compounds could be diazotized readily in water or in methyl or ethyl alcohols, as was shown by the formation of red coupling products when such solutions were treated with alkaline β-naphthol. Warming the methanol solutions or warming the aqueous solutions alone or with potassium iodide gave only oily products.

A solution of the ethoxalylamino ester VIII (4.5 g.) in ethanol (25 ml.) containing sulfuric acid (2 ml.) was boiled for one hour, then cooled to 0° and treated with butyl nitrite (2 g.). After fifteen minutes the solution had lost its yellow color and gave a deep red color with alkaline β-naphthol. It was heated to boiling, but no gas evolution was observed. The addition of ether and water gave a waxy solid (1.7 g.) which was crystallized several times from alcohol. The *cinnoline XII* (0.6 g.) so obtained formed colorless plates that melted at 168–171°. It gave a qualitative test for nitrogen.

Anal. Calc'd for $C_{15}H_{16}N_2O_5$: C, 59.2; H, 5.3.
Found: C, 59.5; H, 5.5.

The ethoxalylamino ester VII (4.1 g.) was alcoholyzed and diazotized in the same way; the orange diazonium solution gave a deep red color with alkaline β-naphthol. When the alcoholic solution was warmed, nitrogen was evolved, but only an oily product was obtained.

This dissolved slowly on boiling with 10% aqueous potassium hydroxide. The solution was acidified and extracted repeatedly with ether, and the product was purified by treatment with charcoal and crystallization from water. There was obtained 0.28 g. of *β-(2-ethoxy-6-carboxybenzoyl)propionic acid* (*XI*) which formed faintly tan needles that melted at 166–168°.

Anal. Calc'd for $C_{13}H_{14}O_6$: C, 58.7; H, 5.3.
Found: C, 58.9; H, 5.5.

Action of alkali on the amino esters IX and X. The yellow amino ester X (0.3 g.) dissolved when it was boiled for thirty minutes with 10% aqueous potassium hydroxide (5 ml.). The resulting yellow solution was treated with sulfuric acid to *p*H 3, and the precipitate was crystallized from water (50 ml.). There was obtained 0.21 g. of *β-(2-amino-4-carboxybenzoyl) propionic acid* which formed bright yellow needles that did not melt at 250° (block). It melted partially when immersed in a bath above 215°, then resolidified and became much lighter in color.

Anal. Calc'd for $C_{11}H_{11}NO_5$: C, 55.7; H, 4.7.
Found: C, 55.8; H, 4.7.

The ethoxalylamino ester VII (8.6 g.) was alcoholyzed with alcoholic sulfuric acid, and the oily product IX was isolated by ether extraction of the diluted and basified solution. The crude IX so obtained was boiled for forty-five minutes with a solution of sodium hydroxide (10 g.) in water (50 ml.). The sodium oxalate which separated on cooling was removed, and the deep red mother liquor was treated with sulfuric acid to *p*H 3. The precipitated *β-(2-amino-6-carboxylbenzoyl) propionic acid* was crystallized from water. It formed faintly tan flat needles (3.7 g.) that sintered at 168° and melted at 180° with gas evolution. It dissolved without color in dilute sodium carbonate.

Anal. Calc'd for $C_{11}H_{11}NO_5$: C, 55.7; H, 4.7.
Found: C, 56.0; H, 4.6.

The mother liquor from the acid was extracted with ether, and the orange-red solid so obtained (0.5 g.) was separated by crystallization from water into the acid just described, and *4-amino-1,3-diketohydrindene-2-acetic acid* (*XIII*) (0.1 g.). This substance formed orange-brown plates that sintered at 192° and melted at 202° with darkening. It gave a deep red solution in aqueous sodium carbonate and a pale yellow solution in dilute hydrochloric acid.

Anal. Calc'd for $C_{11}H_9NO_4$: C, 60.2; H, 4.2.
Found: C, 59.8; H, 4.4.

SUMMARY

In an attempt to prepare a derivative of 1,3-dihydrobenz[cd]indole, the Fischer indole synthesis was applied to the *m*-carboxyphenylhydrazone of α-ketoadipic acid. Ring closure took place in two directions, yielding two isomeric indoles. Oxidation followed by hydrolysis converted the indoles into isomeric aminocarboxybenzoylpropionic acids. Only one of these could be cyclized to an indandione, proving the position of the substituents in it, and leading to positive orientations for the parent indoles.

MINNEAPOLIS, MINN.

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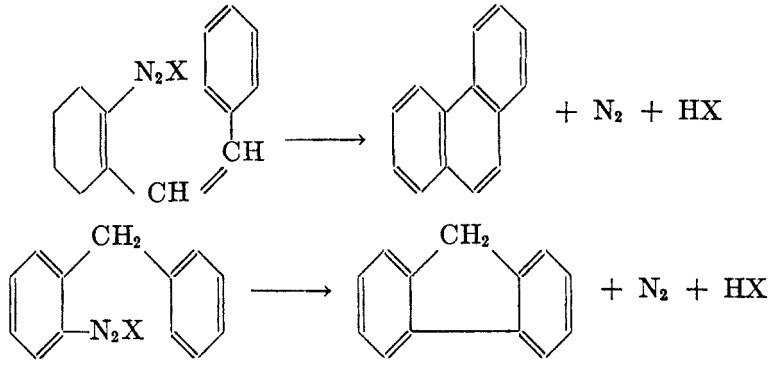
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

AN ATTEMPTED SYNTHESIS OF A CYCLOÖCTATETRAENE. CIS-TRANS ISOMERISM OF SUBSTITUTED DI- AND TRI-PHENYLBUTADIENES [1]

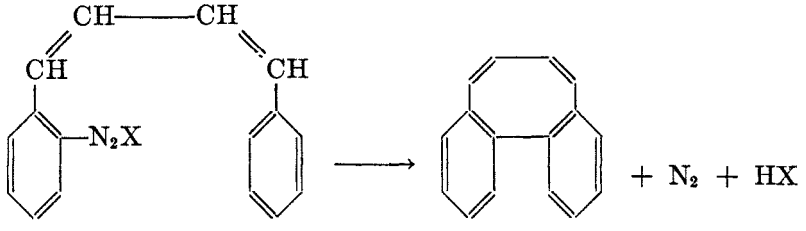
G. BRYANT BACHMAN AND R. I. HOAGLIN[2]

Received January 11, 1943

Diazotized aromatic amines will couple under certain circumstances with other aromatic nuclei, eliminating nitrogen and forming a carbon-carbon bond. When the two nuclei are already linked together at some other point a polycyclic structure of a higher order results. This reaction is the basis of the Pschorr phenanthrene synthesis (1), and has recently been applied by one of us to the synthesis of fluorene derivatives (2).



In the first of these applications a six-membered aromatic ring is created, while in the second a five-membered ring of a mixed type is formed. It occurred to us that the same kind of condensation might also be employed in obtaining an eight-membered unsaturated ring of the cycloöctatetraene type.



This synthesis, like others which have been attempted (21, 22), has been found to be inadequate for the proposed purpose. However, certain observations concerning the preparation of geometrical isomers have been made which make it desirable to report our results at this time.

[1] From the Ph.D. thesis of R. I. Hoaglin. Read before the Organic Section of the American Chemical Society at the Memphis meeting, April 20 to 24, 1942.

[2] Present address, Carbide and Carbon Chemicals Corp., Charleston, W. Va.

A system of two double bonds separated by a single bond permits of a maximum of four isomers when there are at least two different substituents present on each one of the double bonds. The construction of models of 1-phenyl-4-(*o*-aminophenyl)-1,3-butadiene shows that of the four possible configurations, the cis-cis is the only one in which the two phenyl groups approach each other closely enough to make condensation between them likely. The expected product from the cis-cis isomer, 1,2,3,4-dibenzo-1,3,5,7-cycloöctatetraene, could exist either as a somewhat strained ring or as a puckered ring. The cyclized products from each of the other isomers would be severely strained and almost certainly incapable of existence.

But little is known about the preparation of the various possible geometrical isomers of any substituted butadiene. Actually no single case is known in which

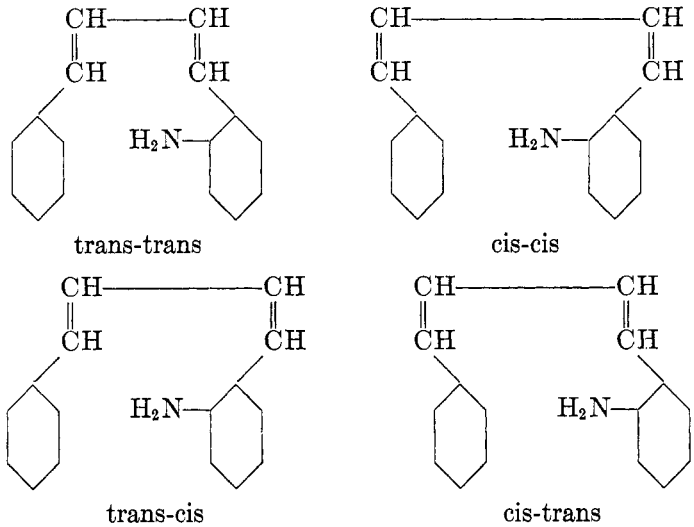


FIG. 1[3]

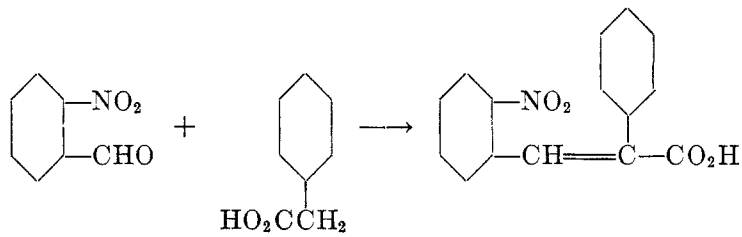
all four possible isomers have been synthesized, one case is known in which three isomers have been synthesized and the fourth obtained from natural sources (3), and two cases are known in which the three possible forms (cis-trans and trans-cis forms being identical because of symmetrical substitution) have been synthesized (4, 5).

The general problem of synthesis of the four isomers has proved so difficult, especially in so far as the cis forms are concerned, that at one time the opinion

[3] Throughout this paper the configurations of the diphenylbutadienes will be the same as shown in Fig. 1, *i.e.*, on the basis of the relationship of the two phenyl groups to each other. Thus, consistency for purposes of discussion will be maintained. Where four different substituents are present on a given C=C nucleus the terms cis and trans obviously have no meaning, unless a general naming system has been adopted. For such purposes it is the usual practice to call the lower-melting or less stable form *allo*, although this is not always done.

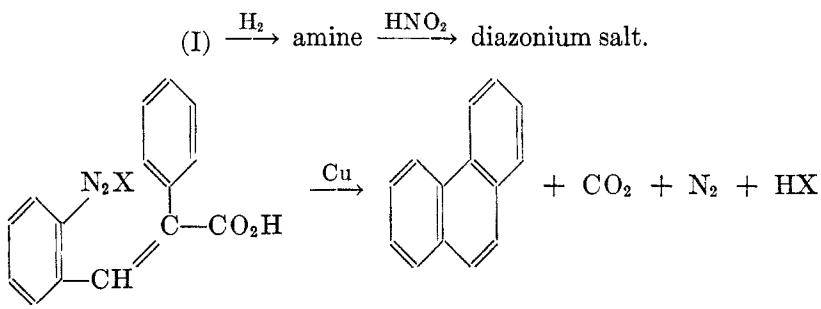
was expressed (6) that such isomers could not exist and even that the electron distribution in such a system precluded the possibility of their existences (7). The latter viewpoint is incorrect and must be abandoned in the light of the data already presented. However, it is true that some factor, probably electron mobility (8), does lead to greater lability in these conjugated systems, and that this same factor prevents the isolation of the unstable or cis forms in many cases where their formations are to be expected. A comprehensive study of the factors involved in the synthesis of cis-trans isomers and in their relative stabilities has not yet been made.

We have approached the synthesis of the desired dienes through the corresponding diene carboxylic acids for the reason that more is known about methods of obtaining the possible geometrical isomers of this class of compounds than of any other class of substituted olefins. The Perkin reaction has been employed in



A cis *o*-nitrostilbene acid
(I)

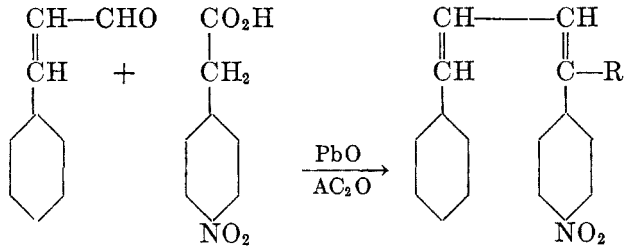
the synthesis of various *o*-nitrostilbene carboxylic acids, the configurations of which have been shown to be of the cis type by conversion to phenanthrene and its derivatives (9, 10).



A literature survey shows that the Perkin reaction usually gives predominantly a product in which the *beta* substituent is trans to the carboxyl group and cis to the *alpha* substituent. This form may or may not be the higher-melting (10). On the other hand if the carboxyl group is eliminated *during the synthesis* the product usually possesses the trans configuration provided an *alpha* substituent other than hydrogen is present to make cis and trans forms possible.

The Kuhn-Winterstein (11) modification of the Perkin synthesis employs the free acid, instead of its sodium salt, and litharge (PbO) as a condensing agent. These workers obtained only a trans-trans hydrocarbon, 1,4-diphenyl-1,3-

butadiene, from cinnamaldehyde and phenylacetic acid. It has been shown however by Bergmann and Weinberg (12), that this method yields not only a hydrocarbon (IIb) but also an equal amount of an acid (IIa) when *p*-nitrophenylacetic acid replaces phenylacetic acid.



(IIa) R = CO_2H
(IIb) R = H

The configuration of neither of these products was demonstrated, although in our opinion IIa was probably trans-cis by analogy with products obtained by similar syntheses in the stilbene series, *e.g.* I. The hydrocarbon IIb would be trans-trans if formed according to the mechanism proposed by Bergmann and Weinberg for the formation of analogous stilbene derivatives. It would probably be trans-cis if formed by decarboxylation of IIa since Ruggli and Staub (13) have shown that such decarboxylations do not usually alter the configuration under ordinary conditions.

Another approach to this group of compounds is made possible by a recently developed synthesis of Meerwein and co-workers (14). Many unsaturated acids react with diazonium salts in the manner shown below for cinnamic acid and benzene diazonium chloride.

$$C_6H_5CH{=}CHCO_2H + C_6H_5N_2Cl \longrightarrow C_6H_5CH{=}CHC_6H_5 + CO_2 + N_2 + HCl \qquad III$$

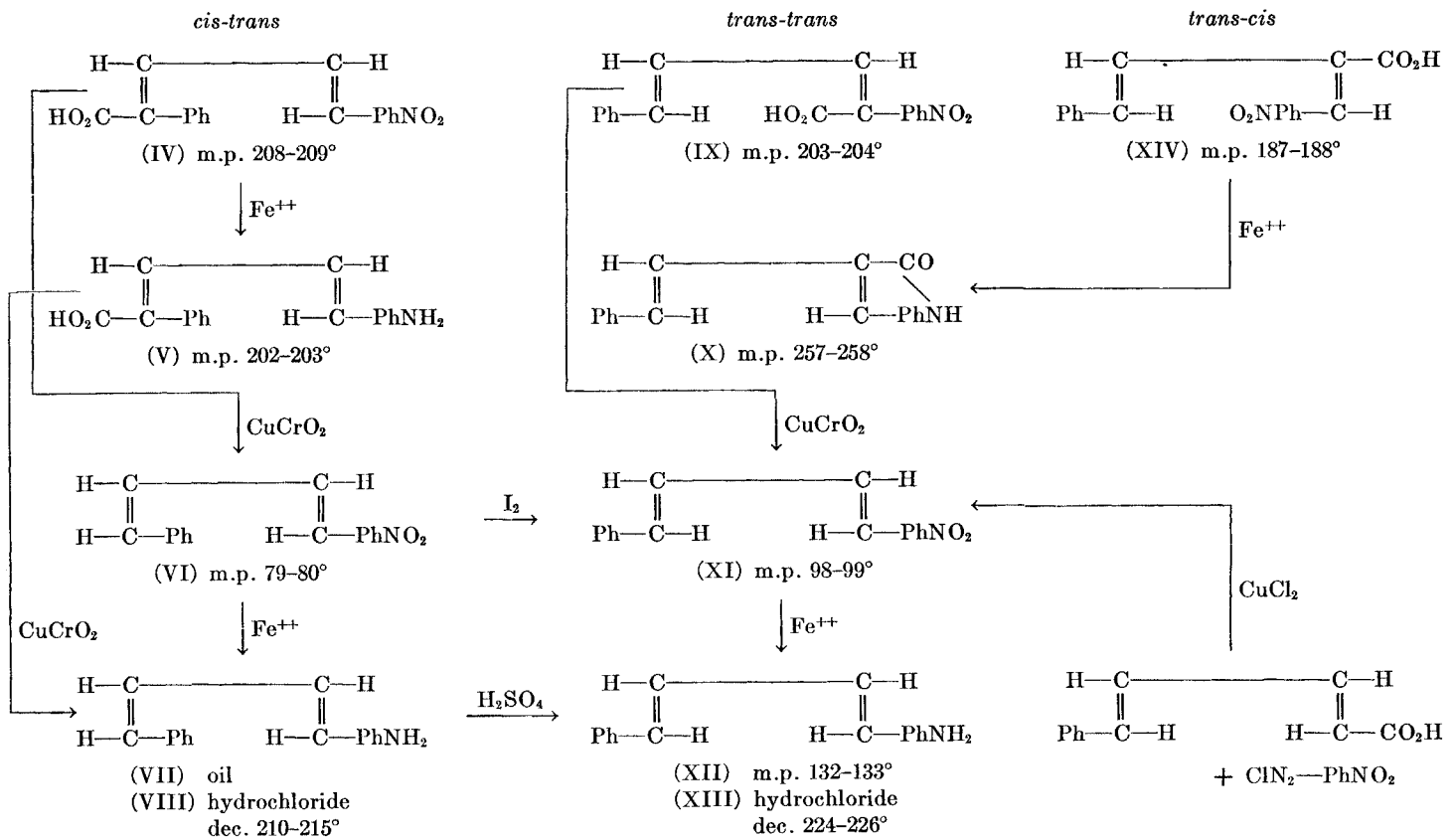
The product in this particular case is trans-stilbene. Bergmann and Weinberg also employed this method in the synthesis of a IIb whose configuration was the same as the IIb obtained by the Kuhn-Winterstein procedure. It is clear that this synthesis tends to yield a trans form. It is probable also that the hydrocarbon IIb is trans-trans and resulted from a direct synthesis as postulated by Bergmann and Weinberg, rather than being trans-cis and arising through a decarboxylation of IIa.

Our results are summarized in Figure 2. We have applied each of the above described syntheses in various ways and have isolated products which are rendered probable on the basis of evidence to be presented. Each of the three series cis-trans, trans-trans, and trans-cis will be discussed in order. For reasons which will appear later, efforts to enter the cis-cis series were abandoned.

Cis-trans series. The first compound in this series, 2-phenyl-5-(*o*-nitrophenyl)-2,4-pentadienoic acid (IV), was made by the condensation of *o*-nitrocinnamaldehyde with phenylacetic acid. The yield by the Perkin procedure using the

FIGURE 2

DERIVATIVES OF 1,4-DIPHENYL-1,3-BUTADIENE

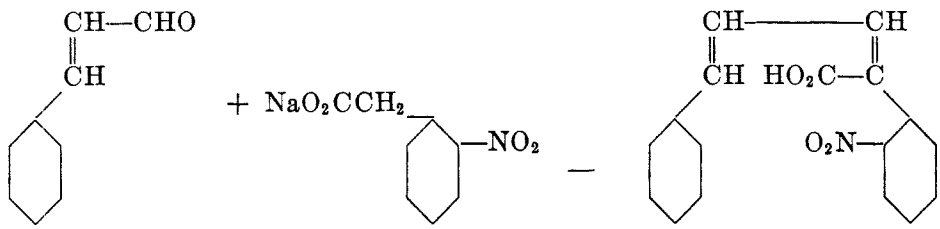


sodium salt of the acid was much better in this case than the yield by the Kuhn-Winterstein modification using a mixture of the free acid and litharge. Both methods gave the same product.

The cis-trans configuration of this acid is probable for the following reasons. The simple cinnamaldehydes (*i.e.*, those with no substituents other than hydrogen on the double bond) are apparently stable only in the trans forms. This trans configuration would be expected to carry over to the product of a condensation reaction. The cis configuration on the other double bond is likely through analogy with the related synthesis of I. Its configuration is made even more probable by the ready isomerization to a higher-melting isomer (XI) of the corresponding nitro hydrocarbon (VI) obtained by decarboxylation of the acid. Such an isomerism would not be expected to occur if both double bonds were initially trans.

Reduction of IV with ferrous sulfate and ammonia yielded the corresponding amino acid (V). Upon decarboxylation this acid yielded an amine (VII) identical with that obtained by reducing the nitro hydrocarbon (VI). The yields were much better when decarboxylation preceded reduction. The amine itself was also readily converted into a higher-melting isomer (XII) indicating that the cis configuration in this case was not disturbed by either decarboxylation or reduction.

Trans-trans series. Trans-trans-1-(*o*-nitrophenyl)-4-phenyl-1,3-butadiene (XI) was made in three different ways: (a) the cis-trans form (VI) was isomerized to XI by heating with a trace of iodine in nitrobenzene; (b) the reaction of 5-phenyl-2,4-pentadienoic acid with *o*-nitrobenzene diazonium chloride yielded XI directly; (c) decarboxylation of 1-(*o*-nitrophenyl)-4-phenyl-1,3-butadiene-1-carboxylic acid (IX) yielded XI. The acid IX resulted unexpectedly from the condensation of cinnamaldehyde with sodium *o*-nitrophenylacetate.

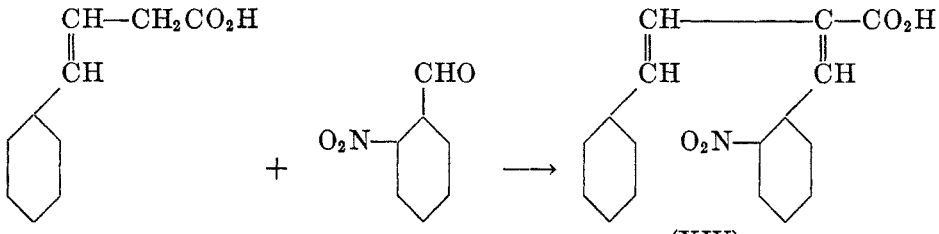


(IX)

By analogy with the syntheses of I and IV a trans-cis configuration was expected. That this configuration was not obtained is probable because of the formation of the stable trans-trans nitrohydrocarbon (XI) from IX by decarboxylation. This explanation is considered more probable than the other possible one, namely that the decarboxylation of IX was accompanied by isomerization. Probably the trans configuration was conditioned by steric hindrance between the carboxyl group and the *o*-nitro group.

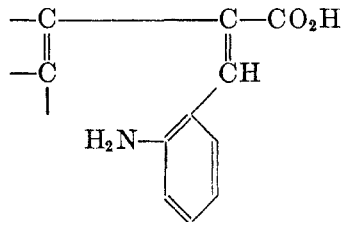
Reduction of the nitro hydrocarbon (XI) gave an amine (XII) which was stable to isomerization and which was identical with the amine obtained by isomerizing the cis-trans amine (VII).

Trans-cis series. By the condensation of *o*-nitrobenzaldehyde with sodium 4-phenyl-3-butenoate an acid (XIV) was obtained whose configuration is presumably trans-cis by analogy with other compounds obtained by similar syntheses (19).



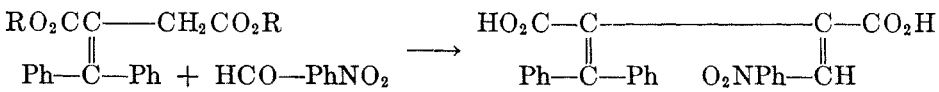
(XIV)

Unfortunately all efforts to isolate a nitro hydrocarbon from decarboxylation experiments with this acid were unsuccessful. Furthermore reduction of XIV yielded an amino acid which immediately lactamized to X. It is clear from models that such a ring closure could only occur readily if the $—NH_2$ and $—CO_2H$ groups were cis to each other. Although the original acid XIV may have had a trans-trans configuration it is more probable, in our opinion, that the isomerization occurred during reduction to the amino acid. If such be true then the preparation of a diene containing a structure with carboxyl and *o*-aminophenyl

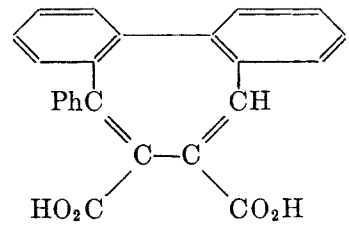


groups trans to each other, may be a practical impossibility in this series because of the apparent lability of this group. Such lability is not strange in view of the presence of a powerful electron donor group (NH_2) at one end and a powerful electron acceptor group (CO_2H) at the other end of a conjugated system. Arrangements of this type permit tautomeric electronic shifts of considerable magnitude and the configuration about the central bond is thereby greatly labilized. On the other hand Stoermer and Oehlert (15) had no trouble with the preparation of similar acids in the stilbene series. Lactams were obtained only in the event that in the original nitro acid the $—C_5H_4NO_2$ and $—CO_2H$ groups were cis to each other. The difference in behavior may be due to the generally greater lability of the diphenylbutadiene system.

Cis-cis series. In view of the practical and theoretical difficulties outlined in the above paragraph, efforts to enter the cis-cis series of compounds of this type were temporarily abandoned. Instead, a 1,1,4-triphenylbutadiene derivative was prepared according to the following reaction.



Hope of success in converting this 1,1-diphenyl-4-(*o*-nitrophenyl)-1,3-butadiene-2,3-dicarboxylic acid (XV) into a cycloöctatetraene by reduction and diazotization was based on three points: (a) The configuration of the double bond on the left is inevitably cis for one of the phenyl groups; (b) the presence of a second carboxyl group on the carbon atom *beta* to the first carboxyl group should diminish the magnitude of the tautomeric electronic shifts in the double bond on the right and hence should stabilize it; and (c) the replacement of the hydrogen atom in the 1-position by a phenyl group prevents a coupling from occurring at that position. Such a coupling would form a six-membered ring and yield a derivative of naphthalene. Finally, this compound presents the further advantage of making it possible, in the event of successful ring closure, to determine whether the cycloöctatetraene ring is merely puckered or whether the bond angles are strained and the ring is planar. In the event of puckering, the two benzene rings would not necessarily occupy the same plane and the system would be optically active.



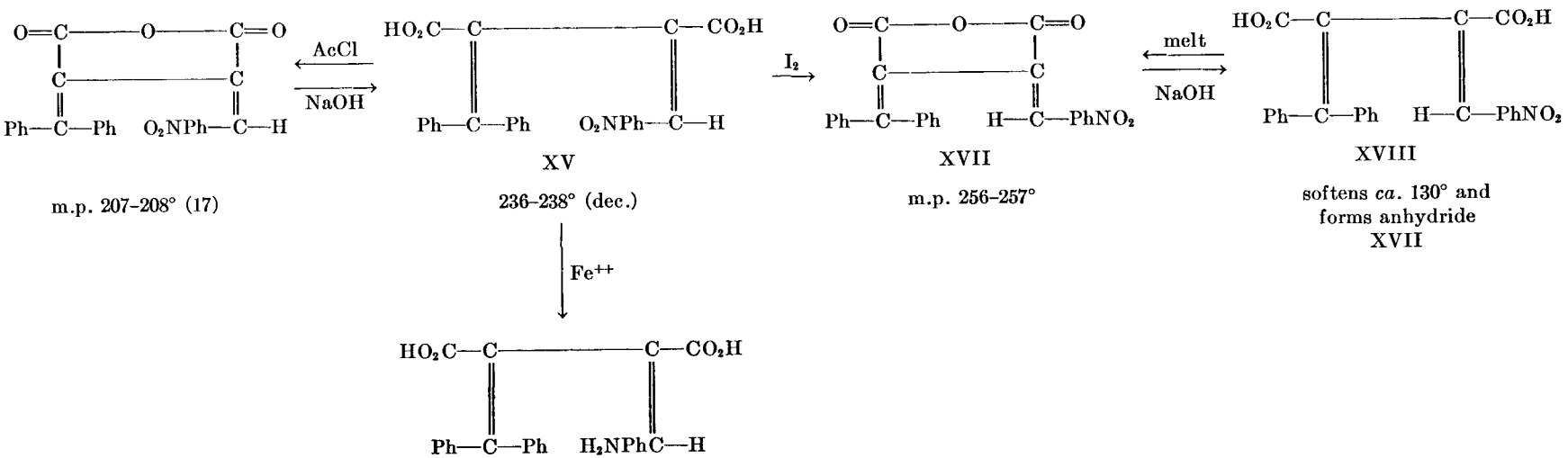
Resolution might be effected through the carboxyl groups, and the relative stability of the isomers would indicate the ease with which one puckered form of the ring is converted to another. This type of optical isomerism in the biphenyl series has been noted before (16), and the isolation of relatively stable optical isomers indicates the ease with which large rings undergo puckering.

The acid XV was obtained readily from succinic ester by condensation first with benzophenone and then with *o*-nitrobenzaldehyde. These compounds and the corresponding amino acid (XVI) (Fig. 3) were originally prepared by Stobbe (17). We were able to improve the yields in the first condensation materially by altering his procedure somewhat. The amino acid finally obtained did not lactamize so that it probably possessed a cis configuration (according to Fig. 1). It was diazotized without difficulty, but all efforts to cause the desired cyclization to occur were unsuccessful—only resinous products could be isolated. The diazotization was carried out in both water and dioxane with similar results. The cyclizations were attempted with copper powder alone and in the presence of sodium hypophosphite. In every case nitrogen was evolved, but acidification of the product gave a dark amorphous precipitate that resisted purification.

Isomerizations. It has already been mentioned that the cis-trans nitrohydrocarbon (VI) and the corresponding amine (VII) were readily isomerized to more stable isomers. This was accomplished with the nitro hydrocarbon by heating its solution in nitrobenzene to boiling for about half an hour in the presence of a trace of iodine. This procedure also caused an isomerization of the acids XIV and XV but failed to change IV and IX. The triphenylbutadiene diacid (XV) was converted into an anhydride (XVII) (m.p. 256–257°) by this treatment.

FIGURE 3

RELATIONSHIPS OF DERIVATIVES OF THE TRIPHENYLBUTADIENE DICARBOXYLIC ACID SERIES



This was different from the anhydride (m.p. 207–208°) obtained by Stobbe (17) on treating XV with acetyl chloride. On hydrolysis the anhydride (XVII) yielded a hydrated acid (XVIII) which was different from the original acid (XV) and which when heated reverted to the anhydride after merely softening but not melting. This ease of anhydride formation indicates a closer approach of the two carboxyl groups in this acid as compared to the original acid. Models show that this behavior would be expected in the trans compound. Steric hindrance between the phenyl and nitrophenyl groups prevents a close approach of the carboxyl groups in the cis isomer. This is a further indication that the diacid (XV) has the postulated cis structure. The anhydride of the isomerized acid was reduced with ferrous ion to an amino dicarboxylic acid whose analysis indicated that it had not lactamized. Insufficient material was available for a more detailed study of the amino derivative. Relationships of these derivatives of the triphenylbutadiene dicarboxylic acid series are shown in Figure 3.

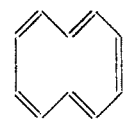
DISCUSSION

The properties of cycloöctatetraene, especially its relative instability and reactivity, are of considerable significance to our theories of the nature of the aromatic nucleus. The continuously conjugated system of double bonds present in benzene may be the cause of the general inertness of that substance. If such conjugation is a sufficient cause of the inactivity then cyclobutadiene and cycloöctatetraene should resemble benzene (cyclohexatriene) very closely in chemical properties. So far all attempts to synthesize cyclobutadiene have been unsuccessful, but this may or may not mean that such a substance, once made, would be unstable and reactive. The burden of proof therefore lies heavily upon cycloöctatetraene. Willstätter's original synthesis of this substance (18) led to a product which was very unstable. This proved so surprising that organic chemists have made sporadic attempts ever since to devise new syntheses for this important compound. Other workers have pointed out the possibility that the compound prepared by Willstätter was not cycloöctatetraene but something else, and many chemists have been reluctant to accept as proven facts the existence and great reactivity of this substance.

As a matter of fact the reactivity of a hydrocarbon having the structure of a cycloöctatetraene may be predicted on the basis of the resonance theory. The resonance energy which stabilizes benzene (39 k cals/mole) would be greatly reduced in cycloöctatetraene in spite of an increase in the number of double bonds and resonance forms in that substance. This is a result of the fact (as shown clearly by models) that the eight-membered fully conjugated ring must exist either in a strained or in a puckered form. If the ring is strained then a considerable portion of the expected resonance energy will be lost in straining the atomic bonds from their normal angles. If the ring is puckered then atomic motions are necessary to alter the pucker in going from one resonance form to another. Resonance is greatly diminished in non-planar rings of this type due to these atomic movements. Probably the actual form taken by cycloöctatetraene would be a partially puckered, partially strained ring with greatly reduced resonance energy. The low resonance energy would lead to reactivity of the type normally associated with double bonds.

Our inability to achieve the synthesis of a cycloöctatetraene derivative through diazotization and coupling of the amino acid (XVI) may be laid to one or the other of the following causes: (a) The intermediates prepared did not have the expected configurations; (b) the energy and unfavorable steric factors involved in the formation of the cycloöctatraene ring were too great to be overcome by this type of synthesis, and a substitute reaction (perhaps phenol formation) occurred; (c) the expected product formed, but being very labile underwent an immediate further change, such as a polymerization. Of these explanations the second appears to us the most likely. In the first place, the proposed configurations of the amino acids studied, especially that of XVI, seem reasonably probable. In the second place, even the formation of relatively stable rings containing five and six atoms is easily hindered by steric influences in the Pschorr synthesis. Finally there was no evidence of the formation of an unstable intermediate product of the type postulated in (c). The recently reported failure of Rapson and Shuttleworth (21) to obtain 1,2,3,4-dibenzocycloöctatetraene by the action of metallic copper on 1,4-bis-(*o*-iodophenyl)-1,3-butadiene must on the other hand be attributed to the geometrical configuration of their intermediate. This diiodo compound was almost undoubtedly trans-trans since it was obtained directly from a Kuhn-Winterstein modification of the Perkin synthesis.

As a means of verifying the theoretical implications of the resonance theory in its applications to the structure of aromatic compounds a cyclodecapentaene should be prepared. Such a compound may be predicted to be relatively stable because of high resonance energy. Its molecules could take up the configuration



which models show to be nearly planar and but little more strained than naphthalene. Other cyclopolyenes of this type containing 6 + 4n carbon atoms should also be planar molecules and hence stable, in the sense that naphthalene and anthracene are stable. It is our hope to attempt the synthesis of such molecules following the war.

EXPERIMENTAL

2-Phenyl-5-(o-nitrophenyl)-2,4-pentadienoic acid (IV). a. Perkin synthesis. A mixture of 17.7 g. (0.1 mole) of *o*-nitrocinnamaldehyde, 15.8 g. (0.1 mole) of the sodium salt of phenylacetic acid (dried at 130°), and 100 g. of acetic anhydride was heated with occasional shaking to an oil-bath temperature of 110° for 12 hours. After cooling, the dark semi-solid reaction mixture was hydrolyzed with water and then poured into 1 liter of hydrochloric acid (1:3), whereupon the yellow nitro acid precipitated. Yields of 80–85% were obtained. Crystallization from 95% alcohol gave long yellow needles, m.p. 208–209°.

Anal. Calc'd for $C_{17}H_{13}NO_4$: C, 69.10; H, 4.44.
Found: C, 69.0; H, 4.2.

b. Kuhn-Winterstein reaction. A mixture of 15.9 g. (0.09 mole) of *o*-nitrocinnamaldehyde, 12 g. (0.09 mole) of phenylacetic acid, 10 g. (0.045 mole) of lead oxide (PbO), and 18 g. (0.2 mole) of acetic anhydride was heated under reflux four hours (140–145°, oil-bath temperature). The reaction mixture remained completely liquid even after cooling over-

night. It was extracted with several portions of sodium carbonate solution, and the soluble portion was treated with dilute hydrochloric acid to give a yellow amorphous product. After a single purification from 95% alcohol this formed long yellow needles, m.p. 208–209°. A mixture of this material and that obtained by the Perkin reaction in the preceding description gave no depression of the melting point. The yield of nitro acid was 25%.

Anal. Calc'd for $C_{17}H_{13}NO_4$: C, 69.10; H, 4.44.
Found: C, 69.0; H, 4.4.

The neutral or soda-insoluble portion was very gummy and had a resinous appearance. No nitro hydrocarbon could be isolated from this mixture.

1-(o-Nitrophenyl)-4-phenyl-1,3-butadiene-1-carboxylic acid (IX). This compound was made only by the Perkin condensation of cinnamaldehyde and the sodium salt of *o*-nitrophenylacetic acid. The sodium salt of *o*-nitrophenylacetic acid was prepared by the method of Mayer and Balle (19). The sodium salt,[4] 20.3 g. (0.1 mole), with 13.2 g. (0.1 mole) of cinnamaldehyde and 25 g. of acetic anhydride, was heated ten hours at an oil-bath temperature of 110–120°. The mixture was cooled, warmed with water to hydrolyze the acetic anhydride, and then with dilute ammonia to extract the nitro acid. A considerable quantity of cinnamaldehyde remained unreacted. The ammoniacal solution was filtered, extracted with ether to remove impurities, and the nitro acid precipitated by pouring into dilute hydrochloric acid. After purification it formed canary yellow crystals, m.p. 203–204°, (yield 23.5%).

Anal. Calc'd for $C_{17}H_{13}NO_4$: C, 69.10; H, 4.44.
Found: C, 69.4; H, 4.5.

1-(o-Nitrophenyl)-4-phenyl-1,3-butadiene-2-carboxylic acid (XIV). This nitro acid was also obtained both by the Perkin synthesis and by the Kuhn-Winterstein modification of it.

a. Perkin reaction. A mixture of 9.2 g. (0.05 mole) of the dry sodium salt of 4-phenyl-3-butenoic acid (15), 7.5 g. (0.05 mole) of *o*-nitrobenzaldehyde, and 12 ml. of acetic anhydride was warmed on a steam-cone under a reflux condenser. A vigorous reaction resulted within three minutes, the mixture became very dark, and heating was discontinued until the reaction subsided. The mixture was heated another 20 minutes on the steam-cone, then allowed to cool and solidify. The product was dissolved in sodium carbonate solution, and the solution extracted with ether to remove non-acid impurities. The nitro acid was precipitated by adding the solution slowly to a cold, dilute solution of hydrochloric acid, with constant stirring to prevent the precipitate from becoming gummy. The acid was an amorphous, yellow product, which after boiling with Norit in 95% alcohol solution, crystallized in beautiful, small, canary-yellow crystals, m.p. 187–188°. The yield was only about 17%.

b. Kuhn-Winterstein. A mixture of 16.2 g. (0.1 mole) of 4-phenyl-3-butenoic acid, 15.1 g. (0.1 mole) of *o*-nitrobenzaldehyde, 11.1 g. (0.05 mole) of litharge (PbO), and 20 g. (0.2 mole) of acetic anhydride was caused to react as in previous condensations. The product was an amorphous, brown material, which after purification with Norit, crystallized from 95% alcohol in small yellow crystals, m.p. 187–188°. The yield of crude material was about 64%, considerably better than that produced by the Perkin synthesis.

Anal. Calc'd for $C_{17}H_{13}NO_4$: C, 69.10; H, 4.44.
Found: C, 69.2; H, 4.5.

1-(o-Nitrophenyl)-4-phenyl-1,3-butadiene (cis-trans) (VI). One part of the nitro acid, 0.1 part of the Adkins-Connor decarboxylation catalyst (20), and 5 parts of quinoline were heated in a flask equipped with a stirrer, thermometer, and air condenser, to 210–220° for 30–45 minutes. The mixture was cooled, diluted with ether, and filtered to remove the catalyst. The ether solution was shaken with several portions of dilute hydrochloric acid to remove the quinoline, and then with dilute alkali to remove unreacted acid. Evapora-

[4] The preparation of *o*-nitrophenylacetic acid by the method of Mayer and Balle gave double the yields reported by these authors when the sodium salt of the nitrophenylpyruvic acid was oxidized by H_2O_2 directly instead of isolating and oxidizing the free acid. Yields averaging 55% were obtained.

tion of the ether solution left an oil which solidified on cooling. The residue was taken up in either glacial acetic acid or 95% alcohol, from which solvents the nitro hydrocarbon crystallized in light tan needles, m.p. 79–80°, (yield 75%).

Anal. Calc'd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22.
Found: C, 76.4; H, 5.56.

1-(o-Nitrophenyl)-4-phenyl-1,3-butadiene (trans-trans) (XI). a. By decarboxylation. Using the same procedure as given in the previous preparation, trans-trans-1-(*o*-nitrophenyl)-4-phenyl-1,3-butadiene was prepared from the corresponding nitro acid, 1-(*o*-nitrophenyl)-4-phenyl-1,3-butadiene-1-carboxylic acid. The nitro hydrocarbon crystallized from 95% alcohol in light tan needles, m.p. 98–99°. A mixture of the cis-trans and trans-trans isomers melted considerably lower than the cis-trans modification.

Anal. Calc'd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22.
Found: C, 76.7; H, 5.4.

b. By isomerization. One gram of 1-(*o*-nitrophenyl)-4-phenyl-1,3-butadiene (cis-trans) was dissolved in 10 ml. of nitrobenzene, a crystal of iodine added, and the mixture heated to the boiling point for 20–25 minutes. The mixture was concentrated to about 1 ml., taken up in alcohol, and cooled, to yield a dark, rather crude product. Crystallization from glacial acetic acid or 95% alcohol gave light tan needles, m.p. 98–99°. A mixture of this material and that obtained by decarboxylation showed no depression in melting point.

c. By direct synthesis. *o*-Nitroaniline, 8.6 g (0.0625 mole), was suspended in 25% hydrochloric acid and diazotized at 0° with 4.3 g. (0.0625 mole) of sodium nitrite in 7.5 ml. of water. A small amount of undiazotized amine remained insoluble. The solution was filtered and added dropwise to a solution of 10.9 g. (0.0625 mole) of 5-phenyl-2,4-pentadienoic acid (20) in 175 ml. of acetone. A solution of 2.5 g. of cupric chloride and 13.7 g. of sodium acetate in 12.5 ml. of water was added slowly with stirring to the resulting yellow solution. An immediate and vigorous evolution of nitrogen resulted. The color of the solution changed from yellow to green and the temperature rose to 20°. After stirring 1.5 hours, the mixture was steam-distilled to remove nitrobenzene. On cooling, the residue formed a mixture of a grayish, crystalline material and a black, gummy product. The crystalline material was unreacted 5-phenyl-2,4-pentadienoic acid as evidenced by its melting point. The gummy residue hardened on standing, and after triturating with ammonia solution was powdered and extracted continuously with a hexane fraction (b.p. 60–70°) in a Soxhlet extractor. The extract deposited a yellow, fluffy, crystalline product, which upon recrystallization from 95% alcohol solution gave yellow needles m.p. 98–99°, (yield 10%). No depression in melting point was noted with a mixture of this compound and that obtained by decarboxylation.

Anal. Calc'd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22.
Found: C, 76.4; H, 5.6.

1-(o-Aminophenyl)-4-phenyl-1,3-butadiene (cis-trans) (VII). Two grams of the corresponding nitro hydrocarbon was dissolved in 50 ml. of warm 95% alcohol. To this was added with stirring a mixture of 16 g. of $FeSO_4 \cdot 7H_2O$, 80 ml. of concentrated ammonia, and 80 ml. of water. The mixture was heated on the steam-cone and stirred for two hours. After standing overnight the reduction mixture was filtered with suction and the residue dried. This black residue containing the amine was allowed to stand in ether several hours, filtered, and the ether solution of the amine dried over potassium carbonate. Dry hydrogen chloride gas was passed into the ether solution precipitating the amine hydrochloride in gray crystalline form. It began to soften at 195°, and decomposed at 210–215°. The free amine is an oil.

Anal. Calc'd for $C_{16}H_{16}ClN$: C, 74.55; H, 6.26.
Found: C, 74.6; H, 6.7.

1-(o-Aminophenyl)-4-phenyl-1,3-butadiene (trans-trans) (XII). a. By isomerization. An ether solution of the cis-trans amine, obtained as described in the preceding procedure, was evaporated to dryness and the residue boiled with dilute sulfuric acid. The amine sulfate precipitated on cooling. It was filtered, and without drying was washed into dilute alkali. On warming, the amine precipitated as a dark, amorphous material, which

separated from alcohol-water solution as orange-yellow, fluffy crystals, m.p. 132–133°. The hydrochloride (XIII) consisted of cream-white flakes, decomposing at 224–226°.

Anal. Calc'd for $C_{16}H_{15}N$: C, 86.84; H, 6.83.
Found: C, 86.3; H, 6.9.

b. By reduction. The trans-trans nitro hydrocarbon was reduced in the same way as described for the cis-trans isomer. The product of this reaction gave no depression of the melting point when mixed with that obtained by isomerization. The amine hydrochloride was made in the usual way and decomposed at 224–226°.

2-Phenyl-5-(o-aminophenyl)-2,4-pentadienoic acid (V). An ammoniacal suspension of 14.7 g. (0.05 mole) of the nitro acid (IV) was added with constant stirring to a boiling mixture of 100 g. of $FeSO_4 \cdot 7H_2O$, 300 ml. of water, and 250 ml. of concentrated ammonia. The amino acid was recovered from the filtered mixture by neutralization with hydrochloric acid (1:3). The product formed fluffy crystals from alcohol, m.p. 202–203°, yield 85–90%.

Anal. Calc'd for $C_{17}H_{15}NO_2$: C, 76.95; H, 5.70.
Found: C, 76.8; H, 6.0.

Lactam of 1-(o-aminophenyl)-4-phenyl-1,3-butadiene-2-carboxylic acid (X). Following the same procedure as described for the amino acid (V), 1-(o-nitrophenyl)-4-phenyl-1,3-butadiene-2-carboxylic acid was reduced with ferrous sulfate. The product, after crystallization from absolute alcohol, consisted of yellow plates, m.p. 257–258°. It was insoluble in acid and base and did not give a test for the primary amine group by diazotization. The most probable configuration for this compound is a lactam structure.

Anal. Calc'd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66.
Found: C, 82.6; H, 5.4; N, 5.7.

1,1-Diphenyl-4-(o-aminophenyl)-1,5-butadiene-2,3-dicarboxylic acid (XVI). This acid (cis form) was prepared from succinic ester by Stobbe's (17) method with similar results in each step except the first. We obtained 90% yields in the condensation of succinic ester with benzophenone to give 1,1-diphenyl-1-propene-2,3-dicarboxylic acid. This greatly improved yield may be attributed to the use of strictly anhydrous sodium ethoxide as the condensing agent and to the maintenance of a temperature of 0° during the early stages of the reaction. Furthermore, our nitro acid XV (solvent-free) showed the m.p. 237–238° (dec.) as compared to the product containing one molecule of ethanol and melting at 223–224° (dec.) obtained by Stobbe. As noted by Stobbe, the final product is an amorphous yellow material which resists crystallization. The hydrochloride decomposes at 276–278°.

Isomerization of cis-1,1-diphenyl-4-(o-nitrophenyl)-1,3-butadiene-2,3-dicarboxylic acid (XV). Formation of the trans anhydride XVII. The nitro acid (XV) was refluxed with nitrobenzene containing a trace of iodine for 20 minutes. The product was isolated as a light brown amorphous substance, m.p. 256–257°. Analysis and solubility relationships showed it to be an anhydride (XVII).

Anal. Calc'd for $C_{24}H_{15}NO_6$: C, 72.55; H, 3.80.
Found: C, 72.6; H, 3.6.

The anhydride XVII was dissolved in alkali and reprecipitated by addition of dilute hydrochloric acid, giving an acid (XVIII), which was not completely soluble in absolute alcohol. Light tan needles crystallized when the alcohol solution was diluted with about twice its volume of water and cooled. The portion not soluble in absolute alcohol melted at 256–257° and was identical with the original anhydride (XVII). This shows the ease of anhydride formation from the acid. The hydrolyzed product was also recrystallized by dissolving it in benzene and adding hexane until incipient precipitation was reached. When dry it softened at about 130°, resolidified, and finally melted at 256–257°, the melting point of the anhydride. Analysis showed the product to be the dibasic acid, hydrated with one molecule of water.

Anal. Calc'd for $C_{24}H_{17}NO_6 \cdot H_2O$: C, 66.50; H, 4.39.
Found: C, 66.7; H, 4.5.

Diazotization and attempted cyclizations of (XVI). a. In aqueous solution. A fine suspension in water of the amino acid (XV) was prepared by rapidly precipitating with excess dil. sulfuric acid a solution of 1.93 g. (0.005 mole) of the amino acid in dil. sodium

hydroxide. The suspension was cooled to 0° and a cold solution of 0.35 g. of sodium nitrite in 25 ml. of water added slowly with stirring. Starch-iodide paper showed the presence of nitrous acid. The yellow diazotized mixture was stirred at 0° for about 4 hours, then treated with 3–4 g. of precipitated copper powder. The mixture was stirred vigorously and heated on the steam-cone at 50–53° for six hours. A test for diazotization with alkaline β-naphthol was positive at this point. The mixture was heated another two hours at 60–70°. No test for the diazonium group was noted after this time. The color of the mixture was dark brown. It was filtered and the residue washed with ammonia to remove the acid product, leaving the copper behind. The ammoniacal solution was cooled and neutralized carefully with dilute acid, giving a dark gelatinous precipitate. No crystalline product could be isolated from this gelatinous material.

b. Diazotization in dioxane. The amino acid, 1.93 g. (0.005 mole), was dissolved in about 75 ml. of dioxane, giving a dull red solution. To this solution was added 1 ml. of concentrated sulfuric acid. After cooling the mixture to room temperature, 0.6 g. of amyl nitrite, diluted with 15 ml. of dioxane, was added slowly with stirring. After stirring at room temperature for 2 hours, the mixture was added slowly to a mixture of 1 g. of copper powder, 10 g. of sodium hypophosphite and 10 g. of water held at 45–55°. After the addition of the diazo solution was complete, the temperature was raised to 80° for 15–20 minutes. This mixture was cooled and poured into 500 ml. of water containing sodium hydroxide. The copper powder was removed by filtration. The alkaline solution was neutralized with dilute sulfuric acid, giving a dark amorphous precipitate, from which no crystalline product could be obtained.

Similar unsuccessful attempts were made to cyclize (V), although this acid probably has a cis-trans structure.

SUMMARY

An unsuccessful attempt has been made to apply the Pschorr phenanthrene synthesis to the preparation of a dibenzocycloöctatetraene. Theoretical implications of the work have been discussed.

A number of cis-trans isomeric derivatives of di- and tri-phenylbutadienes have been prepared and characterized.

LAFAYETTE, IND.

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[CONTRIBUTION NO. 37 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

THE STABILITY OF 2,2′-DIHYDROXYDIPHENYLMETHANE

C. A. BUEHLER, DOUGLAS E. COOPER, AND EUGENE O. SCRUDDER

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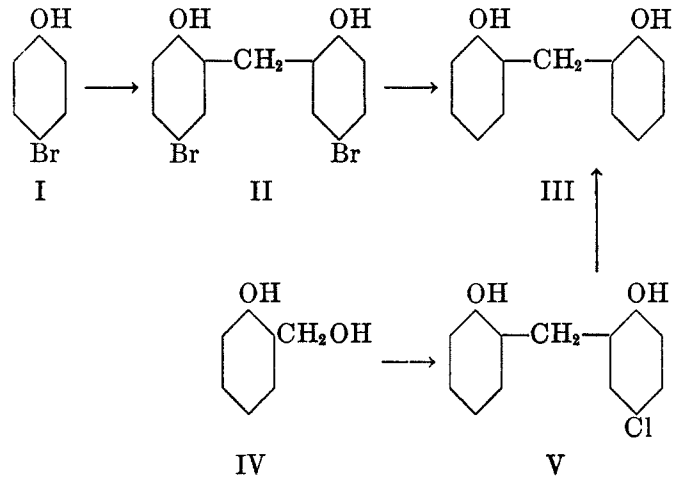
The literature contains several references (1) to the ease with which 2,2′-dihydroxydiphenylmethane loses water to form xanthene. In fact, Megson (2) makes the positive statement that xanthene "is the only form in which 2,2′-dihydroxydiphenylmethane exists."

Our interest in this particular dihydroxydiphenylmethane arose in the search for a simple method to identify its derivatives which were to be expected in the condensation of formaldehyde with various *p*-substituted phenols. When the first attempts to prepare the corresponding xanthenes from what were thought to be 2,2′-dihydroxy-5,5′-dichloro- and 2,2′-dihydroxy-3,3′,5,5′-tetrachlorodiphenylmethanes, by the use of ordinary dehydrating agents, were unsuccessful, it was decided to re-examine the stability of 2,2′-dihydroxydiphenylmethane. This substituted diphenylmethane was synthesized by two methods, as shown in Formulas I–V.

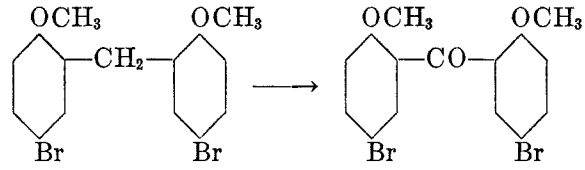


p-Bromophenol, I, gave, with formaldehyde and sulfuric acid, 2,2′-dihydroxy-5,5′-dibromodiphenylmethane, II, which on reduction with sodium and amyl alcohol (3) produced 2,2′-dihydroxydiphenylmethane, III, a stable white solid, m.p. 119–120°. The latter is soluble in alkali, gives no color with ferric chloride, and forms a dibenzoate.

Since large amounts of resinous materials were produced in the synthesis described above, purification of the dihydroxydibromodiphenylmethane proved to be extremely troublesome. To obviate this difficulty a second synthesis (4) was devised. Saligenin, IV, gave, on treatment with *p*-chlorophenol in the presence

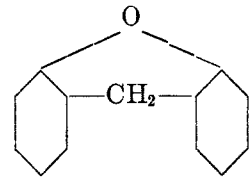
of hydrochloric acid, 2,2′-dihydroxy-5-chlorodiphenylmethane, V, which on reduction as before produced the desired 2,2′-dihydroxydiphenylmethane, III.

Since II is an unknown compound[1] it was necessary to establish its structure as a means for proving the structure of III. That II is 2,2′-dihydroxy-5,5′-dibromodiphenylmethane was shown by its methylation with dimethyl sulfate to give the known methoxy derivative, VI, and this on oxidation with chromium trioxide in acetic acid produced the known keto derivative, VII.



VI VII

Additional proof of the structure of III was shown by its conversion into the known xanthene, VIII,



VIII

by distillation at ordinary pressure. This dehydration was not successful with several ordinary dehydrating agents which were tried. In fact, our experience with the more readily available homolog, 2,2′-dihydroxy 5,5′-dimethyldiphenylmethane (5) was similar in that satisfactory dehydration was accomplished only by distilling at ordinary pressure.

EXPERIMENTAL PART

Synthesis of 2,2′-dihydroxydiphenylmethane

2,2′-Dihydroxy-5,5′-dibromodiphenylmethane. A solution of 296 cc. of concentrated sulfuric acid and 520 cc. of water in a three-liter, three-necked flask in a water-bath at 80–90° was refluxed and stirred while a mixture of 184 g. of *p*-bromophenol, m.p. 61–63°, and 12 cc. of U.S.P. 40% formaldehyde was introduced. Each four hours 4 cc. more of formaldehyde was added until a total of 12 additional cc. had been utilized. After four more hours of stirring and heating, the viscous red mass, 220 g., which had formed, was removed and washed with cold water. Further purification was accomplished by stirring the crude condensation product vigorously in boiling water for several hours. To remove the resins present the crude 2,2′-dihydroxy-5,5′-dibromodiphenylmethane was dissolved in 600 cc. of hot methanol and the solution was poured, with vigorous stirring, into six

[1] 2,2′-Dihydroxy-5,5′-dibromodiphenylmethane is described in Swiss Patent 137,927 (to I.G. Farbenindustrie Akt-Ges.) although there is no evidence of its structure other than the fact that it was produced from *p*-bromophenol.

times its volume of boiling water. The dirty white emulsion which formed coagulated on standing cold to give an upper layer of fluffy, almost white needles and a lower layer of a reddish brown resin. By reworking the resin and recrystallizing the needles from methanol-water (1/6), using Norit, 16.7 g. of product, m.p. 180–182°, was obtained. A final crystallization gave crystals, m.p. 183–184°.

Anal. Calc'd for $C_{13}H_{10}Br_2O_2$: Br, 44.64.
Found: Br, 44.55, 44.77.

The *dibenzoate* prepared in the usual manner melted at 192°.

Anal. Calc'd for $C_{27}H_{18}Br_2O_4$: Br, 28.23.
Found: Br, 28.01, 28.03.

2,2'-Dihydroxydiphenylmethane. The method of preparation employed was that suggested by Auwers (3). Sodium was added in small pieces through the top of the condenser to a refluxing solution of 7 g. of 2,2'-dihydroxy-5,5'-dibromodiphenylmethane in 100 cc. of *n*-amyl alcohol in an oil-bath at 160–170°. After the mass in the flask became almost solid, 25 cc. more of amyl alcohol was added and refluxing was continued for half an hour longer. Upon cooling, the excess of sodium was taken up in methanol and then sufficient water was added to dissolve the cake of sodium bromide which had separated. After acidification with glacial acetic acid, which changed the color from red to yellow, the solution was distilled to remove most of the methanol. Water was then added until an amyl alcohol layer separated and the solution was freed from amyl alcohol by distillation with steam. The liquid remaining was filtered and upon cooling, long brown needles, 3.9 g., m.p. 114–116°, separated. One crystallization from water gave white needles, m.p. 119–120°, which were soluble in alkali but produced no color with ferric chloride.

Anal. Calc'd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04.
Found: C, 77.22, 77.49; H, 6.05, 6.15.

The *dibenzoate* was prepared by dissolving 0.2 g. in 20 cc. of benzene and adding 0.5 cc. of benzoyl chloride. After two hours refluxing the benzene was evaporated and an oil remained. Upon stirring the oil with 5% sodium hydroxide solution, a solid was obtained. Three crystallizations from ethanol-water (3:1) gave white needles, 0.06 g., m.p. 76–77°.

Anal. Calc'd for $C_{27}H_{20}O_4$: C, 79.39; H, 4.94.
Found: C, 79.24, 79.22; H, 4.99, 5.04.

2,2'-Dihydroxy-5-chlorodiphenylmethane. This method was an adaptation of one (4) already published. Saligenin, 10 g., was dissolved by warming in 200 g. of *p*-chlorophenol (b.p. 213–214°) and to the rotated solution cooled to 30°, 0.5 cc. of concentrated hydrochloric acid was added dropwise. After cooling again to 30°, 25 cc. more of the acid was added in a single portion and the mixture was stirred for forty minutes. Distillation at reduced pressure in an all-glass apparatus gave 5.7 g. of the dihydroxychlorodiphenylmethane, b.p. 220–222° (6 mm.). The solid formed on cooling was crystallized first from a ligroin-benzene mixture and then from water to give white crystals, m.p. 128–129°.

Anal. Calc'd for $C_{13}H_{11}ClO_2$: Cl, 15.11; mol. wt., 235.
Found: Cl, 14.91, 14.98; mol. wt. (cryoscopic, benzene), 235, 239.

The *dibenzoate* prepared in the usual manner and crystallized from methanol melted at 80–81°.

Anal. Calc'd for $C_{27}H_{19}ClO_4$: Cl, 8.01.
Found: Cl, 7.99, 7.97.

2,2'-Dihydroxydiphenylmethane. 2,2'-Dihydroxy-5-chlorodiphenylmethane, 5.7 g., was reduced with sodium and amyl alcohol as described previously to give 2.7 g. of the crude dihydroxydiphenylmethane. One crystallization from water produced 2 g., m.p. 114–116°, while another crystallization elevated the m.p. to 119–120°.

Anal. Calc'd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04.
Found: C, 77.74, 77.97; H, 6.35, 6.20.

Derivatives for structural proof

2,2'-Dimethoxy-5,5'-dibromodiphenylmethane. This procedure is an adaptation of that used by Mosettig and Stuart (6): To 1.9 g. of 2,2'-dihydroxy-5,5'-dibromodiphenylmethane

dissolved in a mixture of 10 cc. of acetone and 10 cc. of an aqueous solution of 6.6 g. of potassium hydroxide, 16 cc. of dimethyl sulfate was added in small portions with vigorous shaking. During this process most of the acetone was permitted to escape in vapor form and some solid appeared. Complete separation was effected by pouring the mixture over cracked ice. Four crystallizations from 95% ethanol gave 1.4 g., m.p. 107.5° [Diels and Rosenmund (7) give 108°].

Anal. Calc'd for $C_{15}H_{14}Br_2O_2$: Br, 41.40.
Found: Br, 41.24, 41.29.

2,2′-Dimethoxy-5,5′-dibromodiphenylketone. This oxidation was accomplished essentially by the method of Diels and Rosenmund (7): To 1 g. of the dimethoxydibromodiphenylmethane dissolved in 10 cc. of hot glacial acetic acid was added in small portions 1.5 g. of chromium trioxide in 20 cc. of glacial acetic acid. This mixture was refluxed for five minutes, diluted with several volumes of water, and extracted with ether. The residue from evaporation of the ether was crystallized three times from ethanol-water (1/1) and once from glacial acetic acid to give 0.06 g. of a tan solid, m.p. 123–124° (Diels and Rosenmund give 123°).

Anal. Calc'd for $C_{15}H_{12}Br_2O_3$: Br, 39.95.
Found: Br, 39.47, 39.41.

Xanthene. 2,2′-Dihydroxydiphenylmethane, 1.1 g., was heated for two hours in a phosphoric acid bath at 150–160° and then it was distilled from a fused zinc chloride bath. The distillate, most of which came over from 140–180°, was cooled and treated with 2% sodium hydroxide solution to remove any phenolic material. Crystallization of the residue from ethanol gave 0.02 g., m.p. 99.5–100.5° [Graebe (8) gives 100.5°]. The product in warm concentrated sulfuric acid gives the characteristic green-yellow fluorescence shown by xanthene.

Anal. Calc'd for $C_{13}H_{10}O$: C, 85.69; H, 5.53.
Found: C, 85.10, 85.00; H, 5.44, 5.44.

SUMMARY

2,2′-Dihydroxydiphenylmethane has been synthesized by two methods and, contrary to literature statements, it has been shown to be quite stable.

Characterization of the compound was accomplished by conversion into several known derivatives.

KNOXVILLE, TENN.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE RATES OF DISSOCIATION OF PENTAARYLETHANES

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Recently a rapid and convenient method for determining the rates of dissociation of pentaarylethanes was described, based on the reaction of iodine with the free radicals produced on dissociation (1).

$$R_3C{-}CHR_2 \overset{k}{\rightleftarrows} R_3C\cdot + \cdot CHR_2$$
$$2R_3C\cdot + I_2 \rightarrow 2\ R_3CI$$
$$2\ R_2CH\cdot + I_2 \rightarrow 2\ R_2CHI$$

The reaction mixture also contained pyridine and ethanol (or methanol); the latter served to react with the triarylmethyl iodide to form the triarylmethyl alkyl ether and the pyridine fixed the hydrogen iodide liberated in this reaction. The pyridine also combined with the diarylmethyl iodide to give the diarylmethylpyridinium iodide. The rate-controlling step in the process is the dissociation of the pentaarylethane into triarylmethyl and diarylmethyl radicals (1, 2). A systematic study of the rates of dissociation was undertaken in order to gain information concerning the effect of various groups on the production of free radicals. From the rate constants of the pentaarylethanes containing four phenyl groups and one aryl group other than phenyl, a comparison of the effects of the aryl groups can be obtained.

The effect of six aryl groups, α-naphthyl, 9-phenanthryl, *p*-tolyl, *p*-anisyl, *p*-biphenyl, and 2-fluoryl, on the dissociation of 1,1,1,2-tetraphenyl-2-arylethanes has been reported (1). We have now synthesized eighteen new pentaarylethanes and measured their rates of dissociation by the iodine reaction. In five of these the aryl group was attached to the triarylmethyl carbon (C_1) and in the other thirteen it was located on the diarylmethyl carbon (C_2). The pentaarylethanes and their rate constants and half-life periods in the iodine reaction at 80° in *o*-dichlorobenzene are shown in Table I and Table II.

The steric effect appears to be a dominant factor in promoting the rates of dissociation, for the rate constants are greater for the pentaarylethanes containing ortho groups (except fluorophenyl) than for those containing the corresponding meta or para groups. The α-naphthyl group is more effective than the β-naphthyl group and the *p*-biphenyl group is more effective than the *m*-biphenyl group in promoting the rate of dissociation. The phenanthryl groups fall in the same order in increasing the rate of dissociation of pentaarylethanes which obtains for increasing the extent of dissociation of the hexaarylethanes; 1-phenanthryl > 2-phenanthryl > 3-phenanthryl (3). Further discussion is reserved until investigations now in progress are completed.

The heat of activation of the dissociation process for two of the pentaaryl-

[1] Part of the material in this paper is from the Ph.D. dissertation of Roger Hoffman, 1942.

TABLE I

RATE CONSTANTS AND HALF-LIFE PERIODS OF 1,1,2,2-TETRAPHENYL-1-ARYLETHANES

(Arranged in order of decreasing rate of dissociation)

$(C_6H_5)_2RC—CH(C_6H_5)_2$

Temp., 80°

NO.	ARYL GROUP R	RATE CONSTANT k	HALF-LIFE (MINUTES)
I	1-Phenanthryl	1.5285[a]	0.45
IV	9-Phenanthryl	0.1212	5.7
V	2-Fluoryl	.0284	24.4
III	3-Phenanthryl	.0138	50.3
II	2-Phenanthryl	.0128	54.2
	Phenyl[b]	.0124	56.0

[a] This value was calculated for 80° by the use of the Arrhenius equation from the rate constant (k = 0.0420) actually determined at 50°.

[b] Determined by Bachmann and Osborn (1).

TABLE II

RATE CONSTANTS AND HALF-LIFE PERIODS OF 1,1,1,2-TETRAPHENYL-2-ARYLETHANES

(Arranged in order of decreasing rate of dissociation)

$(C_6H_5)_3C—CH(C_6H_5)R$

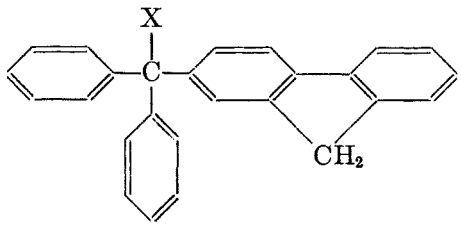
Temp., 80°

NO.	ARYL GROUP R	RATE CONSTANT k	HALF-LIFE (MINUTES)
XVIII	*o*-Biphenyl	0.0641	10.8
VI	1-Phenanthryl	.0552	12.4
	9-Phenanthryl[a]	.0506	13.7
	α-Naphthyl[a]	.0437	15.9
	2-Fluoryl[a]	.0404	17.2
XV	*o*-Anisyl	.0342	20.2
XIII	*o*-Tolyl	.0312	22.2
IX	β-Naphthyl	.0278	24.9
	p-Biphenyl[a]	.0241	28.8
VII	2-Phenanthryl	.0211	32.8
VIII	3-Phenanthryl	.0192	36.1
XVI	*m*-Anisyl	.0175	39.6
XIV	*m*-Tolyl	.0169	41.1
	p-Anisyl[a]	.0166	41.8
	p-Tolyl[a]	.0131	52.8
XI	*m*-Fluorophenyl	.0128	54.2
	Phenyl[a]	.0124	56.0
XVII	*m*-Biphenyl	.0116	62.8
X	*o*-Fluorophenyl	.0110	63.2
XII	*p*-Fluorophenyl	.0104	66.6

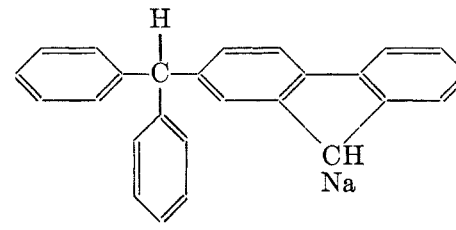
[a] Determined by Bachmann and Osborn (1).

ethanes was determined. For 1,1,2,2-tetraphenyl-1-(9-phenanthryl)ethane (IV), E_d = 27.2 kcal. and for 1,1,1,2-tetraphenyl-2-(1-phenanthryl)ethane (VI) E_d = 26.8 kcal. The value for pentaphenylethane is 27.1 kcal.

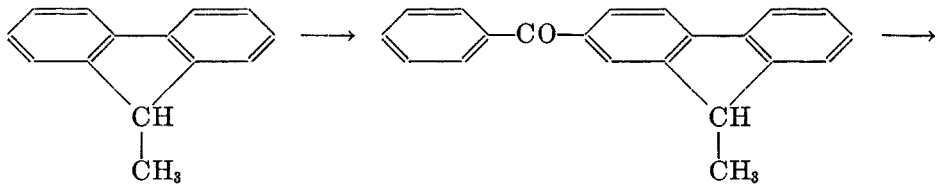
Most of the pentaarylethanes were prepared by interaction of a triarylmethylsodium and a diarylmethyl bromide according to the procedure described previously (2). The method failed when applied to the preparation of 1,1,2,2-tetraphenyl-1-(2-fluoryl)ethane (V). The product of the interaction of diphenyl-2-fluorylchloromethane (XIX) and sodium amalgam was not XX but XXI; in the process an exchange occurred between the sodium and one of the acidic hydrogen atoms in the 9-position of the fluorene group. This was shown by coupling the sodium derivative with methyl iodide to give 2-benzohydryl-9-methylfluorene XXII, whose structure was proved by synthesis from 9-methylfluorene by the method indicated. The product resulting from the coupling of XXI with diphenylmethyl bromide must be 2,9-dibenzohydrylfluorene (XXIII). In agreement with this structure, the compound did not possess the characteristic properties of pentaarylethanes such as cleavage by hydriodic acid in boiling acetic acid, and the formation of color in hot ethyl benzoate solution.

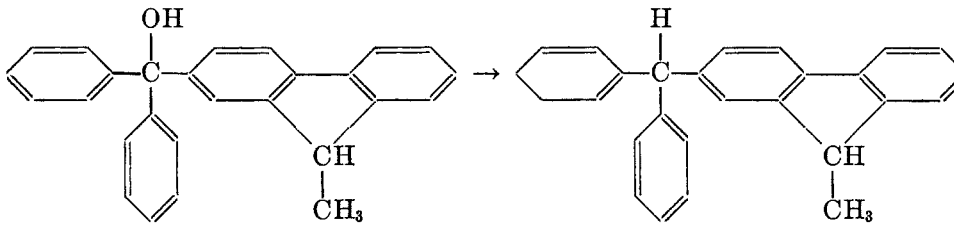


XIX X = Cl
XX X = Na

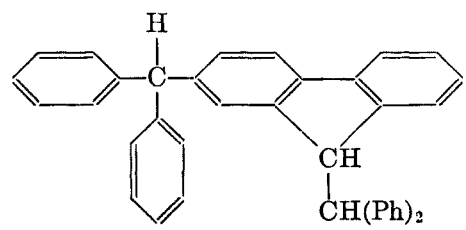


XXI





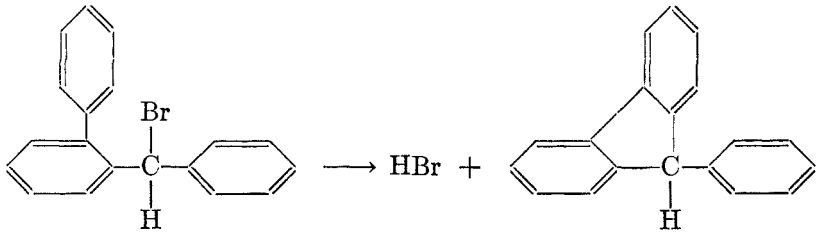
XXII



XXIII

The desired pentaarylethane (V) was obtained by treating a mixture of diphenyl-2-fluorylchloromethane and diphenylmethyl bromide with mercury. In this reaction the diphenyl-2-fluorylmethyl radical is formed initially and it "captures" the diphenylmethyl radical as the latter is formed by the action of mercury on the diphenylmethyl bromide. This method was used also to prepare a number of the other pentaarylethanes.

Some of the liquid diarylmethyl bromides were too unstable to be distilled; they were used successfully without this purification. Although it was possible to obtain *o*-phenyldiphenylbromomethane (XXIV) as colorless crystals, at room temperature it lost hydrogen bromide and gave 9-phenylfluorene.



XXIV

EXPERIMENTAL

1,1,2,2-Tetraphenyl-1-(1-phenanthryl)ethane (*I*). A mixture of 1.1 g. of diphenyl-1-phenanthrylchloromethane (3) and 0.7 g. of diphenylbromomethane was shaken with 0.5 cc. of mercury in 10 cc. of ether and 20 cc. of benzene in a 50 cc. glass-stoppered graduate cylinder, which had been filled with nitrogen and sealed with special stop-cock grease (4). After thirty-six hours, the mixture was filtered and evaporated at room temperature under reduced pressure and the pentaarylethane was obtained as colorless crystals by recrystallization from benzene-acetone; yield 1.2 g. (80%); m.p. 123–134° dec. in air and 125–135° dec. in a vacuum.

Anal. Calc'd for $C_{40}H_{30}$: C, 94.1; H, 5.9.
Found: C, 93.6; H, 6.1.

1,1,2,2-Tetraphenyl-1-(2-phenanthryl)ethane (*II*). This compound was obtained in 59% yield by treating diphenyl-2-phenanthrylmethylsodium (3) with diphenylbromomethane; it crystallized from acetone-petroleum ether in colorless cubes; m.p. 167–188° dec. in air and 190–202° dec. in nitrogen

Anal. Calc'd for $C_{40}H_{30}$: C, 94.1; H, 5.9.
Found: C, 93.7; H, 6.2.

1,1,2,2-Tetraphenyl-1-(3-phenanthryl)ethane (*III*). This compound was prepared in 71% yield from diphenyl-3-phenanthrylmethylsodium (3) and diphenylbromomethane; it crystallized from acetone in clusters of small colorless cubes; m.p. 183–188° dec. in air and 196–198° dec. in nitrogen.

Anal. Calc'd for $C_{40}H_{30}$: C, 94.1; H, 5.9.
Found: C, 93.9; H, 6.0.

1,1,2,2-Tetraphenyl-1-(9-phenanthryl)ethane (*IV*). A solution of 1.87 g. of the methyl ether of diphenyl-9-phenanthryl carbinol (3) in 10 cc. of anhydrous ether and 10 cc. of benzene was shaken with 2 cc. of 45% sodium amalgam for twenty-four hours. To the ice-cold deep green mixture containing diphenyl-9-phenanthrylmethylsodium was added 1.23 g. of diphenylbromomethane dissolved in 5 cc. of benzene, whereupon the color disappeared immediately. By recrystallization of the product from benzene-absolute alcohol, the pentaarylethane was obtained as fine colorless crystals; yield 1.12 g. (42%). After drying

for five hours at 64° and 0.2 mm. pressure, it melted at 149–152° dec. in air and 152–155° dec. in nitrogen.

Anal. Calc'd for $C_{40}H_{30}$: C, 94.1; H, 5.9.
Found: C, 93.8; H, 6.3.

Diphenyl-2-fluorylcarbinol. To a solution of the Grignard reagent prepared from 10 g. of bromobenzene in 40 cc. of ether was added 10 g. of 2-benzoylfluorene (5) dissolved in 25 cc. of benzene and 25 cc. of ether. The mixture was refluxed for two hours, cooled, and hydrolyzed. The product which was isolated from the organic solution was dissolved in acetone, the solution was warmed with Norit for twenty minutes, filtered, partially evaporated and treated with petroleum ether. From the solution the carbinol crystallized in colorless needles; yield 10 g. (78%); m.p. 143–144°.

Anal. Calc'd for $C_{26}H_{20}O$: C, 89.6; H, 5.8.
Found: C, 89.4; H, 5.9.

The *methyl ether* was prepared by adding three drops of concentrated sulfuric acid to a solution of 4 g. of diphenyl-2-fluorylcarbinol in 50 cc. of methanol, refluxing the solution for two hours and then evaporating partially. From acetone-methanol, it crystallized in colorless needles; yield 3.8 g. (93%); m.p. 108–109°.

Anal. Calc'd for $C_{27}H_{22}O$: C, 89.5; H, 6.1.
Found: C, 89.4; H, 6.1.

The *ethyl ether* of diphenyl-2-fluorylcarbinol was obtained by a similar procedure employing ethyl alcohol; it crystallized from alcohol in clusters of fine needles; yield 83%; m.p. 115°.

Anal. Calc'd for $C_{28}H_{24}O$: C, 89.3; H, 6.4.
Found: C, 89.6; H, 6.4.

Diphenyl-2-fluorylchloromethane (XIX). A mixture of 10 g. of diphenyl-2-fluorylcarbinol, 5 cc. of acetyl chloride, and 5 cc. of benzene was refluxed for two hours on a steam-bath. After removal of the excess of acetyl chloride and acetic acid under reduced pressure, 10 cc. of petroleum ether was added. From the solution the chloride crystallized in small flat prisms; yield 8 g. (76%); m.p. 114–115°.

The chloride was prepared also by passing dry hydrogen chloride for one hour into a solution of 5 g. of the carbinol in 25 cc. of benzene containing 1.5 g. of anhydrous calcium chloride in a flask cooled by an ice-water mixture. The filtered solution was concentrated under reduced pressure and treated with petroleum ether; yield 3.6 g. (67%); m.p. 114–115°.

Anal. Calc'd for $C_{26}H_{19}Cl$: Cl, 9.6. Found: Cl, 9.5.

Diphenyl-2-fluorylmethyl peroxide. A mixture of 0.5 g. of diphenyl-2-fluorylchloromethane, 0.5 cc. of mercury, and 40 cc. of anhydrous benzene was shaken for four days in an atmosphere of nitrogen. When exposed to air, the deep red solution of the free radical diphenyl-2-fluorylmethyl became colorless and deposited colorless crystals of the peroxide. After recrystallization from carbon disulfide-petroleum ether, the peroxide melted at 172–173°.

Anal. Calc'd for $C_{52}H_{38}O_2$: C, 89.9; H, 5.5.
Found: C, 89.6; H, 5.6.

1,1,2,2-Tetraphenyl-1-(2-fluoryl)ethane (V). A mixture of 1.83 g. of diphenyl-2-fluorylchloromethane, 1.23 g. of diphenylbromomethane, 0.5 cc. of mercury 30 cc. of anhydrous ether, and 20 cc. of dry benzene was shaken in a nitrogen atmosphere for four days. The pentaarylethane obtained by evaporation of the filtered solution at room temperature crystallized from a solution in acetone-petroleum ether in clusters of colorless cubes; yield 2.1 g. (80%); m.p. 168–176° dec. in air and 187–190° dec. in nitrogen.

Anal. Calc'd for $C_{39}H_{30}$: C, 93.9; H, 6.1.
Found: C, 93.8; H, 6.1.

The structure of the pentaarylethane was proved by its cleavage by hydrogen iodide into diphenyl-2-fluorylmethane and diphenylmethane. To a solution of 10 cc. of glacial acetic acid, 0.05 g. of iodine, 0.15 g. of red phosphorus, and 0.2 cc. of water was added 0.25 g. of the pentaarylethane and the mixture was refluxed in an atmosphere of nitrogen for three

hours. The filtered solution was poured into water, the phosphorus was washed with benzene, and the benzene was added to the solution to extract the products. The benzene solution was washed with alkali and with sodium bisulfite solution and evaporated. From a benzene-petroleum ether solution of the product 0.22 g. of *diphenyl-2-fluorylmethane* crystallized; m.p. 147–148°.

Anal. Calc'd for $C_{26}H_{20}$: C, 93.9; H, 6.1.
Found: C, 93.8; H, 6.1.

A sample of diphenyl-2-fluorylmethane was prepared for comparison. A mixture of 0.5 g. of the methyl ether of diphenyl-2-fluorylcarbinol and 3 g. of 45% sodium amalgam in 25 cc. of anhydrous ether was shaken for twenty-four hours in an atmosphere of nitrogen. The cylinder was set upright in ice-water to freeze the amalgam and 0.5 cc. of alcohol was added to the orange colored solution; the mixture was then poured into water. The product crystallized from alcohol-benzene in flat colorless needless; yield 0.38 g. (80%); m.p. 147–148° alone and when mixed with the product obtained above.

The structure of the pentaarylethane was confirmed by its reaction with iodine. A mixture of 0.4 g. of the compound (V), 0.2 g. of iodine, 10 cc. of benzene, 1 cc. of absolute ethanol, and 1 cc. of pyridine was refluxed for six hours on a steam-bath. From the cooled solution diphenylmethylpyridinium iodide (1) was filtered; after being washed with benzene it was recrystallized from water, from which it separated in yellow prisms; weight 0.27 g.

From the benzene filtrate was isolated 0.2 g. of the ethyl ether of diphenyl-2-fluorylcarbinol; m.p. 115° alone and when mixed with the ether described above.

2-Benzohydryl-9-methylfluorene (XXII). *(a) From 9-methylfluorene.* A mixture of 1 g. of aluminum chloride and 1 g. of benzoyl chloride was warmed over a flame until a clear solution resulted. The cooled mass was dissolved in 10 cc. of carbon disulfide and to the solution was added 1 g. of 9-methylfluorene (6). After one hour in an ice-bath, the precipitate was filtered and hydrolyzed with dilute hydrochloric acid. The product was extracted with benzene, the benzene solution was evaporated partially, and petroleum ether was added. The gummy mass which precipitated was collected and evaporatively distilled under reduced pressure. The 2-benzoyl-9-methylfluorene (1 g.), which was not obtained crystalline, was added to the Grignard reagent prepared from 1 cc. of bromobenzene and the mixture refluxed for three hours. The resulting diphenyl-2-(9-methylfluoryl)carbinol did not crystallize. It was heated with a mixture of 0.1 g. of iodine, 0.3 g. of red phosphorus, 0.1 cc. of water, and 10 cc. of acetic acid for three hours. A little acetone was added to the cooled mixture and the filtered solution was poured into dilute sodium bisulfite solution. The 2-benzohydryl-9-methylfluorene which precipitated crystallized from alcohol in fine colorless needles; yield 0.35 g.; m.p. 119–120°.

Anal. Calc'd for $C_{27}H_{22}$: C, 93.6; H, 6.4.
Found: C, 93.4; H, 6.4.

(b) From the methyl ether of diphenyl-2-fluorylcarbinol. To a solution of the sodium derivative (XXI) prepared from 1.7 g. of the methyl ether of diphenyl-2-fluorylcarbinol in ether was added 1.5 cc. of methyl iodide. After twenty-four hours, the mixture was treated with water and the product was recrystallized from alcohol-ether; yield 1.2 g. (88%); m.p. 119–120° alone and when mixed with the compound prepared in (a).

Anal. Calc'd for $C_{27}H_{22}$: C, 93.6; H, 6.4.
Found: C, 93.3; H, 6.4.

A mixture of 4 g. of 45% sodium amalgam, 2.4 g. of diphenyl-2-fluorylchloromethane, 30 cc. of benzene, and 20 cc. of anhydrous ether was shaken for twenty-four hours and then 1.63 g. of diphenylbromomethane was added to the sodium derivative. After one recrystallization from alcohol-acetone, the product (1.5 g.) which was isolated melted at 185–192°. The compound was not cleaved by hydrogen iodide in boiling acetic acid and gave no color when heated in ethyl benzoate. The structure of the compound was not proved by synthesis but it is probably 2,9-dibenzohydrylfluorene (XXIII).

1,1,1,2-Tetraphenyl-2-(1-phenanthryl)ethane (VI). Phenyl-1-phenanthrylbromometh-

thane was prepared by warming a mixture of 0.5 g. of phenyl-1-phenanthrylcarbinol (7) and 1 cc. of acetyl bromide for one-half hour on a steam-bath. After removal of the liquids by distillation under reduced pressure on a steam-bath, the residual bromide was dissolved in 1 cc. of petroleum ether containing a few drops of benzene; on standing, practically colorless crystals of the bromide (0.5 g.; m.p. 120–121°) separated. The bromide, without further purification, was coupled with triphenylmethylsodium. The pentaarylethane was obtained in colorless crystals from acetone-alcohol; yield 55%; m.p. 174–180° dec. in air and 178–182° dec. in nitrogen.

Anal. Calc'd for $C_{40}H_{30}$: C, 94.1; H, 5.9.
Found: C, 94.3; H, 6.1.

1,1,1,2-Tetraphenyl-2-(2-phenanthryl)ethane (VII). A mixture of 0.8 g. of phenyl-2-phenanthrylbromomethane [m.p. 118–119°; prepared from the corresponding carbinol (7) and acetyl bromide], 0.7 g. of triphenylchloromethane, and 0.5 cc. of mercury in ether and benzene was shaken for thirty-six hours. The oily product which was obtained on evaporation of the filtered solution crystallized when a solution of it in acetone-methanol was allowed to evaporate. The pentaarylethane was recrystallized from acetone-alcohol; yield 1 g. (87%); it was dried for five hours at 100° and 0.2 mm. pressure; m.p. 145–155° dec. in air and 153–157° dec. in nitrogen.

Anal. Calc'd for $C_{40}H_{30}$: C, 94.1; H, 5.9.
Found: C, 93.8; H, 6.1.

1,1,1,2-Tetraphenyl-2-(3-phenanthryl)ethane (VIII). A 60% yield of this compound was obtained from triphenylmethylsodium and phenyl-3-phenanthrylbromomethane [m.p. 103–104°; prepared from the carbinol (7) and acetyl bromide]. From a mixture of acetone, benzene, and petroleum ether it was obtained in the form of fine colorless crystals; m.p. 162–174° dec. in air and 174–178° dec. in nitrogen.

Anal. Calc'd for $C_{40}H_{30}$: C, 94.1; H, 5.9.
Found: C, 93.7; H, 6.2.

Phenyl-β-naphthylbromomethane. To the Grignard reagent prepared from 25 g. of bromobenzene was added 5 g. of β-naphthaldehyde (8) dissolved in 20 cc. of dry benzene. After being refluxed for two and one-half hours on a steam-bath, the mixture was cooled and hydrolyzed with ice-cold ammonium chloride solution. The product obtained by evaporation of the solvents was dissolved in hot petroleum ether (60–70°) and benzene; on cooling, the solution deposited phenyl-β-naphthylcarbinol in clusters of fine colorless needles; yield, 6.2 g. (86%); m.p. 82–83°. Perrier and Caille (9) who prepared this compound by reduction of phenyl-β-naphthyl ketone with sodium amalgam and alcohol reported the m.p. 83.°

A mixture of 3.7 g. of the carbinol, 6 cc. of acetyl bromide, and 10 cc. of benzene was warmed on a steam-bath for one hour. The liquids were removed under reduced pressure; on addition of petroleum ether to the residue, 3.5 g. (80%) of practically colorless crystals of phenyl-β-naphthylbromomethane precipitated; m.p. 74–75°.

Anal. Calc'd for $C_{17}H_{13}Br$: Br, 26.9. Found: Br, 26.8.

1,1,1,2-Tetraphenyl-2-(β-naphthyl)ethane (IX). A 77% yield of this compound was obtained by coupling 1.1 g. of phenyl-β-naphthylbromomethane with triphenylmethylsodium prepared from 1 g. of triphenylchloromethane; by recrystallization from absolute alcohol it was obtained in the form of fine colorless crystals; m.p. 157–168° dec. in air and 177–181° dec. in nitrogen.

Anal. Calc'd for $C_{36}H_{28}$: C, 93.9; H, 6.1.
Found: C, 93.7; H, 6.2.

o-Fluorodiphenylbromomethane. Eight grams of clean aluminum wire was added to 250 cc. of anhydrous isopropyl alcohol. A drop of carbon tetrachloride and 0.1 g. of mercuric chloride were added and after the initial vigorous reaction had subsided the mixture was refluxed for twelve hours. To the aluminum isopropoxide solution was added 18.5 g. of *o*-fluorobenzophenone (10) and the mixture was distilled slowly until no more acetone was

detected in the distillate. From the hydrolyzed mixture a viscous liquid was isolated which crystallized when a solution of it in hot petroleum ether was cooled. The *o*-fluorobenzohydrol formed colorless cubes; yield 18 g. (97%); m.p. 41–42°.

Anal. Calc'd for $C_{13}H_{11}FO$: F, 9.40. Found: F, 9.49.

From 14 g. of the carbinol and 15 cc. of acetyl bromide, 15.5 g. (86%) of *o-fluorodiphenylbromomethane* was obtained as a colorless liquid boiling at 172–178° at 17 mm.

Anal. Calc'd for $C_{13}H_{10}BrF$: F, 7.15. Found: F, 7.10.

1,1,1,2-Tetraphenyl-2-(o-*fluorophenyl*)*ethane* (*X*). From 11.3 g. of o-fluorodiphenylbromomethane and the triphenylmethylsodium prepared from 10.2 g. of triphenylchloromethane, 14.1 g. (83%) of the pentaarylethane (after recrystallization from benzene-petroleum ether) was obtained as colorless crystals; m.p. 138–144° dec. in air and 146–147° dec. in a vacuum.

Anal. Calc'd for $C_{32}H_{25}F$: F, 4.43. Found: F, 4.38.

m-*Fluorodiphenylbromomethane.* To the ice-cold, stirred Grignard reagent which had been prepared from 22.4 g. of *m*-fluorobromobenzene (11) in 50 cc. of ether was added dropwise 12.7 g. of benzaldehyde in the course of an hour. The product was hydrolyzed with ice and ammonium chloride solution and the ether solution was washed with water with 2% sodium hydroxide solution and then with water. The m-*fluorobenzohydrol* was obtained as a colorless viscous liquid by distillation at 178–179° and 16 mm.; yield 12 g. (47%). The product solidified slowly; m.p. 26–27°.

Anal. Calc'd for $C_{13}H_{11}FO$: F, 9.40 Found: F, 9.45.

The carbinol was converted to m-*fluorodiphenylbromomethane* by means of acetyl bromide; the product was a colorless liquid; b.p. 192–193° at 28 mm.; yield 90%.

Anal. Calc'd for $C_{13}H_{10}BrF$: F, 7.15. Found: F, 7.30.

1,1,1,2-Tetraphenyl-2-(m-*fluorophenyl*)*ethane* (*XI*). This compound was prepared by coupling 11.2 g. of *m*-fluorodiphenylbromomethane with triphenylmethylsodium and was recrystallized from benzene-petroleum ether, from which it was obtained in the form of colorless crystals; m.p. 149–153° dec. in air and 168–170° dec. in a vacuum.

Anal. Calc'd for $C_{32}H_{25}F$: F, 4.45. Found: F, 4.35.

p-*Fluorodiphenylbromomethane.* *p*-Fluorobenzohydrol was obtained in 58% yield according to the directions of Schiemann and Pillarsky (12); b.p. 175–178° at 16 mm.; m.p. 48°. By treatment with acetyl bromide, 8 g. of the carbinol gave 9.5 g. (90%) of the bromide; b.p. 176–178° at 14 mm.

Anal. Calc'd for $C_{13}H_{10}BrF$: F, 7.15. Found: F, 7.13.

1,1,1,2-Tetraphenyl-2-(p-*fluorophenyl*)*ethane* (*XII*). From 9.5 g. of *p*-fluorodiphenylbromomethane and triphenylmethylsodium (from 10.2 g. of the chloride), an 87% yield of the pentaarylethane was obtained as colorless crystals after recrystallization from benzene-petroleum ether; m.p. 150–155° dec. in air and 156–157.5° dec. in a vacuum.

Anal. Calc'd for $C_{32}H_{25}F$: F, 4.45. Found: F, 4.38.

1,1,1,2-Tetraphenyl-2-(o-*tolyl*)*ethane* (*XIII*). To 8.32 g. of *o*-tolylphenylcarbinol (13) dissolved in 8 cc. of benzene was added 6 cc. of acetyl bromide and the solution was heated on a steam-bath for one hour. The benzene, acetic acid, and excess of acetyl bromide were removed under reduced pressure, the residual oil was dissolved in 20 cc. of benzene, and the solution was added immediately to the triphenylmethylsodium prepared from 11.16 g. of triphenylchloromethane. The pentaarylethane was obtained in fine colorless crystals by recrystallization from benzene-petroleum ether; yield 14.9 g. (88%); m.p. 139–147° dec. in air and 170.5–171° dec. in a vacuum.

Anal. Calc'd for $C_{33}H_{28}$: C, 93.4; H, 6.6.
Found: C, 93.1; H, 6.6.

1,1,1,2-Tetraphenyl-2-(m-*tolyl*)*ethane* (*XIV*). *m*-Tolylphenylcarbinol (13) (8.32 g.) was converted to the bromide by the procedure used on the isomer, and a benzene solution of the bromide was added to the triphenylmethylsodium prepared from 11.6 g. of triphenylchloromethane. The product was obtained in fine colorless crystals by recrystallization

from benzene-petroleum ether; yield 14.71 g. (87%); m.p. 149–157° dec. in air and 157–159° dec. in a vacuum.

Anal. Calc'd for $C_{33}H_{28}$: C, 93.4; H, 6.6.
Found: C, 93.2; H, 6.6.

1,1,1,2-Tetraphenyl-2-(o-*anisyl*)*ethane* (*XV*). Ten grams of *o*-methoxybenzohydrol (13) was converted to the bromide by means of acetyl bromide in benzene, and the bromide as obtained by removal of the excess of acetyl bromide and benzene was coupled with triphenylmethylsodium. The pentaarylethane crystallized from benzene-petroleum ether in colorless glistening platelets; yield 15.8 g. (90%); m.p. 141–152° dec. in air and 165–166° in a vacuum.

Anal. Calc'd for $C_{33}H_{28}O$: C, 90.0; H, 6.4.
Found: C, 89.9; H, 6.4.

1,1,1,2-Tetraphenyl-2-(m-*anisyl*)*ethane* (*XVI*). *m*-Methoxybenzohydrol (b.p. 160–165° at 0.2 mm.), prepared in 55% yield from benzaldehyde and the Grignard reagent from *m*-bromoanisole, was converted to *m*-methoxydiphenylbromomethane by means of acetyl bromide. The crude product obtained by removal of the excess acetyl bromide and acetic acid was used for coupling with triphenylmethylsodium. The pentaarylethane crystallized in fine colorless crystals from benzene-petroleum ether; yield 44%; m.p. 139–142.5° dec. in air and 144–144.5° dec. in a vacuum.

Anal. Calc'd for $C_{33}H_{28}O$: C, 90.0; H, 6.4.
Found: C, 90.4; H, 6.3.

1,1,1,2-Tetraphenyl-2-(m-*biphenyl*)*ethane* (*XVII*). *m*-Nitrobiphenyl was prepared from *m*-nitroaniline according to the procedure of France, Heilbron, and Hey (14). It was reduced to *m*-aminobiphenyl, from which *m*-iodobiphenyl was prepared through the diazonium reaction. Nineteen grams of *m*-iodobiphenyl and 1.65 g. of magnesium were allowed to react in 40 cc. of anhydrous ether for three hours, the solution was filtered from excess of magnesium, cooled by an ice-bath, and treated dropwise with 5.5 cc. of benzaldehyde in the course of an hour. After the mixture had been stirred for an hour longer, it was hydrolyzed with ice and ammonium chloride solution. The oil which was obtained on evaporation of the ether solution at room temperature was taken up in 51 cc. of warm 80% ethanol; after cooling, the solution was decanted from insoluble gum and evaporated. On addition of petroleum ether to the residue, 11 g. of colorless *m*-phenylbenzohydrol was obtained; m.p. 78.5–79°. Hatl, Pilgrim, and Stephenson (15), who prepared this compound from 3-phenylbenzophenone, reported the m.p. 81°.

m-Phenyldiphenylbromomethane was prepared from the carbinol (2.9 g.) by means of acetyl bromide and the product, freed from acetyl bromide and acetic acid, was coupled with triphenylmethylsodium. From benzene-petroleum ether, the pentaarylethane crystallized in fine colorless crystals; yield 2.67 g.; m.p. 146–153° dec. in air and 168–169° dec. in a vacuum.

Anal. Calc'd for $C_{38}H_{30}$: C, 93.8; H, 6.2.
Found: C, 93.6; H, 6.3.

1,1,1,2-Tetraphenyl-2-(o-*biphenyl*)*ethane* (*XVIII*). Eight grams of *o*-phenylbenzohydrol (16) in 10 cc. of benzene was mixed with 10 cc. of acetyl bromide and the mixture was then warmed for one hour on a steam-bath. The liquids were removed under reduced pressure, 20 cc. of benzene was added, and the mixture again evaporated under reduced pressure. The yellow residual oil crystallized when scratched; it was dissolved in 10 cc. of ether and 40 cc. of petroleum ether was added. The *o*-phenyldiphenylbromomethane which precipitated melted at 83–84°; yield 8.8 g. It immediately began to lose hydrogen bromide and change to 9-phenylfluorene; m.p. 145°. To prepare the pentaarylethane, the bromide was coupled immediately with triphenylmethylsodium. The product crystallized when stirred with absolute alcohol. From benzene-petroleum ether it crystallized in small glistening platelets; yield 35%; m.p. 167–173° dec. in air and 175–178° dec. in a vacuum.

Anal. Calc'd for $C_{38}H_{30}$; C, 93.8; H, 6.2.
Found: C, 93.4; H, 6.1.

Rate measurements. All of the pentaarylethanes were dried at 60–100° at 0.04 mm. until all of the solvent had been removed, as was shown by analysis for carbon and hydrogen. The rates of dissociation of the pentaarylethanes in *o*-dichlorobenzene at 80° were determined by the procedure described by Bachmann and Osborn (1). In many of the determinations, methanol was employed in place of ethanol to form the triarylmethyl alkyl ether; it seemed to give more consistent results than ethanol.

In agreement with previous results, the rate-controlling step proved to be a reaction of the first order, corresponding to the unimolecular process of dissociation. Letting $Z = x/a$, the fraction of pentaarylethane reacting, the equation for the first order reaction becomes

$$k = \frac{-2.3}{t} \log (1 - Z)$$

Z was calculated as the ratio of the actual absorption of iodine to the theoretical absorption. When -log(1-Z) was plotted against t, straight lines were obtained; the slopes of the lines multiplied by 2.3 gave the rate constants k. In Table III are shown typical data obtained in a representative experiment.

TABLE III

TYPICAL DATA OBTAINED IN REPRESENTATIVE EXPERIMENT

Wt. 1,1,1,2-Tetraphenyl-2-(*p*-fluorophenyl)ethane, 0.1040 g. Solvent mixture; *o*-dichlorobenzene, 89.3%; pyridine, 4.7%; methanol., 6.0%. Theoretical absorption of 0.1 *N* iodine, 5 cc. Temp., 80°.

TIME (MIN.)	0.1 *N* IODINE ABSORBED, CC.	−LOG (1−*Z*)	*Z* FOUND	*Z* CALC'D[a]	DIFF.
2.0	0.110	0.0093	0.0211	0.0206	−0.0005
2.5	.134	.0118	.0268	.0257	−.0011
3.0	.156	.0137	.0311	.0307	−.0004
4.0	.204	.0181	.0408	.0408	.0000
5.0	.252	.0225	.0504	.0507	+.0003
7.0	.350	.0315	.0701	.0701	.0000
9.0	.443	.0403	.0887	.0894	+.0007

[a] *Z* calc'd is calculated from the average rate constant at 80°, 0.01040, which was found by multiplying the slope of the line by 2.3.

SUMMARY

Eighteen new pentaarylethanes were prepared and their rates of dissociation into free radicals were measured. Four phenyl groups and one other aryl group were present in each of the pentaarylethanes. In five of these, the aryl group was attached to the triarylmethyl carbon, and in the other thirteen it was located on the diarylmethyl carbon.

The heat of activation for the dissociation process was determined for 1,1,2,2-tetraphenyl-1-(9-phenanthryl)ethane and for 1,1,1,2-tetraphenyl-2-(1-phenanthryl)ethane.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

THE SEARCH FOR SUPERIOR ANTIMALARIALS. I. EXPERIMENTS IN THE VERATROLE GROUP[1]

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Veratrole was selected for this particular investigation because of its ready availability and the ease with which it can be converted into a 5,8-diamino-6,7-dimethoxyquinoline (IV), which carries one of its methoxyls, and both of its amino groups, in chemotherapeutically favorable positions. What will be the effect of the additional methoxyl at 7 is problematical. It is true that not infrequently the introduction into a molecule of a second group of the same kind, instead of increasing the physiological effect, destroys it. On the other hand, the veratrole structure, carrying adjacent methoxyl groups, is present in such physiologically active alkaloids as papaverine, laudanosine, narcotine, narceine, hydrastine, berberine, corydaline, brucine, and a host of others.

The most valuable three antimalarials at present, it is quite generally agreed are, in the order of their usefulness, quinine (and its associated alkaloids), Atabrine, and Plasmochin. These three have in common certain structural features, as will be obvious by an examination of their graphic formulas. It is not an illogical deduction, therefore, that their antimalarial properties are in some way dependent upon the existence in their molecules of such common features. Thus, all of these three drugs are derivatives of quinoline (acridine being a benzoquinoline). All of them carry a methoxyl group in position 6, and a basic group at 4 or 8, on the quinoline nucleus. The function of the chlorine in Atabrine is obscure.

We are focusing our attention upon Plasmochin types, rather than upon quinine or Atabrine substitutes because, in spite of certain valid and familiar objections to Plasmochin, it still remains about the only available antimalarial which is strongly gametocidal in cases of *P. falciparum* infections. The problem is therefore to synthesize a compound which will retain, or even improve upon, the valuable antimalarial properties of Plasmochin, and be free from its objectionable characteristics.

In this preliminary article, a number of simple veratrole derivatives are described which were used as initial materials either in the present communication or in others which will appear shortly.

Some interesting condensations were carried out with the 5,8-diamino-6,7-dimethoxyquinoline (IV) and the anhydrides of succinic, maleic, and phthalic acids, following in general the procedure of Bergmann and Schapiro (1) in their acylation experiments with sulfanilamide and heterocyclic amines. Under the

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conditions of our experiments, the three anhydrides reacted smoothly with both amine groups, giving excellent yields of compounds (V), (VII), and (VIII).

The imides (VI and IX) corresponding to two of these acids (V and VIII) were obtained readily by heating together the diamine (IV) and the acid anhydride, either dry or in boiling dioxane (b.p., 101.5°) solution; but maleic anhydride refused to yield an imide by either process. This agrees with the experience of Bergmann and Schapiro in analogous cases.

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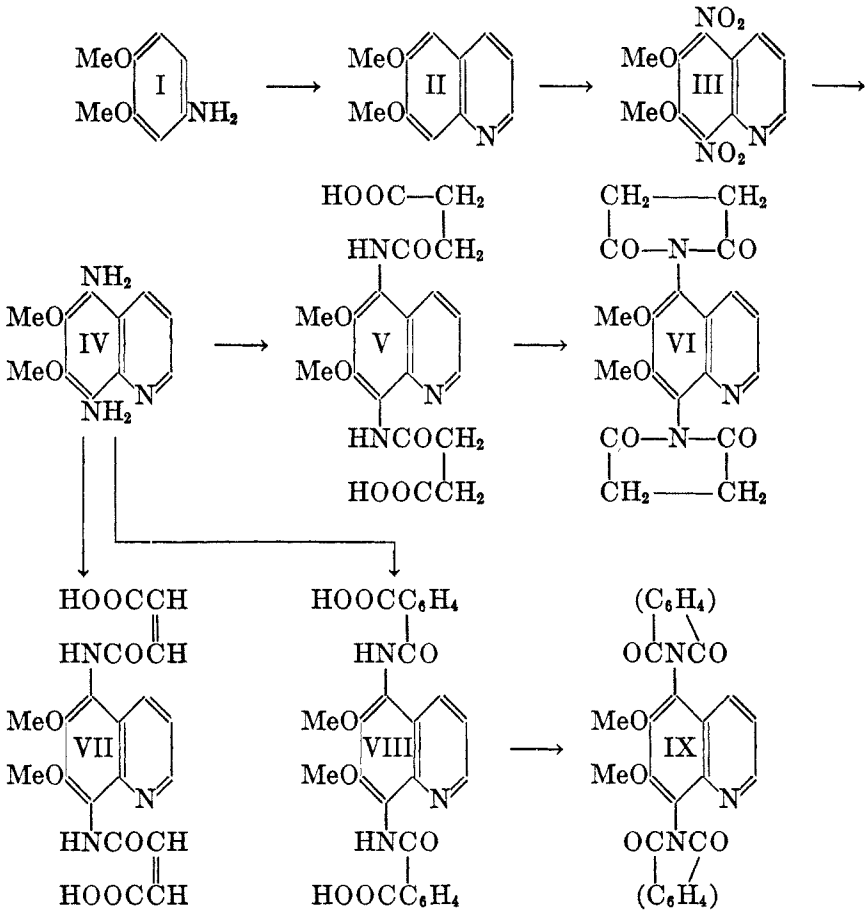


One reason for some experimentation in this direction was that Oesterlin (2) has recently reported that the antimalarial action of Plasmochin is increased by succinic and fumaric acids, which play an important part in cell respiration, and this is probably referable to the action of the drug upon the gametocytes.

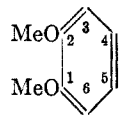
Acknowledgments. Our thanks are due to Mr. Russell Hopkinson, of the Hopkinson Laboratories, Inc., New York, N. Y., whose generous action in founding this research fellowship at Columbia University made this investigation

possible. To the American Cyanamid Co., Stamford, Conn., we wish to express our appreciation of their courtesy in providing us with a supply of acetylsulfanilyl chloride. Further, we are indebted to Mr. Saul Gottlieb of these laboratories, for the analytical results reported.

EXPERIMENTAL

All temperatures recorded, unless otherwise stated, have been corrected for thermometer stem exposure.

All veratrole derivatives are numbered consistently throughout according to the following formula:



4-Nitroveratrole (m.p. 96°) and *4,5-dinitroveratrole* (m.p. 127–128°) are easily obtained by the direct nitration of veratrole, the dilute acid giving the mono-, and the concentrated acid the di-nitro derivative, as already described in various articles in the literature. The yield in both cases is practically that calculated.

3,4,5-Trinitroveratrole has been prepared by the action of fuming nitric acid, or of a mixture of concentrated nitric and sulfuric acids, upon 4-nitroveratrole or veratric acid (3, 4).

By direct nitration of veratrole with a mixture of equal parts of concentrated nitric acid and concentrated sulfuric acid, we have obtained a 75% yield of the trinitro derivative, in pale yellow crystals, m.p. 143° (lit., 144–145°). In carrying out this nitration, the veratrole must be added very slowly and carefully to the mixed acids, or the reaction is likely to become violent. After all of the veratrole has been added, the nitration is completed by heating for an hour at 100°. When cold, the mixture is poured into ice-water, the precipitate collected, washed with water, and crystallized from alcohol.

This trinitro derivative was prepared also from 6-nitroveratraldehyde as follows:

To 50 cc. of a mixture of equal parts of concentrated nitric acid and concentrated sulfuric acid was added slowly 5 g. of the nitro aldehyde, while the reaction vessel was immersed in cold water and the mixture mechanically stirred. After about 30 minutes, the mixture was poured into 500 cc. of ice-water, the precipitate removed and purified as before. White prisms were obtained, m.p. 143°; yield 75%.

Anal. Calc'd for $C_8H_7N_3O_8$: C, 35.2; H, 2.6.
Found: C, 35.4; H, 2.7.

In this nitration presumably the aldehyde group is first oxidized to COOH and the latter then is displaced by the nitro group, as in the oxidation of veratric acid to trinitroveratrole noted above.

4-Aminoveratrole (I). The reduction of 4-nitroveratrole to the corresponding aminoveratrole has been achieved by the action of hydrogen in the presence of the Adams platinum oxide catalyst (5), as well as by other methods. It has now been found that this reduction can be accomplished more satisfactorily and more economically by the use of palladium black. A solution of 30 g. of 4-nitroveratrole in 180 cc. of alcohol, containing 0.3 g. of palladium, was hydrogenated at about three atm. pressure; yield, 24.5 g. (calc'd, 25 g.); m.p. 86° (lit., 86°). Exposed to light and air, this amine gradually turned reddish.

4-Amino-5-nitroveratrole. When a solution of 15 g. of 4,5-dinitroveratrole in 150 cc. of alcohol was hydrogenated at 3 atm. pressure in the presence of excess of palladium catalyst, and the current of hydrogen was continued for some time after the absorption of the gas had ceased, an orange-red precipitate separated, which was removed and purified by recrystallization from alcohol, when it melted at 171° (lit., 171°); yield 70–75%.

To discover whether or not this method of reduction could be used for the conversion of

other aromatic dinitro derivatives into the corresponding amino nitro compounds, it was tried on *o*- and *m*-dinitrobenzenes, and on 2,4-dinitroaniline, but in every case both nitro groups were reduced. It is worth noting, therefore, that in the veratrole series this method of reduction pursues a somewhat different course from that which it follows in the benzene series.

4,5-Diaminoveratrole was prepared most conveniently by reduction of the dinitro compound with tin and hydrochloric acid, as described by Moureu (6); m.p. 131° (lit., 131°); yield, good.

3,4,5-Triaminoveratrole. To a mixture of 9 g. of the trinitro compound and 27 g. of tin was added 100 cc. of concentrated hydrochloric acid, and the mixture was heated for an hour at 100° with frequent stirring. The resultant clear, dark red solution was made alkaline to litmus by sodium hydroxide solution, with external cooling, and extracted with chloroform. Concentration of the chloroform extract deposited the triamine in nearly colorless needles which darkened rapidly when exposed to light and air; m.p., 150–152°; yield, 70%.

Picrate. Purified by repeated crystallization from alcohol, it formed yellow needles, m.p. 86°.

Anal. Calc'd for $C_{14}H_{16}N_6O_9$: C, 40.8; H, 3.9.
Found: C, 40.7; H, 3.9.

6,7-Dimethoxyquinoline (II). Goldschmiedt (7) prepared this compound by the application of the Skraup reaction to 6-aminoveratric acid, the COOH group being eliminated simultaneously. The yield, however, was only "sehr mässige," and his product admittedly was not pure. It is interesting that in this case the tendency to form the 6,7- rather than the 5,6-dimethoxyquinoline, is so strong that the cyclization, instead of occurring at the free *ortho* position 5, displaces the COOH at 1.

We have found that this quinoline derivative is more conveniently prepared by the application of the same reaction to 4-aminoveratrole. After removal of excess nitrobenzene by steam distillation, the solution was made alkaline and distilled again with steam, to eliminate any unchanged aminoveratrole. No unaltered nitrobenzene or aminoveratrole was recovered in these distillations. Since the dimethoxyquinoline itself is not volatile with steam, it was isolated by extraction with ether. The base remaining after evaporation of the dried ether extract was dissolved in dilute hydrochloric acid. The clear solution was warmed and a mixture of zinc chloride and 2 *N* hydrochloric acid added. As the solution cooled, the double zinc chloride salt of the quinoline crystallized out. These crystals were removed, washed, decomposed by concentrated sodium hydroxide solution, and the quinoline again extracted with ether. The ether extract was dried again with sodium sulfate, and the solvent evaporated. The dimethoxyquinoline remained as a brownish yellow oil. By using a continuous extractor for the ether extraction, and omitting the zinc chloride purification, an 83% yield of the dimethoxyquinoline was secured, of sufficient purity for the succeeding reactions. When the crude product was subjected to distillation, in an atmosphere of nitrogen, it came over as a pale yellow oil at 164°/2.3 mm., n_D^{25}, 1.6150.

Anal. Calc'd for $C_{11}H_{11}NO_2$: C, 69.8; H, 5.8.
Found: C, 69.5; H, 5.9.

Hydrochloride. Evaporation of a dilute hydrochloric acid solution of the base, left this salt in pale yellow crystals, which were recrystallized from alcohol, and then appeared in white needles, m.p. (uncorr.) 222°.

Anal. Calc'd for $C_{11}H_{12}ClN_2O$: C, 58.5; H, 5.3.
Found: C, 58.6; H, 5.6.

N-Methyl methosulfate, $C_{11}H_{11}NO_2Me \cdot OSO_3Me$. To a solution of 2 g. of the base in benzene, 1.5 g. of methyl sulfate was added, and the mixture was refluxed for 30 mins. A dark oil collected below the benzene. Most of the benzene was decanted and the residual mixture was heated at 100° to drive off the remainder. The oil remaining was dissolved in warm acetone and precipitated in crystalline form by the addition of ether. Repetition of this

acetone and ether treatment gave pale yellowish crystals, which melted with decomposition at 232°.

Anal. Calc'd for $C_{13}H_{17}NO_6S \cdot H_2O$: C, 46.8; H, 5.7.
Found: C, 46.7; H, 5.2.

The same product was obtained by heating together equimolecular amounts of the base and methyl sulfate for 10 mins. at 100°. On cooling, the quaternary salt crystallized out and was purified from acetone and ether as above. In both cases, the yield was practically that calculated.

Picrate. M.p. 257° (lit., 257°); yellow needle crystals (from alcohol).

Methiodide. A mixture of equal moles of the dimethoxyquinoline and methyl iodide was heated at 100°. As the tube cooled, the methiodide separated as a yellow powder; m.p. (with decomposition) 242°; yield, 90%.

Anal. Calc'd for $C_{12}H_{14}INO_2$: C, 43.5; H, 4.3.
Found: C, 43.4; H, 4.6.

Similar quaternary salts have been made with ethyl iodide; ethyl, *n*-propyl, and *n*-butyl bromides, but not analyzed. These salts may prove interesting for the preparation of new photosensitizing cyanine dyes; and physiologically may possess some curare action.

5,8-Dinitro-6,7-dimethoxyquinoline (III). To a solution of 5 g. of the dimethoxyquinoline in 20 cc. of concentrated sulfuric acid at 0°, 20 cc. of oleum was added slowly. The mixture was transferred to a 3-necked flask, stirred mechanically, and 25 cc. of yellow fuming nitric acid added gradually, maintaining the temperature at or below 10°. After an hour's stirring, the mixture was poured upon ice and left until the yellow precipitate had settled completely, when it was removed, washed with water, and crystallized from alcohol, giving white crystals, m.p. 155°; yield, 90%.

Anal. Calc'd for $C_{11}H_9N_3O_6$: C, 47.3; H, 3.2.
Found: C, 47.5; H, 3.5.

The position of the nitro groups assumed in this compound is based upon the following considerations:

(a) The fact that the benzene nucleus in quinolines is much more sensitive to nitration than the pyridine cycle.

(b) Direct nitration of quinolines by mixtures of nitric acid and sulfuric acid results preferably in 5- or 8-nitro derivatives, and not in nitration of the pyridine cycle (8, 9, 10).

(c) Since the position of the two methoxyl groups is fixed at 6 and 7, positions 5 and 8 are the only ones left free for nitration on the benzene nucleus.

5,8-Diamino-6,7-dimethoxyquinoline (IV). This was prepared by reduction of the corresponding dinitro derivative (VII) with tin and hydrochloric acid, stannous chloride and hydrochloric acid, or by hydrogen in the presence of palladium as catalyst. Of these three methods, the second proved most satisfactory, and was carried out as follows:

A mixture of the dinitro compound with a slight excess of stannous chloride was covered with concentrated hydrochloric acid and vigorously stirred. Reaction took place cold, with formation of yellow crystals presumably consisting of the double tin salt of the diamine hydrochloride. This salt was removed, dissolved in an equal volume of water, the solution made alkaline by the careful addition of concentrated caustic alkali solution, extracted with ether, the ether extract dried with sodium sulfate, and the solvent removed. The residual reddish oil (yield 85%) was purified by distillation under diminished pressure, in an atmosphere of nitrogen, and an orange oil obtained, b.p. 170°/0.2 mm., which was analyzed.

Anal. Calc'd for $C_{11}H_{13}N_3O_2$: C, 60.3; H, 5.9.
Found: C, 60.3; H, 6.2.

Picrate. As soon as the picric acid solution was added to the solution of the diamine, the mixture turned dark and a dark picrate separated, from which a lighter colored product could not be obtained by repeated crystallization from alcohol in the presence of a decolorizing carbon. The crystals so obtained were large needles, m.p. 185–186°.

Dihydrochloride. Dry hydrogen chloride was passed into an anhydrous ether solution of the diamine for 10 minutes. The red precipitate was crystallized repeatedly from alcohol and then formed pinkish crystals, m.p. 186–187°; yield, approximately that calculated.

Anal. Calc'd for $C_{11}H_{15}Cl_2N_3O_2$: C, 45.2; H, 5.2.

Found: C, 45.5; H, 5.3.

Condensation of 5,8-diamino-6,7-dimethoxyquinoline with anhydrides of dibasic acids. The method of preparation was the following: To a solution of 1.5 g. of the diamine (I) in 25 cc. of acetone, there was added 2 equivalents of the anhydride and the mixture was refluxed for three minutes. As the dark red solution cooled, a copious orange brown precipitate separated, which was washed with acetone and purified by repeated crystallization from alcohol. Yields were about 90%.

The condensation products with maleic and phthalic anhydrides both carried water of crystallization, which was not lost when those compounds were heated to 100° over calcium chloride under diminished pressure. On the other hand, the succinic anhydride product crystallized without any solvent of crystallization.

Analyses, etc., of these condensation products are given below:

COMPOUND	FORMULA	APPEARANCE	CALC'D		FOUND		M.P. DECOMP.
			C	H	C	H	
V	$C_{19}H_{21}N_3O_8$	White crystals	54.5	5.0	54.4	5.2	159–160°
VII	$C_{19}H_{17}N_3O_8 \cdot H_2O$	Pale brown crystals	52.7	4.4	53.1	4.7	219–220°
VIII	$C_{27}H_{21}N_3O_8 \cdot 0.5H_2O$	Nearly white crystals	61.9	4.1	61.9	4.2	173–175°

5,8-Disuccinimido-6,7-dimethoxyquinoline (VI). A mixture of 0.7 g. of the diamine (I) with 3.5 g. of succinic anhydride was heated for 2 hrs. at 120°. Excess of succinic anhydride collected as a sublimate in the upper part of the test tube. When the pale brown melt had partly cooled, it was treated with hot water, to remove unchanged succinic anhydride, and then crystallized twice from alcohol. White crystals were obtained, m.p. above 310° (subl.) (Maquenne block); yield, 80%. For analysis, a sample was dried for 5½ hrs. at 100°, over calcium chloride, in an Abderhalden pistol.

Anal. Calc'd for $C_{19}H_{17}N_3O_6$: C, 59.6; H, 4.4.

Found: C, 59.9; H, 4.5.

5,8-Diphthalimido-6,7-dimethoxyquinoline (IX). To a solution of 0.7 g. of the diamine (I) in 10 cc. of dioxane, 1.6 g. of phthalic anhydride was added, and the mixture was refluxed for 2 hrs. A solid separated during the refluxing. When the mixture had cooled, this precipitate was collected and was found to consist of bright yellow prisms, in a yield of 85%. Purified by recrystallization from alcohol and drying over calcium chloride under diminished pressure at 100°, these crystals melted with decomposition at 236–238° (Maquenne block).

Anal. Calc'd for $C_{27}H_{17}N_3O_6 \cdot 2H_2O$: C, 62.9; H, 4.1.

Found: C, 63.1; H, 4.3.

The fact that this product was insoluble in sodium carbonate solution, but dissolved in dilute sodium hydroxide, argues in favor of the imide structure (IX), rather than the dibasic acid (VIII). Further, it melted about 63° higher than that acid, which was prepared in acetone solution. The bright yellow color of (IX) compared with the nearly colorless crystals of (VIII), also indicates an imide rather than a dibasic acid structure. On boiling (VIII) in alcohol for 10 minutes, (IX) is formed, which can be shown easily by the color and the melting point. This transition from an open chain acid to the imide in boiling alcohol was also observed by Shapiro and Bergmann (11).

SUMMARY

(1) A number of nitro- and amino-veratroles have been prepared, either by new methods or as new compounds.

(2) 6,7-Dimethoxyquinoline has been synthesized from 4-aminoveratrole, and converted into its 5,8-dinitro and diamino derivatives.

(3) 5,8-Diamino-6,7-dimethoxyquinoline condenses easily with the anhydrides of succinic, maleic, and phthalic acids to the corresponding amidic acids.

(4) The amidic acids from succinic and phthalic acids readily form the corresponding imides, whereas the maleamidic acid does not.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES
OF THE UNIVERSITY OF FLORIDA]

DERIVATIVES OF PIPERAZINE. XX. MONOALKYLATION OF PIPERAZINE WITH ALKENE OXIDES[1]

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Both monosubstituted and disubstituted piperazines have been obtained by the alkylation of piperazine with alkene oxides. Fourneau and Barrelet (1) obtained the mono- and di-alkylated piperazines from the reaction of piperazine with the oxides of 2-methylbutene-1,3-butoxypropene-1,3-phenylpropene-1, and 3-phenoxypropene-1. A French patent (2) has been granted on this series of amino alcohols, some of which appeared useful as local anesthetics.

In a further search for compounds with local anesthetic properties Fourneau and Samdahl (3) prepared two series of disubstituted piperazines, utilizing alkene oxides as alkylating agents. For one series there were utilized oxides of the type $RC(CH_3)CH_2O$, with R extending from propyl through heptyl; the other series was derived from 3-alkoxypropene-1 oxides, $ROCH_2CHCH_2O$, the alkoxy groups ranging from propoxy through heptoxy.

Mousseron (4) has synthesized the series of mono- and disubstituted piperazines derived from the oxides of cyclopentene, cyclohexene, cycloheptene, cyclooctene, and indene.

The initial investigators of piperazine-alkene oxide reactions, Krasuskii and Kosenko (5), carried out reactions of piperazine with the oxides of 2-methylpropene and trimethylethylene. Failing to isolate a monosubstituted product, they concluded that the reaction proceeds with simultaneous addition of two molecules of alkene oxide to one molecule of piperazine, thereby yielding only disubstituted product. The work of Fourneau and Barrelet (1) disproved this hypothesis in part.

Likewise Krasuskii and Pilyugin (6) obtained only the disubstituted product 1,4-bis-(β-hydroxypropyl)piperazine from the reaction of piperazine with propene oxide.

1,4-Bis-(β-hydroxyethyl)piperazine has been synthesized by the piperazine-ethylene oxide reaction (7), but the intermediate 1-(β-hydroxyethyl)piperazine has been obtained only by tedious indirect methods (8, 9). It was not obtained in sufficient quantity for its physical properties to be described.

In this investigation it was desired to prepare 1-(β-hydroxyethyl)piperazine in amount sufficient for characterization and for use as an intermediate for further syntheses. The reaction of piperazine with ethylene oxide proved to be a convenient method for the synthesis in good yield of this monosubstituted piperazine. Similarly, propene oxide and 2-methylpropene oxide yielded 1-(β-hydroxypropyl)

[1] The material in this paper is abstracted from part of a dissertation submitted by L. J. Kitchen to the Graduate Council of the University of Florida in partial fulfillment of the requirements for the Ph.D. degree, February, 1943.

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piperazine and 1-(β-hydroxy-β-methylpropyl)piperazine, respectively, in good yield.

The reactions were carried out by addition of the alkene oxide to a methanol solution of piperazine, the solution being kept at a temperature of about 80°. Rapid reaction took place at this temperature. The sealed-tube technique of Krasuskii, *et al.* (5, 6) was found to be unnecessary.

In every case some disubstituted product was obtained; the combined yields of monosubstituted and disubstituted piperazines were essentially 100%. In general it appears that the amount of disubstitution was minimized by presence of excess piperazine (Table I). Thus, in reaction of one mole of ethylene oxide with 2.8 moles of piperazine, eighty-six per cent of the piperazine used was obtained in the yield of monoalkylation product. However, when piperazine was treated with the molecular amount of propene oxide, only sixty-two per cent of the piperazine used was present as monoalkylated piperazine when the reaction was complete.

TABLE I

EFFECT OF EXCESS OF PIPERAZINE IN PIPERAZINE-ALKENE OXIDE REACTIONS

ALKENE OXIDE USED	MOLAR RATIO OF PIPERAZINE TO ALKENE OXIDE	MOLAR RATIO OF MONOSUB. TO DISUB. PRODUCT
Ethylene oxide	2.8:1	6.3:1
Propene oxide	1:1	1.6:1
2-Methylpropene oxide	1.33:1	2.7:1

EXPERIMENTAL

The dihydrochlorides were prepared by adding excess dilute hydrochloric acid (bromo phenol blue indicator) to the amine, evaporating to a syrup on the water-bath, cooling, and precipitating by addition of absolute alcohol. The granular crystalline solids were filtered, washed on the filter with 95% alcohol, and recrystallized from aqueous alcohol. The products were dried in a vacuum over phosphorus pentoxide.

The picrates, prepared by mixing alcohol solutions of picric acid and of the amino alcohol, were recrystallized from aqueous alcohol.

All melting points are corrected capillary melting points.

Preparation of 1-(β-hydroxyethyl)piperazine. The reaction was carried out by allowing the ethylene oxide (220 g., 5 moles) to distill into a solution of 1200 grams (14 moles) of piperazine dissolved in 1 liter of warm methanol. The solution was kept at 80° and was agitated during the reaction. The bottle of ethylene oxide was placed in a beaker of warm water, and the ethylene oxide was allowed to distill into the piperazine solution at a regulated rate. The ethylene oxide addition required ninety minutes. The reaction mixture was separated by fractional distillation. After separation of the methanol approximately 544 g. (6.3 moles) of piperazine was recovered. The yield of 1-(β-hydroxyethyl)piperazine obtained by fractionation at reduced pressure was 499 grams (3.8 moles), a yield of 76%. The product, a light yellow viscous liquid with a mild amine odor, had b.p. 119.2°/10 mm.; d_4^{20} 1.0595, d_4^{25} 1.0541; n_D^{22} 1.5069, n_D^{25} 1.5052, $n_D^{29.5}$ 1.5028.

Molecular refraction: Calc'd for $C_6H_{14}N_2O$: 36.77. Found: 36.64.

Dihydrochloride: m.p. 188.6–189.6° [lit., m.p. 182–183° (9)].

Anal. Calc'd for $C_6H_{16}Cl_2N_2O$: Cl, 34.91. Found: Cl, 34.98.

Picrate: m.p. *ca.* 245° (dec.); at temperatures down to about 240°, it slowly decomposed without melting; [lit. m.p. 247–248° (9)].

Phenylthiourea of 1-(β-hydroxyethyl)piperazine. Thirteen grams of the amino alcohol was mixed with 13 g. of phenylisothiocyanate, forming a homogeneous yellow oil; heat was evolved. After being heated for several minutes, the material cooled to an amorphous mass. It was crystallized from absolute alcohol and recrystallized from 95% alcohol, m.p. 114.9–115.3°.

1,4-Bis-(β-hydroxyethyl)piperazine. The 104 g. of residue from the above distillation was 1,4-bis-(β-hydroxyethyl)piperazine. The melting point after recrystallization from absolute ethanol was 134.3–135.0°; that given in the literature is 134–135° (10).

Preparation of 1-(β-hydroxypropyl)piperazine. The reaction was carried out in a manner analogous to the preparation of the hydroxyethyl derivative, 232.4 g. (4.1 moles) of propene oxide being added by means of a dropping-funnel to the piperazine (352.5 g., 4.1 moles) dissolved in 2 liters of methanol. Approximately one hour was required for the addition of the propene oxide. Eighty-six grams (1 mole) of piperazine was recovered from the reaction mixture by distillation. The yield of 1-(β-hydroxypropyl)piperazine, b.p. 108.5°/10 mm., was 260 g. (1.8 moles), a yield of 44%. The amino alcohol, a light yellow viscous liquid with a mild amine odor, had d_4^{20} 1.0103; n_D^{22} 1.4911, n_D^{20} 1.4877.

Molecular refraction: Calc'd for $C_7H_{16}N_2O$: 41.39. Found: 41.42.

Dihydrochloride: m.p. *ca.* 237.3° (dec.).

Anal. Calc'd for $C_7H_{18}Cl_2N_2O$: Cl, 32.66. Found: Cl, 32.68.

Picrate: m.p. 174.5–177.5°.

Phenylthiourea: m.p. 144.0–144.5°.

1,4-Bis-(β-hydroxypropyl)piperazine. The distillation residue, 226 g. of crude 1,4-bis-(β-hydroxypropyl)piperazine, after recrystallization from hexane-absolute alcohol had the m.p. 116.7–117.9°; the melting point given in the literature (6) is 115–116°.

Dihydrochloride of 1,4-bis-(β-hydroxypropyl)piperazine, m.p. 223.7–224.7° (dec.).

1-(β-hydroxy-β-methylpropyl)piperazine. Four hundred thirty grams (4 moles) of piperazine was heated with 500 ml. of methanol until it was completely dissolved. To the hot solution (70–80°) was slowly added 216 g. (3 moles) of 2-methylpropene oxide with frequent shaking during a thirty minute period. The methanol was distilled off, and the piperazine and the two products were separated by distillation and redistillation through a fractionating column. Approximately 190 g. of piperazine was recovered. The monoalkylation product was 302 g. of white crystalline solid (needles), m.p. 71–77°, which was collected at 105–110° at a pressure of approximately 10 mm. The distillation residue, 111 g., had the m.p. 97–102°; mixed m.p. of distillate and residue was 61–75°. A sample of the distillate, 1-(β-hydroxy-β-methylpropyl)piperazine, had the m.p. 80.2–80.5° after two recrystallizations from hexane. The product, a white hygroscopic solid with a slight odor, needles or prisms, had the b.p. 89.3°/3 mm., 106.0°/10 mm.

Dihydrochloride: dec. *ca.* 215° without melting; dec. slowly at temperatures below 215°.

Picrate: m.p. 257° (dec.).

Phenylthiourea: m.p. 129.3–129.5° (from absol. alcohol).

1,4-Bis-(β-hydroxy-β-methylpropyl)piperazine. The 111 g. of residue from the above distillation after recrystallization from hexane-absolute alcohol had the melting point 101.5–102.5°. The melting point of 1,4-bis-(β-hydroxy-β-methylpropyl)piperazine given by Krasuskii and Kosenko (5) is 102–102.5°.

SUMMARY

The reaction of piperazine with the oxides of ethylene, propene, and 2-methylpropene has been shown to yield monoalkylation products as well as the previously described disubstituted piperazines. 1-(β-Hydroxyethyl)piperazine, 1-(β-hydroxypropyl)piperazine and 1-(β-hydroxy-β-methylpropyl)piperazine are described and characterized. The latter two have not been prepared previously.

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[CONTRIBUTION FROM THE ORGANIC CHEMISTRY LABORATORIES
OF THE UNIVERSITY OF FLORIDA]

MONOALKYLATION OF ETHYLENEDIAMINE WITH ALKENE OXIDES[1]

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Knorr and Brownsden (1) have prepared N-(β-hydroxyethyl)ethylenediamine by the reaction of ethylene oxide with an excess of ethylenediamine. When an excess of ethylene oxide was used, the reaction product was the completely alkylated amine, N,N,N′,N′-tetrakis-(β-hydroxyethyl)ethylenediamine (1, 2). N,N′-bis-(β-hydroxyethyl)ethylenediamine also has been obtained from an ethylenediamine-ethylene oxide reaction mixture (3).

In this investigation the corresponding mono-β-hydroxyalkyl ethylenediamines were synthesized by alkylation of ethylenediamine with the oxides of propene, 2-methylpropene, and styrene. The reaction (I) of a substituted ethylene oxide proceeds according to the rule of Krasuskii (4), the oxygen atom remaining attached to the carbon atom which, in the original compound, was associated with the least number of hydrogen atoms.

$$\text{I.}\quad \underset{\diagdown\,\text{O}\,\diagup}{\text{RCH—CH}_2} + \text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2 \rightarrow \text{RCHOHCH}_2\text{NHCH}_2\text{CH}_2\text{NH}_2$$

From our experimental data it appears that in general the yield of the monoalkylated product varies with the amount of ethylenediamine used in excess. When the ratio of ethylenediamine to propene oxide was one to one, the yield was 45%. Styrene oxide with a two-fold excess of diamine gave a 60% yield while a seven-fold excess of diamine with 2-methyl propene oxide gave a 90% yield. Likewise a seven-fold excess of diamine with propene oxide gave a 90% yield.

EXPERIMENTAL

The picrates and hydrochlorides were recrystallized from alcohol or aqueous alcohol. All melting points are corrected.

N-(β-Hydroxypropyl)ethylenediamine. Three hundred forty-two grams (5.9 moles) of propene oxide was slowly added through a separatory funnel to 544 g. of 60.5% aq. ethylenediamine (5.48 moles) dissolved in 2 liters of methanol and contained in a 5-liter, 3-necked flask fitted with a stirrer and a reflux condenser. The temperature was kept at 40–50° by a water-bath. A period of three hours was required for the addition of the propene oxide. The product, a water-white slightly viscous liquid with a mild ammoniacal odor, was obtained by fractional distillation. Two hundred eighty-four grams was obtained, a yield of 41%; b.p. 94°/3 mm., 112°/10 mm.; d_4^{25} 0.9837; $d_4^{28.5}$ 0.9810; n_D^{20} 1.4758; n_D^{25} 1.4738; $n_D^{28.5}$ 1.4725.

Molecular refraction: Calc'd for $C_5H_{14}N_2O$: 33.84. Found: 33.79.

Anal. Calc'd for $C_5H_{14}N_2O$: N, 23.69. Found: N, 23.64.

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[1] The material in this paper is abstracted from part of a dissertation submitted by L. J. Kitchen to the Graduate Council of the University of Florida in partial fulfillment of the requirements for the Ph.D. degree.

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Dihydrochloride: m.p. 184.7–185.0°.

Anal. Calc'd for $C_5H_{16}Cl_2N_2O$: Cl, 37.09. Found: Cl, 37.18.

Picrate: m.p. 191.0–192.5°.

Phenylthiourea. The amino alcohol was mixed with two moles of phenylisothiocyanate, and the mixture was warmed for several minutes. The amorphous product was crystallized and recrystallized from alcohol; m.p. 149.8–150.0°.

N-(β-Hydroxy-β-methylpropyl)ethylenediamine. Two thousand seven hundred nineteen grams of 70% ethylenediamine (31.7 moles) without any added diluent was treated at 70° to 80° with 365 g. (5 moles) of 2-methylpropene oxide in the manner described above during the course of two hours. After removal of the excess ethylenediamine by fractional distillation at atmospheric pressure and then under vacuum, the product was collected. The yield of pure amino alcohol, a water-white slightly viscous liquid with a mild amine odor, was 572 g. (87%), b.p. 91.2°/5 mm.; 103.7°/10 mm.; d_4^{25} 0.9556; n_D^{25} 1.4672; n_D^{25} 1.4655.

Molecular refraction: Calc'd for $C_6H_{16}N_2O$: 38.45. Found: 38.40.

Anal. Calc'd for $C_6H_{16}N_2O$: N, 21.19. Found: N, 21.06.

Dihydrochloride: m.p. 195.7–196.4°.

Anal. Calc'd for $C_6H_{18}Cl_2N_2O$: Cl, 34.57. Found: Cl, 34.62.

Picrate: m.p. 198.5–200.5° (dec.).

N-(β-Hydroxy-β-phenylethyl)ethylenediamine. Two hundred seventy grams (2.25 moles) of styrene oxide dissolved in 500 ml. of methanol was added during a ten minute period to a solution of 440 g. of ethylenediamine (60.5%, 4.5 moles) in 500 ml. of methanol. The mixture was allowed to stand. The temperature gradually rose to the boiling point of the methanol, and some white solid precipitated after about an hour. Two hundred forty-six grams of monoalkylation product was obtained by fractional distillation after the mixture had stood overnight. The viscous yellow oil, b.p. 184.8°/10 mm., solidified in the receiver while still hot. After recrystallization from hexane-absolute alcohol, the m.p. was 76–80°.

Dihydrochloride: m.p., 196.7–200.8°.

Anal. Calc'd for $C_{10}H_{18}N_2O_2$: N, 28.01. Found: N, 28.01.

N-(β -Hydroxyethyl)ethylenediamine. The Carbide and Carbon product was purified by fractional distillation; b.p. 115.3°/6.2 mm.; b.p. 123°/10 mm.; d_4^{25} 1.0254; n_D^{25} 1.4851.

Molecular refraction: Calc'd for $C_4H_{12}N_2O$: 29.22. Found: 29.12.

Picrate: m.p. 224° (dec.).

Dihydrochloride: m.p. 114.3–115.2°.

SUMMARY

The 1,2-amino alcohols obtained by monalkylation of ethylenediamine with the oxides of propene, 2-methylpropene, and styrene are described and characterized. Properties of N-(β-hydroxyethyl)ethylenediamine are given. Good yields of monalkylation product are obtainable by using large excesses of ethylenediamine.

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SOLUBILITIES OF HIGH MOLECULAR WEIGHT SYMMETRICAL NORMAL ALIPHATIC KETONES

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No systematic investigation of the physico-chemical properties of high molecular weight aliphatic ketones has been reported. With the exception of a reference to the solubility of stearone (1) and a few isolated studies on enolization (2, 3), measurements of dipole moments and dielectric constants (4–8) and ebullioscopic behavior (9), very little is known of the behavior of the ketones containing more than nine carbon atoms.

Since a knowledge of the solubilities of these compounds is of appreciable value in the further investigation of their behavior, as well as being essential to a wide variety of experimental procedures, the solubilities of five of the higher homologs were determined in a series of common solvents of widely differing polarities. This paper presents the solubilities of 10-nonadecanone, 12-tricosanone, 14-heptacosanone, 16-hentriacontanone, and 18-pentatriacontanone in the following solvents: benzene, cyclohexane, tetrachloromethane, ethyl acetate, butyl acetate,acetone, 2-butanone, methanol, 95% ethanol, isopropanol, *n*-butanol, nitroethane, and acetonitrile.

EXPERIMENTAL

The ketones used in this investigation were prepared from fatty acids[1] which had been highly purified by previously described methods (10, 11). The ketones were prepared from the ethyl esters of these acids by the acetoacetic ester condensation. This method has been employed for the synthesis of high molecular weight ketones by McElvain (12, 13). Sodium ethoxide was used as the condensing agent. The ketones were obtained from the resulting keto esters by hydrolyzing the latter with 5% alcoholic potassium hydroxide, and were purified by several crystallizations from ethanol. The freezing points of these ketones are listed in Table I.

The methanol used in this investigation was commercial "absolute" (99.9% by weight). The ethanol was commercial "absolute" which was diluted to 95.0% by weight with conductivity water by checking its measured density against known values (20). The benzene was Baker C.P. thiophene-free grade and was dried over sodium wire. The other solvents were of the best grade obtainable and were dried with the usual drying agents and distilled twice before using.

The solubilities of the ketones in these solvents were determined in sealed tubes by the method and with the apparatus previously described (10, 21, 22, 23). Temperatures were measured with an accurately calibrated thermometer which was graduated in 0.1° intervals. Solution temperatures of the ketones were reproducible to ± 0.1°, and are, in general, considered accurate within ± 0.2°.

[1] The freezing points of these acids were 30.62° for capric, 43.77° for lauric, 54.15° for myristic, 62.30° for palmitic, and 69.28° for stearic acid.

RESULTS AND DISCUSSION

The solubilities of the ketones in the non-polar solvents benzene, cyclohexane, and tetrachloromethane are listed in Tables II–IV, and are shown graphically[2] in Figs. 1–3, respectively.

TABLE I

FREEZING POINTS OF PURIFIED KETONES

NO. OF C ATOMS	KETONE	F.P., °C.	REF. (M.P., °C.)
19	10-nonadecanone (caprione)	57.8	58–59 (13)
			58.0 (14)
23	12-tricosanone (laurone)	69.3	68–69 (13)
			69 (15)
			69.5–69.8 (16)
27	14-heptacosanone (myristone)	77.2	78–79 (13)
31	16-hentriacontanone (palmitone)	83.7	82 (15)
35	18-pentatriacontanone (stearone)	88.7	88.0 (14)
			88.0 (17)
			88–89 (18)
			88.7–89 (19)

TABLE II

SOLUBILITIES OF KETONES IN BENZENE

NO. OF C ATOMS	G. PER 100 G. BENZENE			
	10.0°	30.0°	50.0°	80.1°
19	13.8	67.5	510	∞
23	1.2	20.3	142	∞
27	0.3	6.3	64.7	∞
31	≈0.1	1.7	27.7	1200
35	<0.1	0.6	12.7	383

TABLE III

SOLUBILITIES OF KETONES IN CYCLOHEXANE

NO. OF C ATOMS	G. PER 100 G. CYCLOHEXANE			
	10.0°	30.0°	50.0°	81.4°
19	8.6	41.2	482	∞
23	1.6	12.7	118	∞
27	≈0.2	4.1	47.9	∞
31	<0.1	1.4	20.0	1390
35	<0.1	0.5	9.3	480

It can be seen that in these solvents the ketones are, in general, most soluble in benzene and least soluble in tetrachloromethane at any given temperature.

[2] In this report, the solubilities are shown graphically in terms of weight percentage rather than in terms of g. per 100 g. of solvent because of the more convenient scale for diagrammatic presentation.

Since these solvents consist of symmetrical molecules whose low dielectric constants[3] are practically identical, it appears that the resonance of the benzene

TABLE IV

SOLUBILITIES OF KETONES IN TETRACHLOROMETHANE

NO. OF C ATOMS	G. PER 100 G. TETRACHLOROMETHANE			
	10.0°	30.0°	50.0°	76.0°
19	7.5	32.7	270	∞
23	1.8	11.7	73.3	∞
27	0.3	4.5	34.5	2760
31	≈0.1	1.3	18.2	260
35	<0.1	0.2	9.8	133

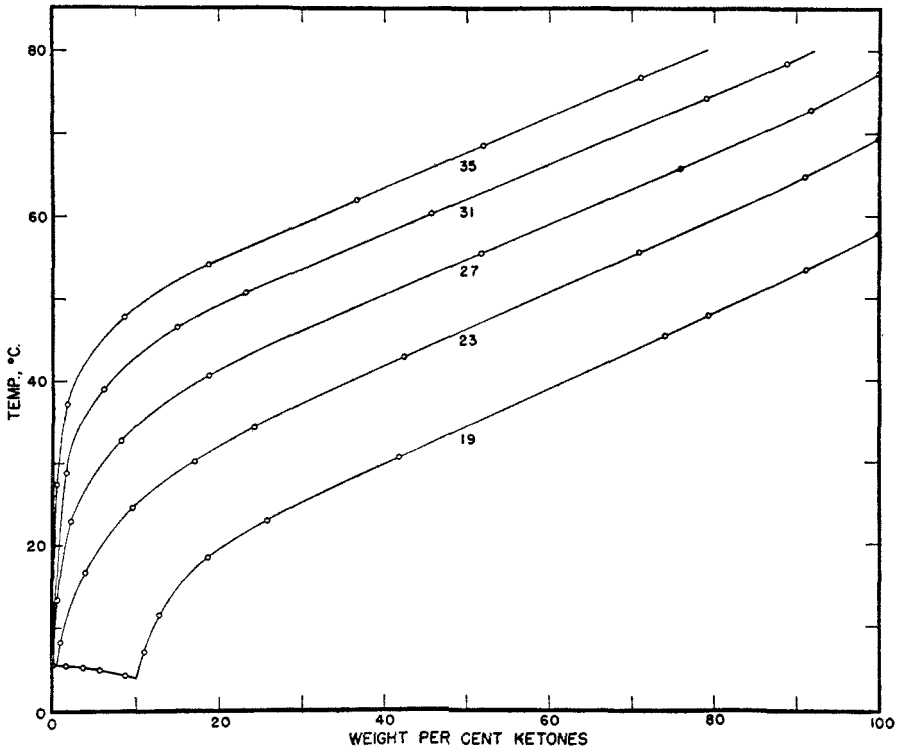

FIG. 1. LIQUIDUS CURVES OF THE KETONES WITH BENZENE

The numbers on the curves refer to the number of carbon atoms in each ketone.

molecule is an important factor affecting the solubility of the ketones in this solvent.

[3] The dielectric constants (24) of the solvents used in this investigation are as follows at room temperature: benzene, 2.3; cyclohexane, 2.4; tetrachloromethane, 2.2; ethyl acetate, 6.2; butyl acetate, 5.0; acetone, 21; 2-butanone, 18; methanol, 33; 95% ethanol, 25; isopropanol, 26; *n*-butanol, 8; nitroethane, 30; and acetonitrile, 38.

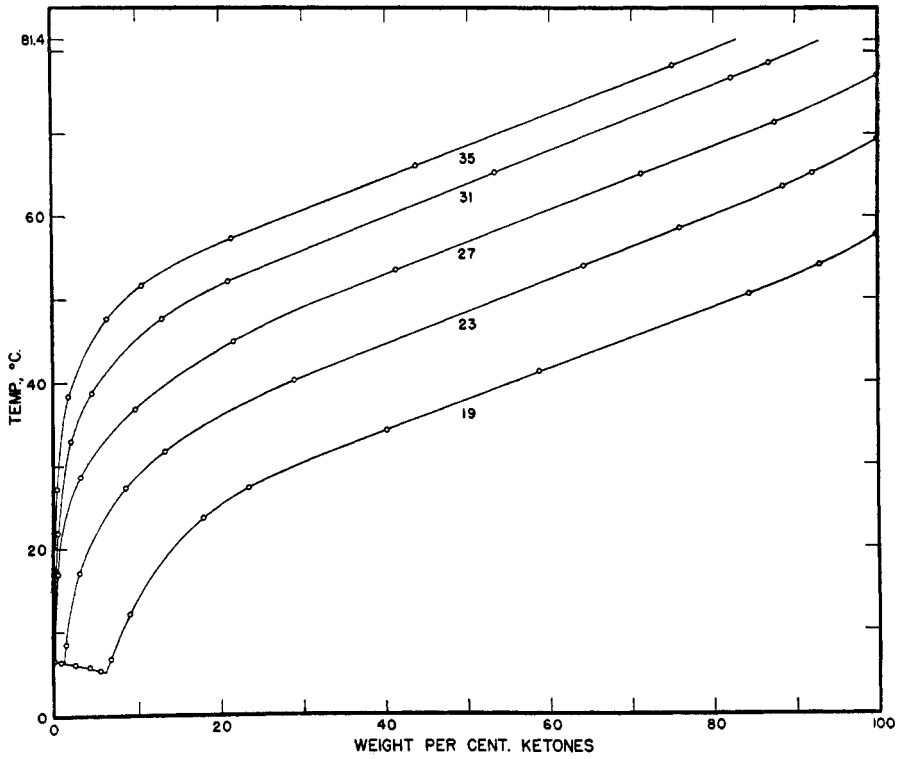

FIG. 2. LIQUIDUS CURVES OF THE KETONES WITH CYCLOHEXANE

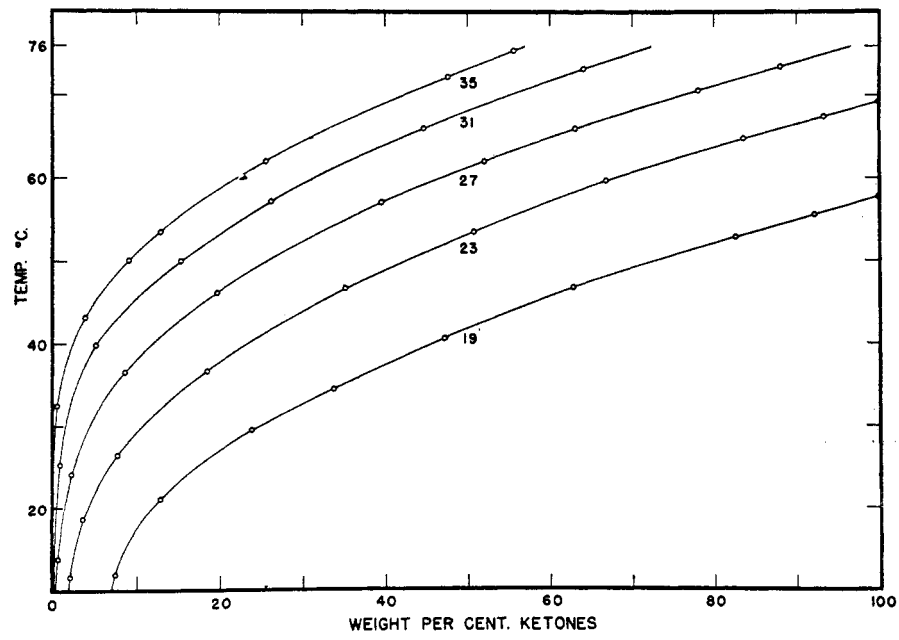

FIG. 3. SOLUBILITIES OF THE KETONES IN TETRACHLOROMETHANE

The eutectics formed by the ketones with benzene occur, in the case of 10-nonadecanone at 10.0% by weight of ketone at 3.9°, for 12-tricosanone at 0.4% and 5.4°, and for the higher homologs at much greater dilutions. With cyclohexane the eutectics occur at 6.2% and 5.1° for 10-nonadecanone, and at 1.2% and 6.3° for 12-tricosanone.

The solubilities of the ketones in ethyl and butyl acetates are listed in Tables V and VI, and are shown graphically in Figs. 4 and 5, respectively.

In both of these solvents the ketones are less soluble at any given temperature than in benzene, cyclohexane, or tetrachloromethane, being, in general,

TABLE V

SOLUBILITIES OF KETONES IN ETHYL ACETATE

NO. OF C ATOMS	G. PER 100 G. ETHYL ACETATE			
	10.0°	30.0°	50.0°	77.2°
19	5.1	16.2	372	∞
23	0.4	2.2	45.4	∞
27	≈0.1	0.3	8.9	∞
31	—	<0.1	2.5	380
35	—	—	≈0.1	120

TABLE VI

SOLUBILITIES OF KETONES IN BUTYL ACETATE

NO. OF C ATOMS	G. PER 100 G. BUTYL ACETATE			
	10.0°	30.0°	50.0°	77.2°
19	6.5	18.6	295	∞
23	0.6	3.7	48.8	∞
27	≈0.1	0.8	12.1	∞
31	—	0.4	3.8	325
35	—	≈0.2	0.9	125

less soluble in ethyl acetate than in butyl acetate. Thus, the ketones tend to be less soluble in the more polar solvents.

This tendency is further shown by the solubilities in acetone and 2-butanone which are listed in Tables VII and VIII, and are shown graphically in Figs. 6 and 7, respectively.

The ketones investigated are less soluble in those solvents possessing high dielectric constants. For example, they are less soluble in acetone than in 2-butanone. Apparently, other factors besides the polarity of the solvent affect their relative solubilities, since the lower ketones of this series are more soluble in 2-butanone than in butyl actate at higher temperatures, in spite of the much lower dielectric constant of the latter.

The solubilities of the ketones in methanol, 95% ethanol, isopropanol, and *n*-butanol are listed in Tables IX–XII, and are shown graphically in Figs. 8–11, respectively.

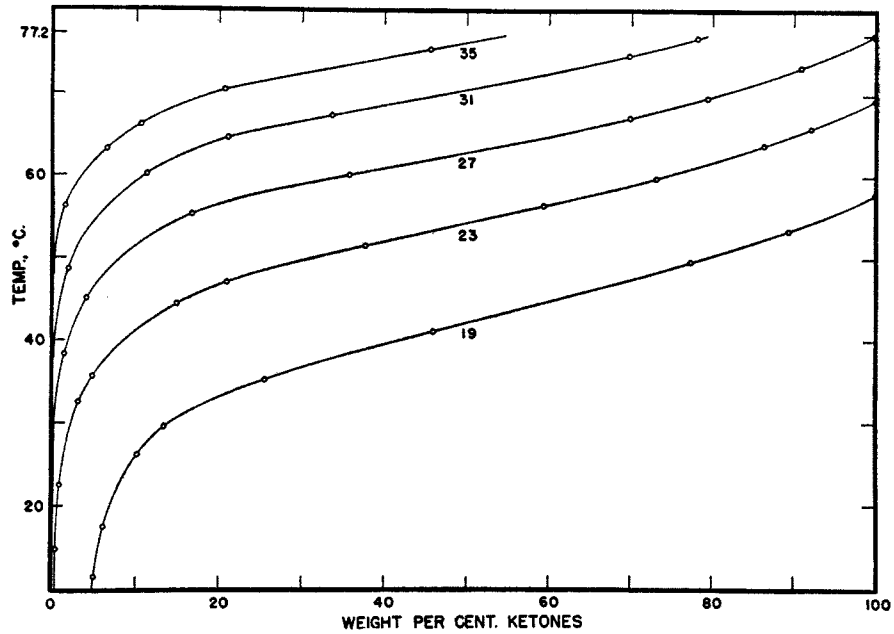

FIG. 4. SOLUBILITIES OF THE KETONES IN ETHYL ACETATE

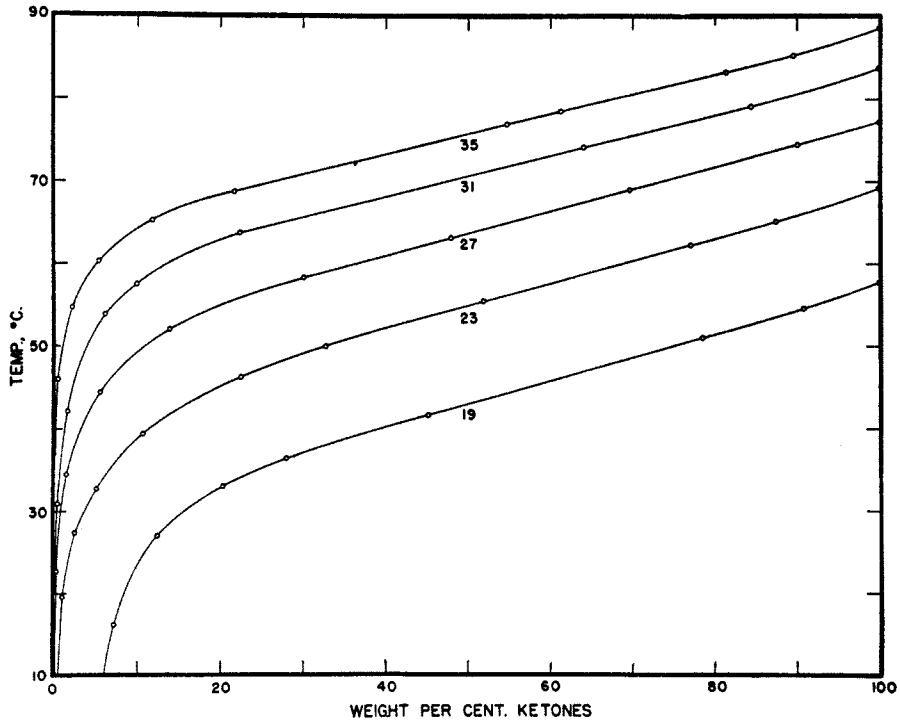

FIG. 5. SOLUBILITIES OF THE KETONES IN BUTYL ACETATE

In these alcohols the solubilities of the ketones at any given temperature decrease progressively with increased dielectric constant of the solvent, with the exception that the ketones are more soluble in isopropanol than in 95%

TABLE VII

SOLUBILITIES OF KETONES IN ACETONE

NO. OF C ATOMS	G. PER 100 G. ACETONE		
	10.0°	30.0°	56.5°
19	3.1	10.6	3450
23	0.5	1.1	144
27	<0.1	0.4	2.7
31	—	≈0.1	1.0
35	—	<0.1	0.4

TABLE VIII

SOLUBILITIES OF KETONES IN 2-BUTANONE

NO. OF C ATOMS	G. PER 100 G. 2-BUTANONE			
	10.0°	30.0°	50.0°	79.6°
19	4.9	22.0	400	∞
23	0.6	3.4	62	∞
27	≈0.1	0.5	10.6	∞
31	—	≈0.1	2.6	810
35	—	—	0.5	290

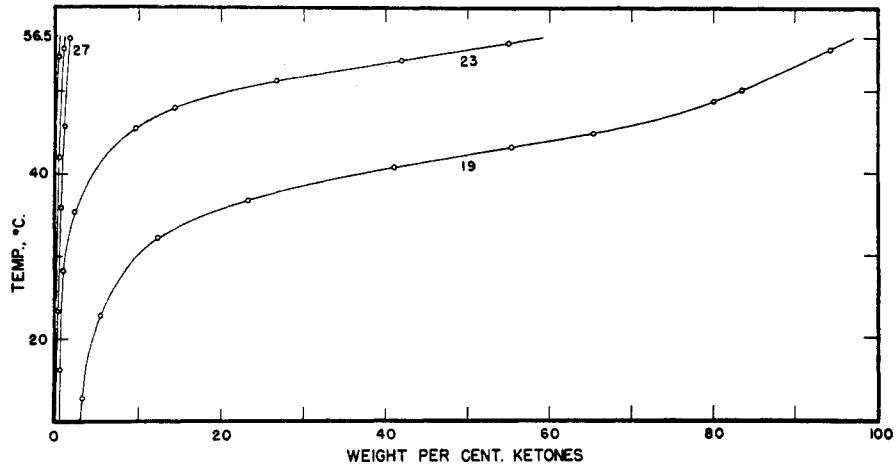

FIG. 6. SOLUBILITIES OF THE KETONES IN ACETONE

ethanol, in spite of the slightly higher polarity of the former. The solubilities in any given alcohol are qualitatively in agreement with the series of solvents presented thus far, with regard to their relative polarities. For example, the

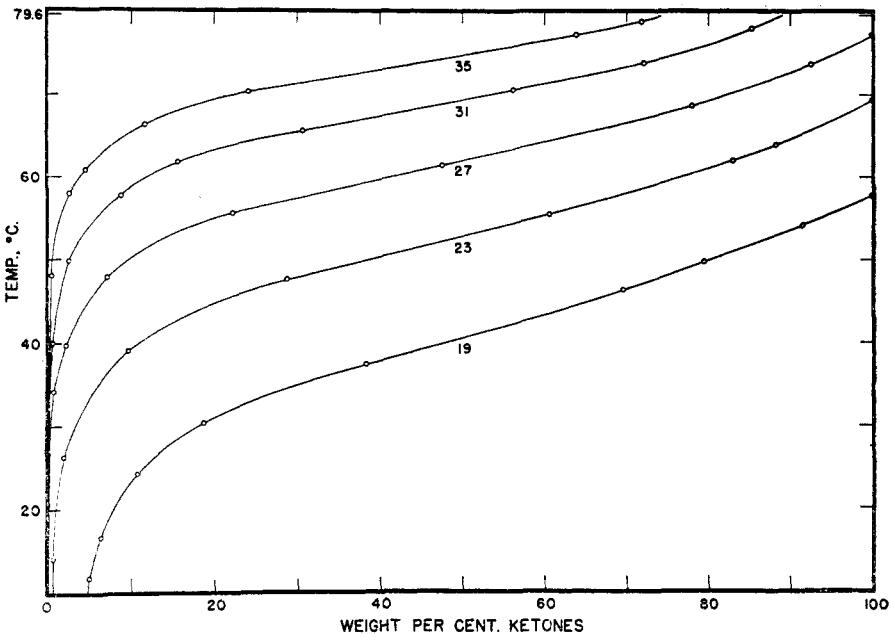

FIG. 7. SOLUBILITIES OF THE KETONES IN 2-BUTANONE

TABLE IX

SOLUBILITIES OF KETONES IN METHANOL

NO. OF C ATOMS	G. PER 100 G. METHANOL			
	10.0°	30.0°	50.0°	64.7°
19	0.6	1.5	69.5	∞
23	≈0.1	0.5	1.7	≈23
27	—	≈0.1	0.4	1.9
31	—	—	≈0.1	0.9
35	—	—	—	0.3

TABLE X

SOLUBILITIES OF KETONES IN 95.0% ETHANOL

NO. OF C ATOMS	G. PER 100 G. 95% ETHANOL				
	10.0°	30.0°	50.0°	65.0°	78.5°
19	1.2	3.2	194	∞	∞
23	0.2	0.6	6.0	900	∞
27	<0.1	≈0.1	0.8	13.8	∞
31	—	—	0.2	2.7	69.5
35	—	—	<0.1	0.4	4.9

solubilities in 95% ethanol are slightly less than those in acetone, and those in *n*-butanol are less than those in ethyl acetate.

In the case of methanol, 12-tricosanone in the liquid state is not miscible with the solvent over a considerable range of concentration. While this is also true

TABLE XI

SOLUBILITIES OF KETONES IN ISOPROPANOL

NO. OF C ATOMS	G. PER 100 G. ISOPROPANOL				
	10.0°	30.0°	50.0°	65.0°	82.3°
19	1.3	4.8	198	∞	∞
23	0.3	0.8	10.3	720	∞
27	<0.1	≈0.1	1.9	25.3	∞
31	—	—	≈0.1	5.0	2530
35	—	—	—	0.6	58

TABLE XII

SOLUBILITIES OF KETONES IN *n*-BUTANOL

NO. OF C ATOMS	G. PER 100 G. *n*-BUTANOL				
	10.0°	30.0°	50.0°	65.0°	80.0°
19	2.2	8.6	218	∞	∞
23	0.4	1.2	16.2	730	∞
27	<0.1	≈0.1	4.4	42.9	∞
31	—	<0.1	0.9	10.7	790
35	—	—	<0.1	1.8	106

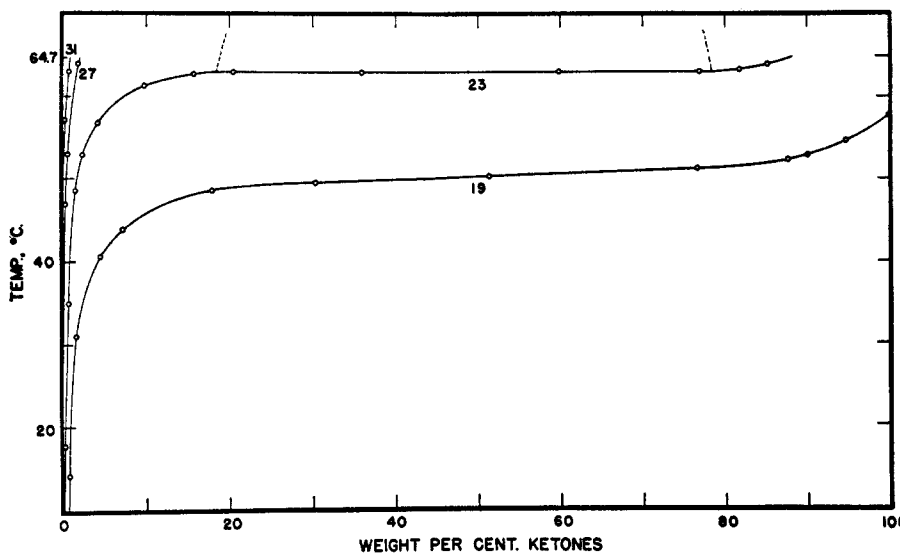

FIG. 8. SOLUBILITIES OF THE KETONES IN METHANOL

of the higher homologs in this solvent, the immiscible region exists above the boiling point of the solvent.

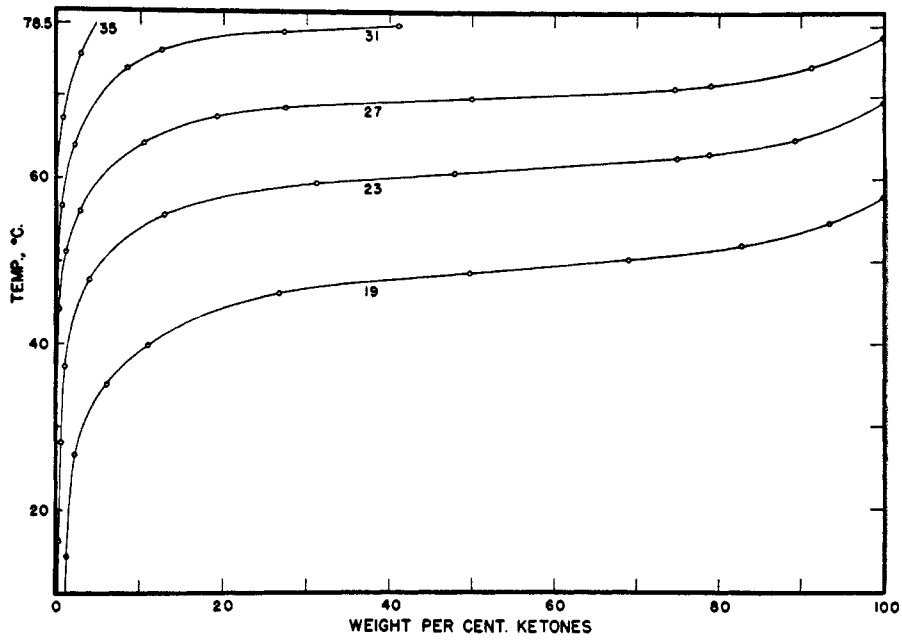

FIG. 9. SOLUBILITIES OF THE KETONES IN 95% ETHANOL

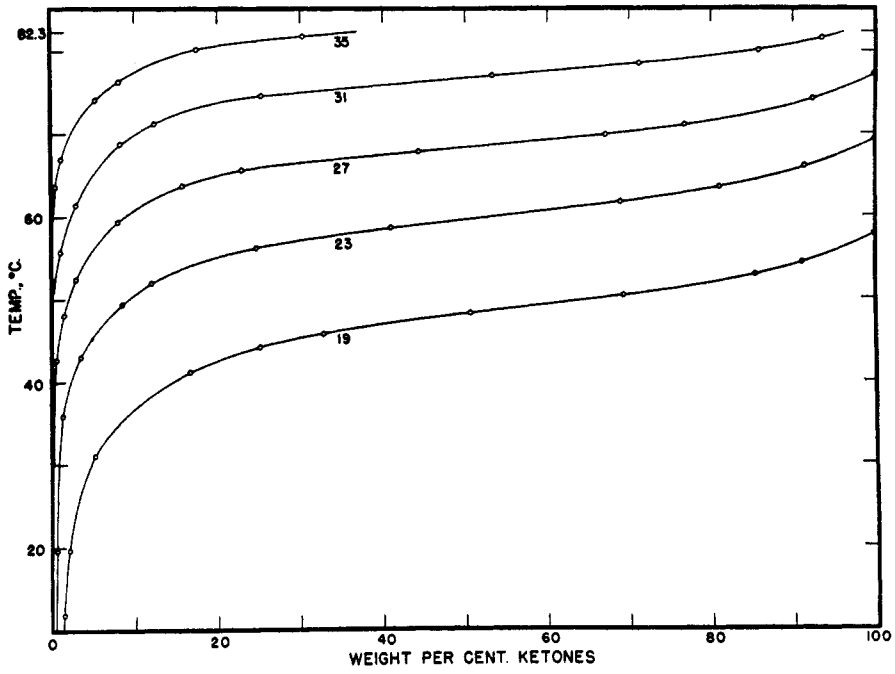

FIG. 10. SOLUBILITIES OF THE KETONES IN ISOPROPANOL

The behavior of the ketones in two other highly polar solvents is illustrated by their solubilities in nitroethane and in acetonitrile which are listed in Tables XIII and XIV, and are shown graphically in Figs. 12 and 13, respectively.

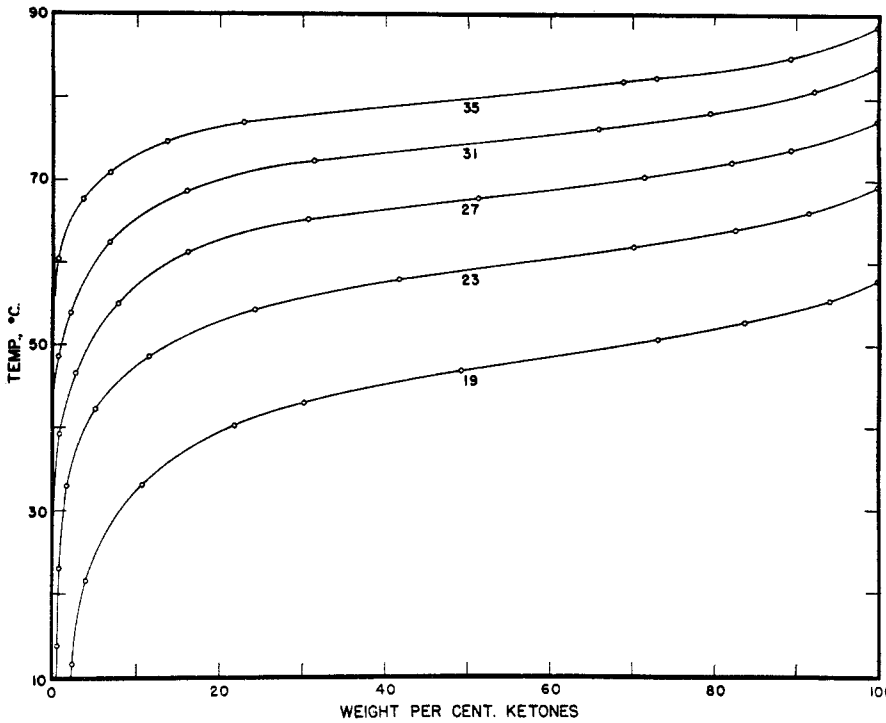

FIG. 11. SOLUBILITIES OF THE KETONES IN *n*-BUTANOL

TABLE XIII

SOLUBILITIES OF KETONES IN NITROETHANE

NO. OF C ATOMS	G. PER 100 G. NITROETHANE				
	20.0°	40.0°	50.0°	60.0°	80.0°
19	1.6	19.8	350	∞	∞
23	0.5	1.5	7.5	230	∞
27	≈0.1	0.2	0.9	5.6	∞
31	—	<0.1	0.2	1.0	965
35	—	—	<0.1	0.2	150

As would be expected, the solubilities of the ketones in nitroethane at any given temperature fall between the corresponding values in methanol and isopropanol, in accord with the respective polarities of these solvents.

The ketones are less soluble in acetonitrile than in any of the solvents investigated. Acetonitrile has the highest dielectric constant of any of the solvents used. The behavior is similar to that observed in methanol, since the liquid

ketones are immiscible with acetonitrile over a considerable range of concentration. In this range they exist as binary liquid systems, the conjugate solutions appearing over a greater range with increased molecular weight of the ketones.

In general, with increasing polarity of the solvent and increasing molecular weight of the ketones, the solution temperatures rise progressively more abruptly

TABLE XIV

SOLUBILITIES OF KETONES IN ACETONITRILE

NO. OF C ATOMS	G. PER 100 G. ACETONITRILE				
	10.0°	30.0°	50.0°	70.0°	82.0°
19[a]	0.8	1.6	27.0	∞	∞
23	<0.1	0.4	1.2	12.4	22.8
27	—	≈0.1	0.2	4.1	8.1
31	—	—	≈0.1	1.0	3.3
35	—	—	<0.1	0.2	1.1

[a] Completely miscible above 60.0° (see Fig. 13).

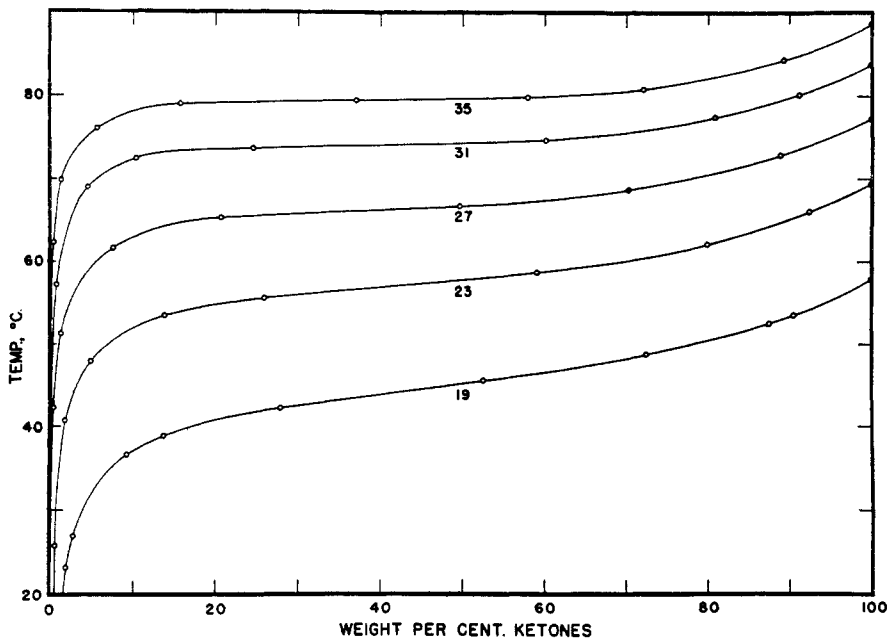

FIG. 12. SOLUBILITIES OF THE KETONES IN NITROETHANE

in the dilute ranges of concentration, while at higher concentrations the slopes of the curves become progressively less steep, until, as for methanol and acetonitrile, the curves are isotherms over considerable ranges of concentration.

The shape of these temperature-concentration curves is characteristic of a wide variety of high molecular weight aliphatic compounds. This characteristic

deviation from a linear relationship has been attributed to intermolecular association (23, 25, 26, 27) as indicated by the cryoscopic behavior of a number of long chain compounds in benzene.

The fact that the ketones enolize, demonstrated at least with several of the lower homologs (2, 3), indicates the existence of intermolecular association, which is further suggested by the appreciable polarity of the ketones (4–7). It has been suggested that the high dielectric constants of the ketones may be due to dipole-dipole couplings (8). However, it has been shown (9) that the ebullioscopic behavior of 14-heptacosanone and 16-hentriacontanone in hexane, cyclohexane, and benzene cannot be explained simply by the association of

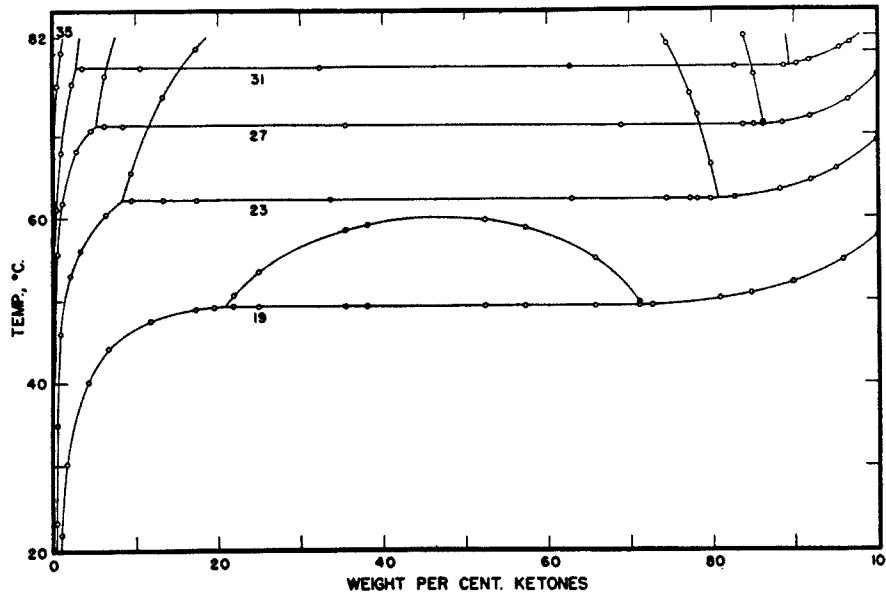

FIG. 13. THE KETONE SYSTEMS WITH ACETONITRILE

these compounds in solution. Hence, in addition to association of the ketones and association of the solvents, there are undoubtedly other factors affecting the solubility, such as association between the solvent and solute.

SUMMARY

The solubilities of 10-nonadecanone, 12-tricosanone, 14-heptacosanone, 16-hentriacontanone, and 18-pentatriacontanone have been determined in benzene, cyclohexane, tetrachloromethane, ethyl acetate, butyl acetate, acetone, 2-butanone, methanol, 95% ethanol, isopropanol, *n*-butanol, nitroethane, and acetonitrile.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

CHLORINE SUBSTITUTION PRODUCTS OF VERATRALDEHYDE, VERATRIC ACID, AND RELATED COMPOUNDS

L. CHAS. RAIFORD AND DON E. FLOYD

Received May 24, 1943

The monochloro substitution products of veratraldehyde were obtained by Raiford and Perry (1) by methylation of the corresponding halogen derivatives of vanillin, the structures of which had previously been established in this Laboratory (2). These aldehydes have now been oxidized by potassium permanganate into the corresponding veratric acids.

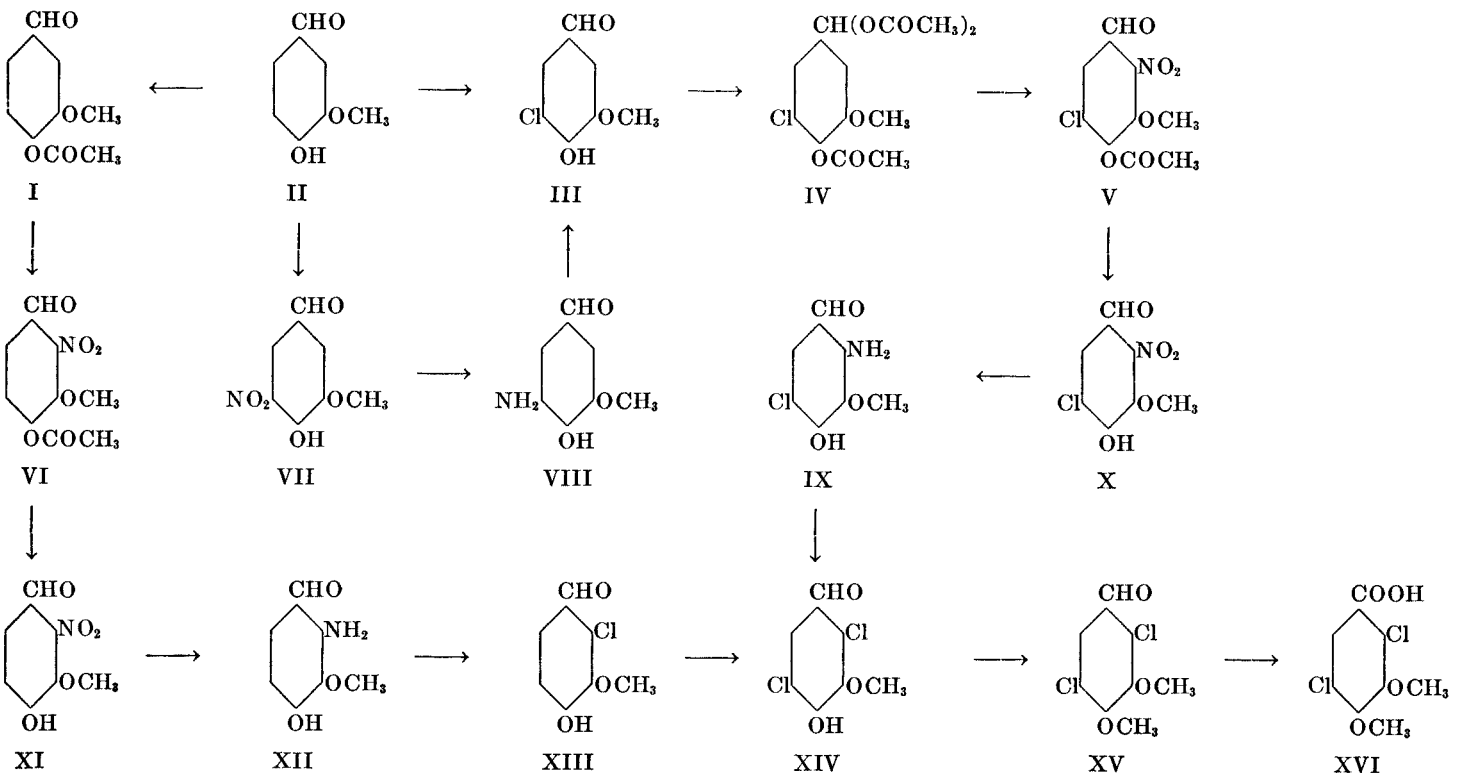
Examination of the literature shows that Feist, Awe, and Völksen (3) obtained in 1936 a compound they regarded as 2-chloroveratric acid and which was recorded as melting at 169°. However, this melting point is out of line when compared with the values obtained for the ortho halogenated substitution products of veratric acid studied by others. In this connection it should be noted that Zincke and Francke (4) prepared the three possible monobromoveratric acids, and called special attention to the fact that the relations between the numerical values of the melting points and the relative positions of the halogen atoms are significant. They found the lowest value for position 6 (COOH = 1), the next higher one for 5 and the highest, 201–202°, for 2. In repetition of Zincke's work in this Laboratory the same order was found (1), and reference to Table II will show that the values determined for the monochloro acids now reported places them in the order found for the bromine derivatives. The 2-chloro compound melts at 200–202°. In addition, only one of these values, that for the 6-isomeride, falls below 179–180°, the recorded melting point of the mother substance, veratric acid (5). Other facts, also, seem to suggest some uncertainty concerning the identity of the acid reported by Feist and co-workers. They did not prepare the remaining isomers of the series so that one could make the comparison emphasized by Zincke. In some preparations they used quite small quantities of starting materials, and they noted that certain reactions tested gave mixtures which might involve difficulty in separation and purification.

In extension of our work in this field it seemed of interest to examine further the chlorine substitution products of veratraldehyde and veratric acid. The method of preparation found satisfactory for the monochloro aldehydes, as indicated above, is that previously employed in the study of the monobromo compounds. Some of the dihalogenated derivatives were methylated with difficulty, or not at all, under the conditions of our experiments; consequently, in these cases, the desired products were obtained indirectly as shown below.

The structure of 2,5-dichloroveratric acid was fixed as follows. A monochlorovanillin previously obtained by Peratoner (6) and by Menke and Bentley (7), who did not orient the halogen atom, was later prepared and studied in more detail by Hann (8) who assumed, without proof, that it was the 5-chloro derivative (CHO = 1). Proof for this position was brought later by Raiford and

FIGURE 1

STRUCTURAL RELATIONS OF 2,5-DICHLOROVERATRIC ACID



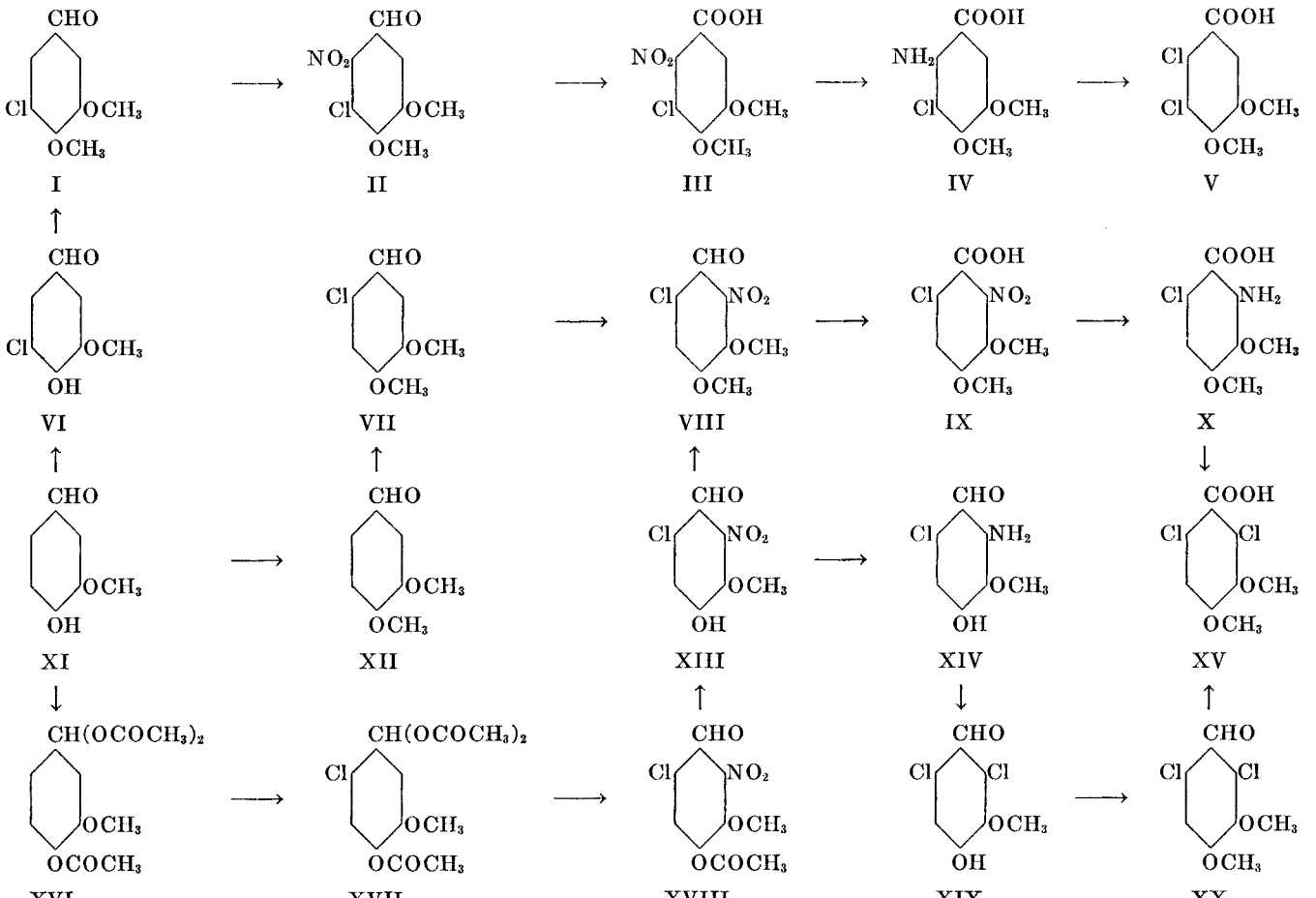
Lichty (9) and confirmed by Raiford and Wells (2). In one part of our work, the nitrovanillin which Vogl (10) proved to have the nitro radical in position 5 was reduced to the corresponding amine, VIII, Figure 1. This was diazotized and the resulting salt was converted by means of cuprous chloride into 5-chlorovanillin, III, which was found to be identical with the product prepared by Hann and others specified above. Heating a mixture of this compound, excess of acetic anhydride, and a few drops of sulfuric acid gave 3-methoxy-4-acetoxy-5-chlorobenzal diacetate, IV. Treatment of this product with fuming nitric acid at about 10° gave compound V, in which the nitro group must have entered position 2 or 6. The acetyl group at position 4 was removed by alkaline hydrolysis and the resulting nitrochlorovanillin, X, was reduced to the corresponding amine IX. Replacement of the amino radical by the method specified above gave the dichlorovanillin XIV.

To determine the position occupied by the second chlorine atom, which is also that taken by the nitro radical in the nitration of IV, compound XIV was prepared from a different starting material. Acetylvanillin was converted by nitration into Pschorr and Sumuleanu's (11) nitrovanillin XI. To fix the position of the nitro radical in that product they methylated the exposed hydroxyl and oxidized the resulting nitroveratraldehyde by potassium permanganate into the related nitroveratric acid. The nitro group was reduced, the resulting amine was diazotized, and the salt was converted by means of cuprous cyanide into the corresponding nitrile. By hydrolysis of the latter they obtained hemipinic acid, 3,4-dimethoxy-*o*-phthalic acid. From this it follows that the amino compound XII, m.p. 127° (12) used in the present work, previously prepared by Sumuleanu (13) who reported 128–129°, and further characterized by Pschorr (14), is 2-aminovanillin. This product was converted by the method indicated above into 2-chlorovanillin, XIII, and direct chlorination of the latter (9) gave compound XIV, which must be the 2,5-dichloro derivative. Methylation of this substance gave the related veratraldehyde XV, which was oxidized by potassium permanganate to 2,5-dichloroveratric acid XVI, m.p. 164–165°. The methyl ester of this compound was found to be a liquid that boiled at 185–187°/5 mm. while that obtained from Mazzara's supposed 2,5-acid (see below) is a solid.

The only dichloroveratric acid found in the literature is recorded by Beilstein (15a) as having at least one of the chlorine atoms in an unknown position. This compound was obtained by Mazzara (16), who treated an ether solution of the methyl ester of protocatechuic acid, previously obtained by Matsmoto (17), with two molecular proportions of sulfuryl chloride, and isolated two dichloro esters, recorded as the 2(?),5- and 5,6(?)-dichloro compounds with melting points of 105° and 223–225°, respectively (15a). Hydrolysis of these esters with caustic potash gave the corresponding protocatechuic acids, m.p. 220° and 239°, with decomposition. By heating a mixture of the higher-melting acid, methanol, methyl iodide, and caustic potash in a sealed tube for 20 hourc at 120°, Mazzara obtained a product that gave a satisfactory C and H analysis for the methyl ester of a dichloroveratric acid. This product melted at 95–96°, and hydrolysis of it with aqueous potash gave an acid, m.p. 182–183°, that was not analyzed

FIGURE 2

STRUCTURAL RELATIONS OF 5,6- AND 2,6-DICHLOROVERATRIC ACIDS



and which was not further characterized by the author except to convert it back into the ester from which it was originally obtained. As support for the suggested position for the second halogen atom in this acid, Mazzara called attention to the fact that the melting point of his product coincided closely with that of the related dibromoveratric acid, m.p. 182°, previously prepared by Boyen (18) (Mazzara records "Royen"), and for which Boyen suggested no structure. Richter (19) listed Boyen's acid as having the halogen atoms in unknown positions. It is true that the current edition of Beilstein (15b) records this product as a 2,5-dibromo compound, but Raiford and Perry (1) have recently shown that these positions were assigned on the basis of insufficient evidence, that this acid melts at 186–187°, and is a 5,6-dibromo derivative.

To establish the structure of Mazzara's acid, 5-chloroveratraldehyde I, Figure 2, was converted by treatment with fuming nitric acid into a mononitro compound, II, m.p. 122–123°, in which the nitro group must have entered position 2 or 6, and which was characterized by conversion into a number of derivatives. It was oxidized by potassium permanganate into the related nitrocarboxylic acid III. This was reduced to the amine, which was then converted, as indicated above, into the dichloroveratric acid, m.p. 186–187°. A mixture of this acid and that of m.p. 164–165°, described above and proved to be the 2,5-dichloro derivative, melted over a range of 145–150°. The one here under consideration must therefore be the 5,6- compound. It was identified with Mazzara's acid by converting it into the methyl ester which was obtained in the form of long colorless needles that melted at 95–96°, as he reported.

The third dichloroveratric acid required by theory, the 2,6-derivative, is related to a new nitrochloroveratraldehyde, VIII, m.p. 101–102°. This compound is different from II and was obtained by two routes. First, in agreement with the observations of Raiford and Ravely (20) to the effect that the alkoxyl radical directs more strongly to the para than to the ortho position, it was found that chlorination of veratraldehyde, XII, gave product VII, which was isomeric with, but different from I, that had been obtained by methylation of 5-chlorovanillin. Nitration of this new chloroveratraldehyde gave compound VIII, which was carried through the changes indicated in Figure 2 to give a dichloroveratic acid, XV, that should be the 2,6-derivative.

By the second route, the monochloro compound XVII, obtained by chlorination (9) of 3-methoxy-4-acetoxybenzal diacetate (21), was converted by fuming nitric acid, and subsequent removal of acetyl, into a chloronitro compound XIII, in which the nitro group must have entered position 2 or 5. But 5 is excluded here, because product XIII was converted by two routes, as shown, into acid XV which is quite different from Mazzara's acid that was proved above to be the 5,6-dichloro compound.

2,5,6-Trichloroveratric acid was obtained by oxidation of the related veratraldehyde which was prepared by methylation of the known trichlorovanillin (9).

EXPERIMENTAL

In general, the compounds listed in the tables were prepared by standard methods. To avoid repetition details have been given for the preparation of four derivatives, repre-

TABLE I

VERATRALDEHYDE SUBSTITUTION PRODUCTS

SUBSTITUENTS	YIELD, %[a]	SOLVENT	CRYSTAL FORM	M.P.° C.	FORMULA	HAL. ANALYSES, %	
						Calc'd	Found
2-Amino-6-bromo-	60*	Dil. ethanol	Orange needles	101	$C_9H_{10}BrNO_3$	30.77	30.54
2,6-Dibromo-	74	Dil. ethanol	Colorless needles	137	$C_9H_8Br_2O_3$	49.38	49.42
2-Bromo-5-chloro-	58	Ligroin (60–70°)	Colorless needles	62–63	$C_9H_8BrClO_3$	41.32	41.51
5-Bromo-6-chloro-	26	Dil. ethanol	Colorless needles	127–128	$C_9H_8BrClO_3$	41.32	41.46
2-Chloro-5-bromo-	61	Ligroin (60–70°)	Colorless needles	51–52	$C_9H_8BrClO_3$	41.32	41.39
5-Chloro-6-bromo-	28	Ligroin (60–70°)	Colorless needles	119–120	$C_9H_8BrClO_3$	41.32	41.26
2,5,6-Tribromo-	27	Dil. ethanol	Colorless needles	129–130	$C_9H_7Br_3O_3$	59.55	59.74
2-Nitro-5-chloro-	47	Dil. ethanol	Fine needles	51–52	$C_9H_8ClNO_5$	14.45	14.38
2-Nitro-6-chloro-	67	Ethanol	Yellow needles	101–102	$C_9H_8ClNO_5$	14.45	14.61
5-Chloro-6-nitro-	90*	Dil. acetic acid	Yellow needles	122–123	$C_9H_8ClNO_5$	14.45	13.70
2,5-Dichloro-	38	Ligroin (35–40°)	Colorless needles	55	$C_9H_8Cl_2O_3$	30.21	30.29
2,6-Dichloro-	60	Methanol	Colorless needles	119–120	$C_9H_8Cl_2O_3$	30.21	30.14
2,5,6-Trichloro-	42	Ligroin (60–70°)	Colorless needles	94–95	$C_9H_7Cl_3O_3$	39.51	39.59
5-Iodo-	76	Ethanol (70%)	Nearly colorless needles	72–73	$C_9H_9IO_3$	43.49	43.21

[a] Figures refer to purified materials, except when starred.

TABLE II

VERATRIC ACID SUBSTITUTION PRODUCTS

SUBSTITUENTS	YIELD, %	SOLVENT	CRYSTAL FORM	M.P. °C.	FORMULA	HALOGEN ANALYSES, %	
						Calc'd	Found
2-Chloro-	87	Acetic acid	Colorless feathers	200–202	$C_9H_9ClO_4$	16.39	16.14
5-Chloro-	90	Dil. acetic acid	Colorless needles	189–190	$C_9H_9ClO_4$	16.39	16.67
6-Chloro-	85	Dil. acetic acid	Nearly colorless needles	175–176	$C_9H_9ClO_4$	16.39	16.18
2-Amino-6-chloro-	66*	Dil. ethanol	Nearly colorless flakes	163–165	$C_9H_{10}ClNO_4$	15.33	15.50
2,5-Dichloro-	90	Dil. ethanol	Colorless needles	164–165	$C_9H_8Cl_2O_4$	28.28	28.36
2,6-Dichloro-	63	Dil. ethanol	Colorless needles	115	$C_9H_8Cl_2O_4$	28.28	28.20
5,6-Dichloro-	74	Dil. acetic acid	Slightly colored needles	186–187	$C_9H_8Cl_2O_4$	28.28	28.35
2,5,6-Trichloro-	93	Dil. ethanol	Colorless needles	123–124	$C_9H_7Cl_3O_4$	37.30	37.17
2-Bromo-5-chloro-	92	Water	Colorless needles	175–176	$C_9H_8BrClO_4$	39.08	39.20
2-Chloro-5-bromo-	93	Dil. ethanol	Colorless needles	183–184	$C_9H_8BrClO_4$	39.08	39.10
5-Bromo-6-chloro-	92	Dil. ethanol	Colorless needles	189–190	$C_9H_8BrClO_4$	39.08	39.18
5-Chloro-6-bromo-	94	Dil. ethanol	Colorless needles	178–179	$C_9H_8BrClO_4$	39.08	39.11
2,5,6-Tribromo-	74	Dil. ethanol	Colorless needles	169–170	$C_9H_7Br_3O_4$	57.28	57.48
2-Nitro-5-chloro-	75	Ethanol (30%)	Nearly colorless needles	179–180	$C_9H_8ClNO_6$	13.57	13.53
2-Nitro-6-chloro-	68	Dil. ethanol	Nearly colorless prisms	192–193	$C_9H_8ClNO_6$	13.57	13.44
5-Chloro-6-nitro-	90*	Ethanol (40%)	Nearly colorless needles	190–191	$C_9H_8ClNO_6$	13.57	13.61
5-Chloro-6-amino	70*	Dil. ethanol	Tan leaflets	188–189	$C_9H_{10}ClNO_4$	15.33	15.51
2-Nitro-6-bromo-	88	Dil. ethanol	Colorless flakes	198–199	$C_9H_8BrNO_6$	26.14	26.27
2-Amino-6-bromo-	84*	Water	Colorless needles	182	$C_9H_{10}BrNO_4$	28.98	29.09
5-Iodo-	76	Acetic acid, 70%	Colorless needles	184–185	$C_9H_9IO_4$	41.36	40.99

* Refers to crude yield; other figures indicate purified material.

senting a methylation, a halogenation, a nitration, and an oxidation. Related compounds were obtained by following these methods with slight variations required in individual cases.

2,5,6-Tribromoveratraldehyde. Five grams of the related tribromovanillin, prepared as directed by Raiford and Stoesser (22), was mixed with 100 cc. of water containing 20 g. of sodium bicarbonate, the mixture was warmed to about 70°, 5 cc. of dimethyl sulfate was added, the whole was stirred for an hour, and filtered. The filtrate was treated with dimethyl sulfate as before, the resulting solid was collected, and the total product was purified by crystallization from a suitable solvent. Analytical data and other properties for this and related aldehydes prepared in a similar way are given in Table I. This method of alkylation was used in several instances, though caustic alkali in place of bicarbonate was more suitable in some cases.

6-Chloroveratraldehyde. Fifty grams of veratraldehyde, prepared according to directions of Barger and Silberschmidt (23), was dissolved in about 75 cc. of chloroform, the liquid was placed in a three-necked flask fitted with a mechanical stirrer and a return condenser, and while the temperature was held at 40–50° chlorine was passed in as long as solid separated. Nitrogen was then bubbled through the mixture to sweep out chlorine and hydrogen chloride, and the solid was collected. Concentration of the filtrate gave more of the product. The total yield was 86%. Crystallization from absolute ethanol gave colorless needles that melted at 144°. This compound, previously prepared by Raiford and Perry (1) in a different way, was found to melt at 141°. A mixed melting point determination of these products showed no depression.

2-Nitro-6-chloroveratraldehyde. Thirty grams of the required chloroaldehyde was added slowly, in small portions and with vigorous shaking, to 120 g. of fuming nitric acid which was held between 0 and 10°. The resulting deep red solution was kept below 10° for fifteen minutes longer, and then poured into about three volumes of cracked ice, and the mixture allowed to stand for an hour to precipitate the product. Crystallization from ethanol gave a 70% yield of pale yellow needles that melted at 101–102°. This product was also obtained by methylation of 2-nitro-6-chlorovanillin (9) by the method described above. Analytical data are given in Table I.

2-Nitro-6-chloroveratric acid. A hot 5% solution of potassium permanganate was added very slowly and with vigorous shaking to a warm (50–60°) solution of 10 g. of the required aldehyde in 60 cc. of pyridine until a faint purple tinge remained, the color was discharged by sodium bisulfite, the mixture was filtered, the filtrate was evaporated to half its volume, and concentrated hydrochloric acid was added. The solid obtained crystallized from dilute ethanol in nearly colorless prisms that melted at 192–193°. The yield of purified product was 68%. Analytical data for this and related compounds are given in Table II.

SUMMARY

1. The monochloroveratraldehydes demanded by theory were previously prepared in this Laboratory by alkylation of the corresponding substitution products of vanillin. These aldehydes have now been converted by oxidation with potassium permanganate into the related veratric acids. It is significant that the relations between the numerical values of the melting points and the positions of halogen in these compounds are of the same order as that previously found for the bromine derivatives.

2. The structures of the dichloro acids have been established by relating them to the required vanillin substitution products in which the halogen atoms have previously been oriented. The only known dichloroveratric acid, that recorded by Mazzara, has been shown to be the 5,6-dichloro compound.

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CONSIDERATION OF GENERAL METHODS FOR THE FORMATION OF KETENES

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Ketene is best made by pyrolysis of acetone, but this is a specific method, since other ketenes are not suitably made by pyrolysis of other ketones. Similarly, the type of reaction represented by the conversion of azibenzil into diphenylketene is not general. Pyrolysis of N-dialkyl- (or N-diaryl-) phthalimides is a satisfactory means of making disubstituted ketenes but, since pyrolysis of N-alkylphthalimides fails to yield monosubstituted ketenes, this method also lacks general application (1).

One method, and the only method, which has been quoted as having general application is the action of zinc on 2-bromoalkanoyl bromides:

$$R_2CBrCOBr + Zn \longrightarrow R_2{=}C{=}C{=}O + ZnBr_2$$

Unquestionably, this method works well for disubstituted ketenes. The steps are simple and the yields are good. When applied to the synthesis of ketene or monosubstituted ketenes a different situation is observed. The yields of ketene reported by Staudinger and Kubinsky (2) by the action of zinc on bromoacetyl bromide, bromoacetyl chloride, chloroacetyl bromide, and chloroacetyl chloride, respectively, were 12, 3.7, 0, and 0%. One cannot doubt that Staudinger was dealing with ketene in the first two of these experiments since the reaction product was stated to yield acetanilide on reaction with aniline, and since its physical constants (3) were determined: m.p. −151°; b.p. −56°. More recent work (4) gives higher values for both properties: m.p. −134.6°; b.p. −41°, but the order of magnitude is reasonable. This method has been reported also (5) for the preparation of methylketene, ethylketene, and phenylketene from α-bromopropionyl bromide, α-bromo-*n*-butyryl bromide and phenylchloroacetyl chloride, respectively. These ketenes were obtained only in dilute solution in ether and in small yields (4 to 13%). They have never been isolated as such.

The purpose of the present work was to study this reaction to see how general it was for the formation of ketene or monosubstituted ketenes. We repeatedly carried out Staudinger and Klever's directions (3) for the preparation of ketene from zinc shavings and bromoacetyl bromide in ether but in no experiment were we able to detect any ketene. They collected a weak ether solution of ketene and later treated it with aniline. Failing to obtain any acetanilide by this method, we passed the reaction products directly into aniline. Here again, no acetanilide was found but instead a considerable quantity of aniline hydrobromide. From a synthetic mixture, made up by dissolving aniline hydrobromide and 2% of acetanilide in the same quantity of aniline as that used in the run itself, no difficulty was experienced in detecting the acetanilide. No more than a 2% yield of ketene could have been formed, therefore, and more

likely there was none at all. Staudinger and Klever reported a 12% yield and made no mention of hydrogen bromide in the reaction products. No suggestion is apparent to explain the discrepancy in results but evidently Staudinger and collaborators had some hidden factor at hand. Until this is discovered and made controllable, it seems evident that the reaction should be removed from the list of methods for the production of ketene.

Staudinger's yields were low and he mentioned that this low yield might be caused by condensation of the acid halide by the zinc bromide. He did not identify any of the condensation products. We extracted the non-volatile reaction product with ether. It reacted vigorously with ammonia to yield an amide which, in turn, reacted with bromine to yield tribromoacetoacetamide. These steps seem plausible but no assurance of the position of the halogens is implied in these formulas:

$$2BrCH_2COBr \xrightarrow{ZnBr_2} BrCH_2COCHBrCOBr\ (I) + HBr$$

$$I + 2NH_3 \longrightarrow BrCH_2COCHBrCONH_2\ (II) + NH_4Br$$

$$II + Br_2 \longrightarrow BrCH_2COCBr_2CONH_2\ (III) + HBr$$

III could also be formed by reaction of Br_2 + $BrCH_2COCH_2CONH_2$ (IV). The acid bromide corresponding to IV could be visualized as coming from bromoacetyl bromide and zinc by way of a modified Reformatzky reaction. Structure I might rearrange to $Br_2CHCOCH_2COBr$ for it is known that $CH_3COCHBrCOOC_2H_5$ rearranges to $BrCH_2COCH_2COOC_2H_5$ and that $CH_3COCHBrCOBr$ rearranges to $BrCH_2COCH_2COBr$ (7).

Both ethyl acetate and ethyl bromoacetate were isolated in small yields. To explain their formation it may be assumed that acetyl bromide (from ketene and hydrogen bromide) and bromoacetyl bromide reacted with ethanol which, in turn, was formed by action of hydrogen bromide on ethyl ether.

Powdered zinc or zinc shavings did not react with pure bromoacetyl bromide at room temperature, but a vigorous reaction started as soon as absolute ether was added. In a vapor phase process wherein the vapor of the acid bromide was passed over zinc shavings at 200° very little reaction took place. At 300°, however, reaction occurred but again hydrogen bromide was the only volatile product.

Since the probable reason for the absence of ketene in these experiments was the high catalytic activity of zinc bromide, it seemed apparent that if ketene could be made by the action of sodium on bromoacetyl bromide it could be preserved because of the non-catalytic nature of sodium bromide. Staudinger and Klever, who reported the non-formation of ketene from these reagents in the presence of ether as solvent, did not try the reaction at higher temperatures and in the absence of ether. We found non-reaction, however, between bromoacetyl bromide and molten sodium.

Copper-bronze (with ether) was another metal tried. Reaction was slower than with zinc but here again the only volatile product was hydrogen bromide.

Several other related reactions were tested in the hope of obtaining ketene. One such was the reaction of zinc and ethyl chloroacetate. Some hydrogen

chloride was evolved, but no ketene. Another was the reaction of zinc and 2-acetoxypropionyl bromide, in which reaction hydrogen bromide was liberated but no methylketene.

Summerbell and Umhoefer (6) found that a solution of the binary system of magnesium and magnesium iodide in butyl ether was a dehalogenating agent towards 2,3-dichlorodioxane and 2,3,5,6-tetrachlorodioxane. We found that this reagent brought about an exothermic reaction with chloroacetyl chloride. Iodine was liberated but there was no evidence for ketene. Bromoacetyl bromide reacted less vigorously, but otherwise the results were similar.

When a solution of sodium iodide in acetone was mixed with chloroacetyl chloride, heat was evolved and iodine was liberated. No ketene escaped as a volatile product. It may be concluded, therefore, that no general method of synthesis is known which may be relied on for the production of ketene or monosubstituted ketenes.

EXPERIMENTAL PART

Bromoacetyl bromide and zinc. A 3-necked flask was fitted with an inlet tube for an inert gas (hydrogen or nitrogen, dried by calcium chloride), a dropping-funnel for addition of the acid bromide, and a delivery tube to conduct the escaping gases below the surface of aniline in an Erlenmeyer flask. In some experiments undiluted bromoacetyl bromide was used and in others the acid bromide was diluted with absolute ether prior to use. Data for several representative runs are presented in Table I.

Search for acetanilide and characterization of aniline hydrobromide. The ether was distilled from the aniline and a 5-fold volume of benzene was added to the aniline. A salt separated, which was collected on a filter and identified as aniline hydrobromide in this manner. (a) It was insoluble in benzene or ether but soluble in water. (b) A yellow oil formed on top of the water solution when sodium hydroxide solution was added. (c) It did not melt up to 260°. (d) Bromine water reacted with the water solution forming tribromoaniline, m.p. 119°. (e) Silver nitrate solution gave rise to silver bromide.

The benzene and aniline were distilled to a temperature of about 260°. About 0.5 g. of solid remained. It was aniline hydrobromide. No acetanilide could be found in it.

Products in the reaction mixture. The reaction mixture was a brown, viscous mass. Such a product, obtained from 40 g. of bromoacetyl bromide in 160 cc. of ether on 30 g. of zinc shavings, was extracted with 40–50 cc. of ether. This extract was treated with 20 cc. of conc'd ammonium hydroxide, after which the mixture was made acidic with sulfuric acid. The solution was concentrated somewhat, then was treated with an excess of bromine water. A white precipitate of tribromoacetoacetamide separated and it was recrystallized from 5 cc. of a 1:1 alcohol and water solution; m.p. 118°, weight, 0.5 g.

Anal. Calc'd for $C_4H_4Br_3NO_2$: Br, 70.9; mol. wt. 338.

Found: Br, 71.6; mol. wt., 350 ± 15.

Evidence that ethyl acetate and ethyl bromoacetate were reaction products was obtained in another identical run (from 40 g. of bromoacetyl bromide). The ether extract of the reaction mixture was poured into 50 cc. of 1 *N* ammonium hydroxide and mixed well. The ether layer was separated and the water layer extracted twice with 20-cc. portions of ether. The combined ether solutions were dried over calcium chloride and distilled. About 0.5 cc. of ethyl acetate was collected: b.p. 73–75°, d_{20}^{20} 0.895, n_D^{20} 1.3720. About 1 cc. of ethyl bromoacetate was collected at 155°: d_{22}^{22} 1.49, n_D^{22} 1.4527, lachrymatory, insoluble in water. It contained 48.1% Br (Calc'd Br, 47.8).

Reaction of bromoacetyl bromide and zinc in the vapor phase. The delivery tube of a 50-cc. Claisen flask was attached to a Pyrex tube, 30 x 4 cm. One neck of the Claisen flask was

fitted with a tube for passing nitrogen through the apparatus, and the other neck was closed. A piece of wire gauze was wrapped around the Pyrex tube so that it could be heated fairly uniformly by two Bunsen burners with wing tops. A 350° thermometer was also fitted into the Pyrex tube from the same end as the delivery tube of the Claisen flask. The Pyrex tube was filled with zinc shavings and was connected downward to the neck of the second Claisen flask. The other neck of this Claisen flask was connected upward to a short reflux condenser. The delivery tube of the second Claisen was closed or sealed. The top of the condenser was connected by a short glass tube to a U-tube containing aniline.

Thirty grams of bromoacetyl bromide was distilled from the first Claisen flask over the heated zinc. A stream of nitrogen swept any products and unreacted acid bromide from the reaction tube into the second Claisen and up the condenser. Any liquids were condensed and drained back into the second Claisen flask, while the gases went through the U-tube containing aniline.

TABLE I

BROMOACETYL BROMIDE AND ZINC

RUN	$BrCH_2COBr$, G.	ETHER, CC.	Zn, G. (SHAVINGS, S.) (POWDER, P.)	INERT GAS	TEMP.	$C_6H_5NH_3Br$, G.
1	15	60	10 s	H_2	(a)	0.5
2	15	60	10 p	H_2	(a)	—
3	15	60	10 s	—	(a)	0.4
4	20	20	10 s (b)	H_2	(c)	0.1
5	20	100	10 s	—	(d)	5.0
6	12	100	10 p	N_2	(c)	1.0
7	5	0	2 p or s	—	0°	(e)
8	5	0	2 p or s	—	20°	(f)

(a) Oil-bath at 60° until reaction started, then removed. The reaction lasted 15 min.

(b) This more concentrated ether solution formed a tarry mass almost as soon as it touched the zinc.

(c) Reaction started at room temperature and distillation temperature was soon reached.

(d) Bath temp. of 70–80° was maintained throughout, thereby forcing a rapid distillation of the ether.

(e) No reaction whatsoever.

(f) No reaction until 5 cc. of ether was added. Then the mixture slowly warmed and finally reacted vigorously.

When the reaction tube was heated to 200°, 27–28 g. of the acid bromide was recovered and the zinc appeared unaffected. No reaction product was found in the aniline. At 300°, the reaction was much greater, as shown by a brown coating which formed on the zinc, but 0.5 g. of aniline hydrobromide was the only compound found in the aniline.

Bromoacetyl Bromide and Metals other than Zinc

Copper-bronze. The conditions of run 1, Table I, were maintained except that 12 g. of copper-bronze powder was substituted for the zinc shavings. Reaction was slower than with the zinc but the products were the same. No acetanilide was found but 0.5 g. of aniline hydrobromide was isolated.

Sodium. A small clean piece (about the size of a pea) of sodium and 2 cc. of pure bromoacetyl bromide were heated to the boiling point of the acid bromide with practically no reaction. Bubbles did form very slowly on the molten sodium but there was no vigorous reaction. Sodium did not react any faster in a concentrated ether solution of the acid

bromide. Fifteen grams of bromoacetyl bromide in 50 cc. of ether was refluxed for several hours with 10 g. of sodium wire. A slow reaction took place, giving the solution a muddy color. Any gases coming from the reflux condenser were passed through aniline. A little aniline hydrobromide (about 0.1 g.) was found. The products in the flask were not identified.

Magnesium. A few magnesium turnings (about 0.3 g.) were put into 2 cc. of pure bromoacetyl bromide and heated to the boiling point of the bromoacetyl bromide without any reaction taking place. When 3 cc. of ether was added to the mixture, a slow reaction occurred, which was evidenced by slow evolution of a gas.

Magnesium and iodine, the binary system of "Mg + MgI_2". Ten grams of magnesium turnings was placed in a liter flask and dried therein by heating in a stream of dry nitrogen. After it had cooled, 100 cc. of dry ethyl ether was added. Then 13 g. of iodine was added in portions. The mixture was stirred mechanically until the red color of the iodine disappeared. The ether solution was decanted from the unused magnesium into a dropping-funnel. In another dropping-funnel was placed 14 g. of bromoacetyl bromide and 50 cc. of ethyl ether. The mixtures in the two dropping-funnels were delivered gradually and simultaneously beneath the surface of 20 cc. of ether. Vigorous stirring was maintained. Iodine was liberated slowly. Any gaseous products, together with ether, were conducted into an aniline trap with the aid of a slow stream of nitrogen and gentle suction. No acetanilide was found on working up the aniline.

Other Reactions

Ethyl chloroacetate and zinc. A refluxing mixture of 12 g. of ethyl chloroacetate, 35 cc. of butyl acetate, and 15 g. of powdered zinc reacted rapidly after an induction period of about ten minutes. Any effluent gas was conducted into aniline. The absence of ketene was demonstrated by the non-formation of acetanilide.

When isopropyl ether was used as a solvent, no reaction occurred on refluxing until most of the ether had been distilled off (bath temperature, 100°). The reaction then gave rise to hydrogen chloride as judged by the isolation of 3 g. of aniline hydrochloride (from 17 g. of the chloro ester), but no acetanilide. Zinc shavings did not react with ethyl chloroacetate, hence the use of zinc powder.

Chloroacetyl chloride and "Mg + MgI_2". Details of this reaction followed those described above with bromoacetyl bromide. The reaction was more vigorous, but otherwise was similar. In a run using 12 g. of chloroacetyl chloride there was considerable heat of reaction and iodine was liberated. No acetanilide was obtained from the aniline trap. The same formation of iodine but not ketene was observed at a reaction temperature of −10° or +140°. In the latter experiment butyl ether was used instead of ethyl ether.

Chloroacetyl chloride and sodium iodide. To a solution of 30 g. of sodium iodide in 100 cc. of dry acetone was added slowly a mixture of 16 g. of chloroacetyl chloride in 50 cc. of acetone. There was heat of reaction and the solution was refluxed for thirty minutes. Any evolved gas was conducted through aniline, but no acetanilide was found on working it up. Iodine was formed in the reaction flask.

2-Acetoxypropinonyl bromide and zinc. The acid bromide was made from 2-acetoxypropionic acid by reaction with phosphorus tribromide at 60°. Distillation at reduced pressure (56–60° at 21 mm.) was followed by fractionation at atmospheric pressure. The fraction which boiled at 160° was used.

Addition of 35 g. of 2-acetoxypropionyl bromide in 75 cc. of ether during one hour to a vigorously stirred mixture of 35 g. of zinc dust and 75 cc. of ether was accompanied by warming. A slow stream of nitrogen was maintained. A condenser and receiver were attached to the flask, followed by an aniline trap. About 10 cc. of liquid was condensed in the receiver. The addition of aniline yielded aniline hydrobromide which was precipitated by addition of benzene. No propionanilide was found here or in the aniline trap, hence there was no evidence for methylketene.

SUMMARY

The reaction of zinc and bromoacetyl bromide has been carried out under a variety of conditions without obtaining any evidence for the production of ketene. These products were characterized as reaction products: hydrogen bromide, ethyl acetate, ethyl bromoacetate, and dibromoacetoacetyl bromide. The last of these compounds was converted to tribromoacetoacetamide.

Copper-bronze also gave rise to hydrogen bromide but no ketene. Zinc and ethyl chloroacetate yielded hydrogen chloride without ketene. Likewise, methylketene was not obtained from 2-acetoxypropionyl bromide but hydrogen bromide was produced. When sodium iodide or the binary system "magnesium plus magnesium iodide" reacted with chloroacetyl chloride or bromoacetyl bromide, iodine was liberated but no ketene was formed. Molten sodium was surprisingly indifferent towards bromoacetyl bromide.

To date there is no satisfactory method for the preparation of monosubstituted ketenes.

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THE DIENE SYNTHESIS WITH β-NITROSTYRENE

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Our work on the use of β-nitrostyrene in the diene synthesis, interrupted on account of the illness of one of the authors, was recorded in a preliminary note a few years ago (1). It has since been concluded as time permitted, and is described in this paper.

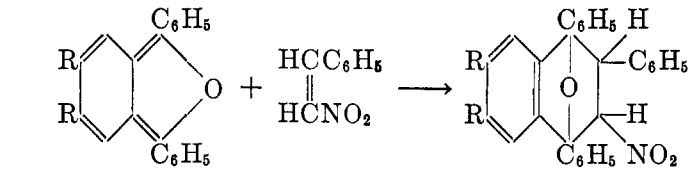
β-Nitrostyrene added readily to butadiene, isoprene, 2,3-dimethylbutadiene, 2,3-diphenylbutadiene, 1,4-diphenylbutadiene, phellandrene, cyclopentadiene, cyclohexadiene, 1,3-diphenylisobenzofuran, and 1,3-diphenyl-5,6-dimethylisobenzofuran. While it gave an addition product with 2,5-dimethyl-3,4-diphenylcyclopentadienone (2), secondary products were isolated from tetraphenylcyclopentadienone and methyleneanthrone; the latter gave *Bz*-1-phenylbenzanthrone, and the tetraphenylketone gave pentaphenylbenzene. It is very interesting to note that although it did not appear to enter into reaction with simple furans (1), it formed addition products very easily with isobenzofurans.

The addition and reactions used to prove the structure are conveniently illustrated by 1,3-diphenylisobenzofuran (I, R = H) and (a) nitrostyrene, and (b) styrene. Both of the addition products (II, III) were readily dehydrated by hydrogen bromide in acetic acid to give naphthalene derivatives, (IV, VI). The nitro compounds were reduced to the corresponding amines, (V), which, upon diazotization with butyl nitrite in acetic acid and reduction by alcohol, gave the same triphenylnaphthalenes, (VI), as were secured from the styrene addition products (III). The hydrocarbon, 1,2,4-triphenylnaphthalene, has been described in the recent literature (3); the properties agree in all respects.

The same reactions were carried through with 1,3-diphenyl-5,6-dimethylisobenzofuran (I, R = CH_3); it was converted into 1,2,4-triphenyl-6,7-dimethylnaphthalene (VI, R = CH_3). These results show that the diene synthesis has taken place in normal fashion. The reactions afford a convenient method for the synthesis of polysubstituted naphthalene derivatives.

Additional evidence supporting the conclusion that the reaction has taken place in the manner expected is afforded by the production of *Bz*-1-phenylbenzanthrone from the addition product secured by the use of methyleneanthrone (VII–IX), and of pentaphenylbenzene (X), from the interaction with tetraphenylcyclopentadienone. In this last instance, the loss of carbon monoxide from the addition product is in accord with the behavior of the dimethyl homolog (2).

The aliphatic dienes gave derivatives of tetrahydrobiphenyl (XI). These exhibit the characteristic properties of such structures; thus, they dissolve in alkaline solutions by virtue of the acidic hydrogen in the position *alpha* to the nitro group, and these solutions take up one equivalent of bromine; they add one



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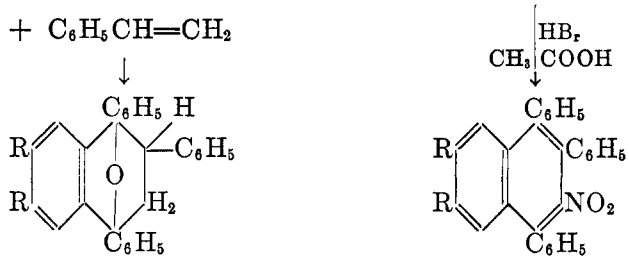
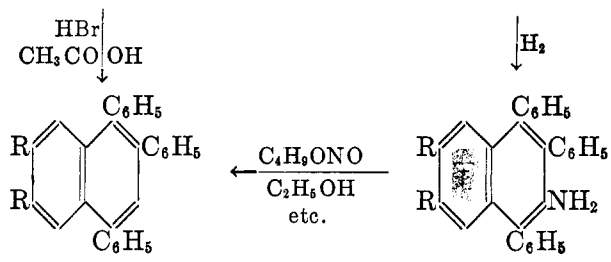
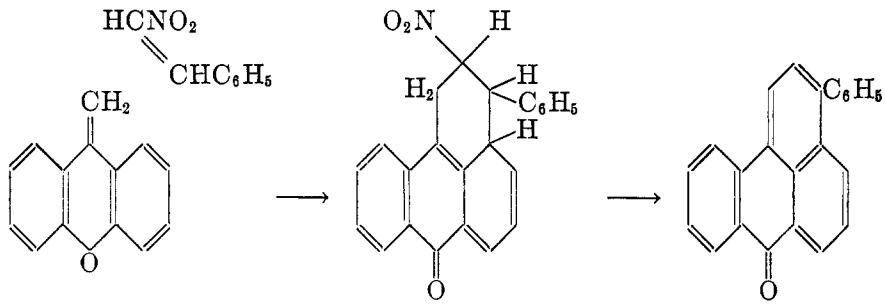


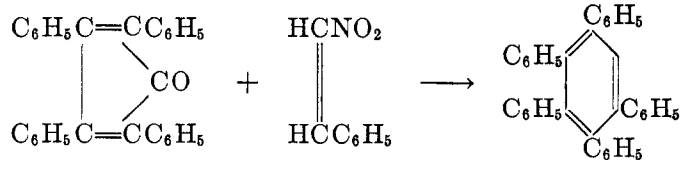
III IV



VI V

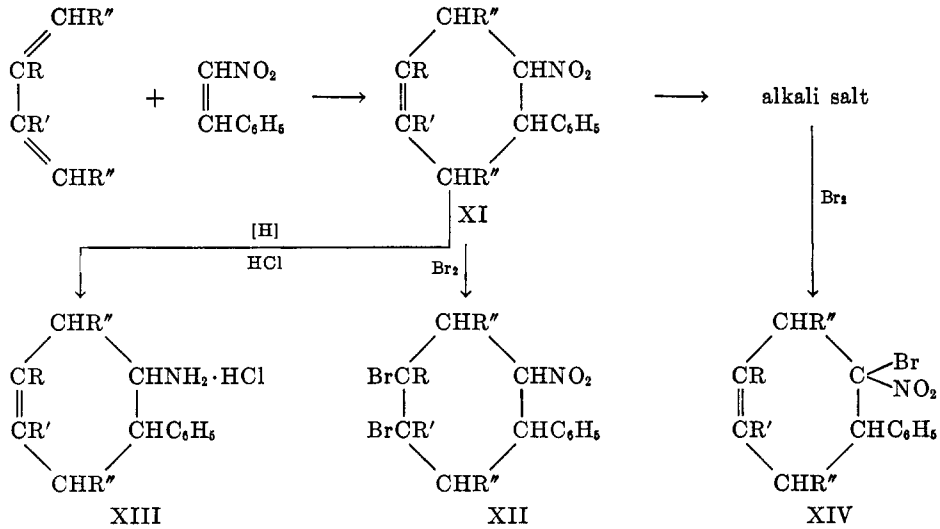


VII VIII IX

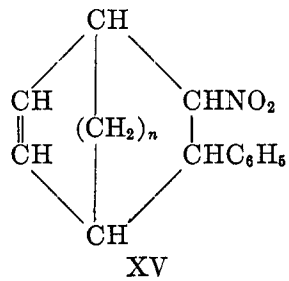


X

molecule of bromine to the double bond; they are reducible to amines.[1] The products are represented by structures XI–XIV.



The structures of the substances obtained by the use of the cyclic dienes were not determined, but by analogy with the above, it seems highly probable that they have the bridged-ring structure shown in XV.



XV

Most of the addition products can be distilled, but the one formed from 1,4-diphenylbutadiene dissociated into its components at the boiling point, and in solution below 100°; thus, on treatment with bromine, the tetrabromide of 1,4-diphenylbutadiene resulted.

Attempts to dehydrogenate some of the addition products by the use of sulfur or chloranil were unsuccessful; much hydrogen bromide was evolved when bromine was used, but the products were intractable black tars.

EXPERIMENTAL

I. The addition products. A. From dienes. The actual procedure was varied according to the nature of the diene. In some instances the use of alcohol as a solvent gave an increased yield. The properties are given in Table I.

[1] The investigation of these amines was carried out by Dr. Nightingale at the University of Missouri.

TABLE I

PROPERTIES OF THE ADDITION PRODUCTS

NO.	ADDEND	SOLVENT	YIELD %	M.P., °C.	FORMULA	CALC'D, %			FOUND, %		
						C	H	N	C	H	N
XI; R,R′,R″ = H	Butadiene	toluene	70	103	$C_{12}H_{13}NO_2$	70.9	6.4	6.9	71.3	6.6	6.7
XI; R = CH_3; R′,R″ = H or R′ = CH_3; R,R″ = H	Isoprene	—	58	52	$C_{13}H_{15}NO_2$	71.9	7.0	6.5	72.4	7.1	6.2
XI; R,R′ = CH_3; R″ = H	2,3-Dimethylbutadiene	—	82	96	$C_{14}H_{17}NO_2$	73.2	7.4		72.9	7.4	
XI; R,R′ = H; R″ = C_6H_5	1,4-Diphenylbutadiene	o-$Cl_2C_6H_4$	80	130	$C_{24}H_{21}NO_2$	81.1	5.9	3.9	80.9	5.8	4.2
XI; R,R′ = C_6H_5; R″ = H	2,3-Diphenylbutadiene	o-$Cl_2C_6H_4$	9	175	$C_{24}H_{21}NO_2$	81.1	5.9	3.9	81.2	6.0	3.8
XV; n = 1	Cyclopentadiene	—	quant.	145/1 mm.[a]	$C_{13}H_{13}NO_2$	72.6	6.1	6.5	72.6	6.1	6.4
XV; n = 2	Cyclohexadiene	—	25	138–142/1 mm.[a]	$C_{14}H_{15}NO_2$	73.3	6.6	6.1	72.9	6.4	6.3
	Phellandrene	—	45	85 195/1 mm.[a]	$C_{18}H_{23}NO_2$	75.8	8.4	4.9	76.3	8.1	4.5
VIII	Methyleneanthrone	acetic acid	3	255	$C_{23}H_{13}NO_3$	78.6	3.7	4.0	78.6	3.7	4.1
II; R = H	1,3-Diphenylisobenzofuran	ethanol	quant.	163	$C_{28}H_{21}NO_3$	80.2	5.0		80.1	4.9	
II; R = CH_3	1,3-Diphenyl-5,6-dimethyl-isobenzofuran	ethanol	quant.	182	$C_{30}H_{25}NO_3$	80.5	5.6		80.6	5.7	

[a] = boiling point.

1-Nitro-2-phenyl-1,2,3,6-tetrahydrobenzene (*XI; R,R′,R″ = H*). A mixture of 13 g. of butadiene, 22.5 g. of β-nitrostyrene, and 30 cc. of toluene was heated in a sealed tube for five hours at 150°. The product crystallized, and was cooled, filtered, and then recrystallized from methanol.

1-Nitro-2-phenyl-4,5-dimethyl-1,2,3,6-tetrahydrobenzene (*XI; R,R′ = CH_3; R″ = H*) was secured by refluxing equal weights of the components on the steam-bath for several hours; methanol was used for purification. 1-Nitro-2-phenyl-4(or 5)methyl-1,2,3,6-tetrahydrobenzenes could not be obtained by this procedure, but after standing in a warm (70–80°) place for five months, it yielded 58% of addition product.

The phenylated dienes were added in an indifferent medium, but the cyclic dienes served as their own solvent. Although 1-nitro-2,3,6-triphenyl-1,2,5,6-tetrahydrobenzene (XI; R,R′ = H; R″ = C_6H_5) dissociated into its components on attempted vacuum-distillation, it was easily isolated in the solid state after steam-distilling the solvent and treating the residue with ethanol. Oxides of nitrogen were evolved during the formation of 1-nitro-2,4,5-triphenylbenzene (XI; R,R′ = C_6H_5; R″ = H); the structure of a by-product, m.p. 76°, was not determined.

Tetraphenylcyclopentadienone did not react in the absence of a solvent, but in trichlorobenzene, oxides of nitrogen and carbon monoxide were given off; pentaphenylbenzene was formed. It was identified by comparison with a sample at hand.

Acetic acid was used to dissolve methyleneanthrone and nitrostyrene. During the sixteen-hour refluxing, oxides of nitrogen were evolved. The first product that crystallized was the known *Bz*-1-phenylbenzanthrone; it was identified by comparison with an authentic specimen. The second substance that separated was the addition product (VIII). When this was oxidized with chromium trioxide in acetic acid, it formed α-benzoylanthraquinone, m.p. and mixed m.p. 227°.

B. From furans. 1,2,4-Triphenyl-3-nitro-1,4-oxido-1,2,3,4-tetrahydronaphthalene (*II, R = H*) was prepared by refluxing a mixture of 7 g. of 1,3-diphenylisobenzofuran, 4 g. of β-nitrostyrene, and 200 cc. of alcohol for three hours, and working up by appropriate manipulation. The 6,7-dimethyl homolog was likewise obtained; in both instances the yield was practically quantitative. Furan, sylvan, and 2,5-dimethylfuran did not appear to react at 100° or in a sealed tube; the nitrostyrene was recovered unchanged.

II. The bromination products. A. 1-Nitro-2-phenyl-4,5-dibromo-4,5-dimethylcyclohexane (*XII, R,R′ = CH_3; R″ = H*). A solution of 2.3 g. of the addition product from 2,3-dimethylbutadiene in 10 cc. of chloroform was treated cold with 1.6 g. of bromine in 5 cc. of the same solvent. The bromine reacted at once, without evolution of hydrogen bromide [correction of statement in Note (1)]. After appropriate manipulation, a white dibromide, m.p. 69°, was obtained.

Anal. Calc'd for $C_{14}H_{17}Br_2NO_2$: Br, 40.9. Found: Br, 41.1.

In a similar manner, 1-nitro-2-phenyl-4,5-dibromocyclohexane (XII; R,R′R″ = H), m.p. 107°, was secured.

Anal. Calc'd for $C_{12}H_{13}Br_2NO_2$: Br, 44.1. Found: Br, 44.1, 44.1.

B. When the addition product from 1,4-diphenylbutadiene was submitted to a similar procedure, even though the temperature was prevented from rising above 0° at any time, the known 1,4-diphenyl-1,2,3,4-tetrabromobutane was the sole halogen-containing material. It was identified by comparison with a specimen prepared from the hydrocarbon directly (4).

C. 1-Bromo-1-nitro-2-phenyl-4,5-dimethyl-1,2,3,6-tetrahydrobenzene (*XIV; R,R′ = CH_3; R″ = H*). The sodium salt was obtained by shaking 2.3 g. of the nitro compound with 0.5 *N* alcoholic potassium hydroxide. To this was added 2 g. of bromine; the mixture was heated to boiling, and the potassium bromide filtered. The filtrate was diluted, extracted with ether, and the oil remaining after removal of the solvent allowed to crystallize. The bromonitro compound was recrystallized from dilute methanol; m.p. 68–69°.

Anal. Calc'd for $C_{14}H_{16}BrNO_2$: C, 54.2; H, 5.2; N, 4.5.
Found: C, 54.2; H, 5.1; N, 4.3.

On being heated, it decomposed almost explosively, with copious evolution of hydrogen bromide; the carbonaceous residue has a fragrant odor. This drastic decomposition was unexpected, for similar substances are tractable (5). With a view to decreasing the violence of the reaction, a *p*-cymene solution was used; it gave off gas from 100–165°. After one and one-half hours at the higher temperature, a vacuum distillation was attempted; even at 3 mm. there was a violent decomposition with production of carbonaceous material having a fragrant odor.

III. The aliphatic amines. 1-Amino-2-phenyl-1,2,3,6-tetrahydrobenzene hydrochloride (XIII; R,R',R'' = H). A solution of 4.1 g. of the addition product from butadiene in 50 cc. of alcohol was reduced by hydrogen in the presence of a Raney nickel catalyst; after it was filtered, the solution was saturated with hydrogen chloride. The hydrochloride melted above 220°.

Anal. Calc'd for $C_{12}H_{16}ClN$: N, 6.7. Found: N, 6.7.

1-Amino-2-phenyl-4,5-dimethyl-1,2,3,6-tetrahydrobenzene was secured by a similar procedure. The free amine was an oil, b.p. 129–132°/3 mm. The hydrochloride melted at 173° with decomposition.

Anal. Calc'd for $C_{14}H_{20}ClN$: N, 5.9. Found: N, 6.2.

IV. The naphthalene series. A. Dehydration of the addition products. 1,2,4-Triphenyl-3-nitronaphthalene (IV; R = H). A suspension of 10 g. of the addition product in 50 cc. of acetic acid containing 30–32% hydrogen bromide was allowed to stand for four hours, heated to boiling, and cooled; 7 g. of the naphthalene derivative, m.p. 218–219°, was obtained. By the same procedure, 1,2,4-triphenyl-6,7-dimethyl-3-nitronaphthalene (IV; R = CH_3), m.p. 237–238°, was also prepared.

Anal. Calc'd for $C_{28}H_{19}NO_2$: C, 83.8; H, 4.7.
Found: C, 83.9; H, 4.7.
Calc'd for $C_{30}H_{23}NO_2$: N, 3.3. Found: N, 3.0.

B. The amines. 1,2,4-Triphenyl-3-aminonaphthalene (V; R = H). Reduction of the nitro compound by the use of zinc dust and acetic acid proceeded smoothly; the amine had the m.p. 256–257°. 1,2,4-Triphenyl-6,7-dimethyl-3-aminonaphthalene, m.p. 226–227°, was similarly prepared.

Anal. Calc'd for $C_{28}H_{21}N$: N, 3.8. Found: N, 3.6.
Calc'd for $C_{30}H_{25}N$: C, 90.2; H, 6.3; N, 3.5.
Found: C, 89.7; H, 6.5; N, 3.5.

C. Diazotization and reduction. 1,2,4-Triphenylnaphthalene. To a suspension of 0.8 g. of the amine in 10 cc. of acetic acid and 5 cc. of absolute ethanol at 0° was added 1.5 g. of butyl nitrite, and then 5 cc. of a solution of acetic acid saturated with hydrogen chloride. After three hours at 0° it was filtered and poured into 100 cc. of boiling absolute ethanol. After suitable manipulation, 0.4 g. of hydrocarbon was isolated; it melted at 158–159° in agreement with the literature (3). The dimethyl homolog exhibited the same behavior. Both hydrocarbons were synthesized and proved to be identical in all respects with the specimens prepared from the amines, as just described.

D. Synthesis. 1,2,4-Triphenylnaphthalene and 6,7-dimethyl-1,2,4-triphenylnaphthalene (VI). The addition products (III) were first obtained by refluxing a mixture of 8 g. of the isobenzofuran, 4 g. of styrene, and 20 cc. of xylene for two hours, and suitable manipulation. 1,2,4-Triphenyl-1,4-oxido-1,2,3,4-tetrahydronaphthalene (III; R = H), m.p. 116–117°, and the 6,7-dimethyl homolog (III; R = CH_3), m.p. 172–173°, crystallized from alcoholic benzene.

Anal. Calc'd for $C_{28}H_{22}O$: C, 89.8; H, 5.9.
Found: C, 89.6; H, 5.9.
Calc'd for $C_{30}H_{26}O$: C, 89.6; H, 6.5.
Found: C, 89.6; H, 6.5.

Dehydration was accomplished as described under the nitro compound, using an acetic acid solution of hydrogen bromide. 1,2,4-Triphenyl-6,7-dimethylnaphthalene had the m.p. of 167–168°.

Anal. Calc'd for $C_{30}H_{24}$: C, 93.8; H, 6.3.
Found: C, 93.6; H, 6.1.

1,2,4-Triphenylnaphthalene was also synthesized by this procedure.

Anal. Calc'd for $C_{28}H_{20}$: C, 94.4; H, 5.6.
Found: C, 94.3; H, 5.9.

SUMMARY

β–Nitrostyrene readily enters into the diene synthesis. It has been added to open-chain and cyclic aliphatic dienes, to unsaturated cyclic ketones, and to isobenzofurans.

The addition products, isolated in all but one instance, appear to have the properties expected.

The series of reactions affords a convenient method for securing polysubstituted naphthalenes.

ROCHESTER, N. Y.

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THE TRANSAMINATION REACTION. THE MECHANISM OF THE REACTION BETWEEN *alpha* KETO ACIDS AND *alpha* AMINO ACIDS

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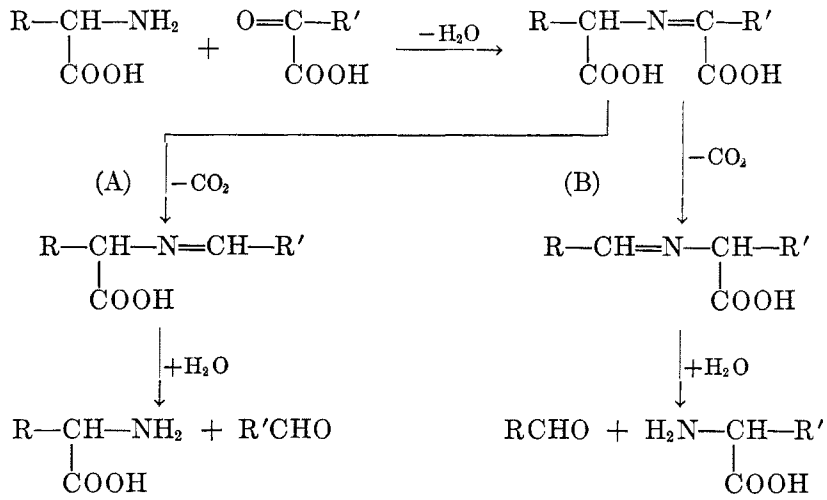
Several years ago one of us described a reaction in which an *alpha* keto acid was aminated and reduced to the corresponding amino acid at the expense of another amino acid (1). Subsequently, on the basis of a study of an extensive series of reactions, the following mechanism was proposed (2).



Soon thereafter an analogous reaction, catalyzed by enzyme systems of certain animal tissues, was described by Braunstein and Kritzmann (3) who introduced the term *Umaminierung*—transamination—to describe such reactions.

It has been suggested (2) that the process of decarboxylation involved in the above mechanism was intimately associated with the shift of the double bond in the methyleneazomethine ($\geqslant$C—N=C$\leqslant$) system. At that time few data were available regarding the function in the reaction of the *alpha* hydrogen of the amino acid. Experiments with α-amino-α-phenylbutyric acid (2) had shown that the reaction was not dependent upon the presence of hydrogen in the *alpha* position and indicated that hydrogen from the medium was necessary for the completion of the reaction. However, the assumption that the *alpha* hydrogen did not enter into reactions involving other amino acids would have been unwarranted without further evidence. Data concerning the reactivity of the *alpha* hydrogen of amino acids during such reactions were needed.

The use of deuterium as a tracer in reactions of this type promised insight into

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the mechanism. Two procedures could be employed in such studies, the use of ordinary reactants in an aqueous medium containing a known percentage of deuterium or the use of *alpha* deuterio amino acids in ordinary aqueous media. Both procedures were eventually employed but the first was chosen for the initial investigations because of the ease of application. To avoid unnecessary complications the reaction between α-aminophenylacetic acid and pyruvic acid, which proceeds almost exclusively according to scheme (B) was chosen for study. When the reaction was carried out in water containing deuterium, depending upon the reactivity of the *alpha* hydrogen of the amino acid, two results could be anticipated. If the *alpha* hydrogen was not involved in the reaction, the aldehyde (R—CHO) would be free of deuterium while the new amino acid [R′—CH-(NH_2)COOH] would pick up deuterium in the *alpha* position from the medium. On the other hand, if the *alpha* hydrogen was involved (reactive), the aldehyde should contain deuterium (R—CDO) picked up from the medium while the new amino acid might contain deuterium or not. With regard to the last point, the experiments of Fredenhagen and Bonhoeffer (4) on the Cannizzaro reaction in deuterium oxide showed the possibility of an intramolecular shift of a hydrogen from one carbon atom to another without exchange with the medium. Furthermore, the finding of Thompson and Cromwell (5) that the deuterium in an aromatic aldehyde (ArCDO) is not susceptible to exchange in an aqueous solution excluded the possibility that deuterium might enter or leave the aldehyde group through exchange with the medium.

Similar results were anticipated when the second procedure using an *alpha* deuterio amino acid and pyruvic acid in ordinary water was investigated. Should the *alpha* deuterium of the amino acid enter into the reaction, the aldehyde (RCHO) would contain no deuterium while the new amino acid should contain deuterium provided no exchange with the medium takes place during the shift across the methyleneazomethine bridge. On the other hand, if the *alpha* deuterium is not involved, the aldehyde (RCDO) should contain deuterium while the new amino acid would be free of the isotope.

The results of experiments in which α-aminophenylacetic acid and pyruvic acid were allowed to react in water containing deuterium indicated that the *alpha* hydrogen of the amino acid is not involved in the reactions.

In our first experiments (Table I), benzaldehyde was isolated and analyzed as the phenylhydrazone, which proved to contain only a trace of deuterium. The alanine, isolated and analyzed as the phenyl isocyanate derivative, contained the equivalent of about two atoms of deuterium. Apparently the isotope had replaced hydrogen on both the *alpha* and *beta* carbon atoms. Attempts to remove the *alpha* deuterium by converting the phenyl isocyanate derivative into 3-phenyl-5-methylhydantoin, followed by treatment with aqueous alkali, were only partially successful. When the hydantoin was treated cold with one equivalent of aqueous potassium hydroxide, the ring was opened, but only about one-sixth of an atom equivalent[1] of deuterium was removed. Treatment with

[1] Atom equivalent of deuterium as used here may be defined as follows:

$$\text{At. Equiv. D} = \frac{\text{At. percent D(compound)}}{\text{At. percent D(source)}} \times n$$

where n is equal to the number of hydrogen atoms in the compound.

boiling aqueous alkali at concentrations similar to those used by Dakin (6) and by Bovarnick and Clarke (7) for the racemization of hydantoins, and later with sufficient hot aqueous alkali to cause ring opening, brought about the removal of about one-quarter of an atom equivalent of isotope. These results appeared to indicate that the alanine had not picked up the anticipated amount of deuterium in the *alpha* position, and raised the question of a possible loss of deuterium from the aldehyde group of the benzaldehyde during the formation and purification of the phenylhydrazone.

TABLE I

REACTION OF α-AMINOPHENYLACETIC ACID AND PYRUVIC ACID IN HEAVY WATER SOLUTION
DEUTERIUM CONTENT OF PRODUCTS

EXP. NO.	ALANINE AS		BENZALDEHYDE PHENYLHYDRAZONE AT. EQUIV. D
	α-PHENYLUREIDOPROPIONIC ACID AT. EQUIV. D[b]	3-PHENYL-5-METHYLHYDANTOIN AT. EQUIV. D	
I	2.03	—	0.01
II	—	2.05	.1
		1.73[a]	
III	2.00	2.00	.01
		1.88 } [a]	
		1.83 }	

[a] After successive treatments with aqueous alkali.
[b] See Footnote 1.

TABLE II

REACTION OF α-AMINOPHENYLACETIC ACID AND PYRUVIC ACID IN HEAVY WATER SOLUTIONS
DEUTERIUM CONTENT OF PRODUCTS

EXP. NO.	ALANINE AT. EQUIV. D	*p*-NITROBENZYL ACETATE AT. EQUIV. D	BENZALDEHYDE AS	
			BENZYL 3,5-DINITROBENZOATE AT. EQUIV. D	BENZOIC ACID AT. EQUIV. D
IV	1.95	1.55[a]	0.10	0.00
V	1.67	0.70	.04	.01
VI	1.94	1.27	.10	.03
VII	1.71	1.17	—	—
VIII	1.72	1.23	.10	.00

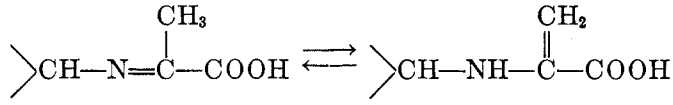
[a] Isolated and analyzed as silver acetate.

To test these possibilities, in subsequent experiments (Table II) benzaldehyde was converted into benzyl alcohol and benzoic acid by a Cannizzaro reaction. Both products were isolated and subjected to isotope analysis, the former as the 3,5-dinitrobenzoate. Although all the deuterium of the benzaldehyde should have been concentrated in the benzyl alcohol by this procedure (4), the results again indicated the presence of only a trace of the isotope. Alanine, isolated and analyzed as such, again contained 1.75 to 2 atom equivalents of deuterium. Upon oxidation of the alanine to acetic acid, which was isolated and analyzed

as *p*-nitrobenzyl acetate, approximately half an atom equivalent of deuterium was lost, leaving as much as one and one-half atom equivalents of deuterium in the methyl group of the acetic acid.

The fact that only about half an atom equivalent of deuterium was found in the *alpha* position of the alanine instead of the anticipated one atom equivalent is probably due to differences in the relative reactivities of protons and deuterons, especially since we are not dealing with an equilibrium reaction in this case. Differences in reactivity as great as tenfold (8) have been assumed to explain the results of various experiments. A quantitative interpretation of our results is difficult since deuterium may be lost from the methyl group of alanine during oxidation, and even from the methyl group of acetic acid under the conditions of our experiments. This is borne out by our observation that the acetic acid formed during the oxidation of alanine with silver oxide in water containing deuterium oxide contains about one-third of an atom equivalent of deuterium. Similarly, silver acetate on being heated in heavy water under the conditions of our oxidations, picks up about nine-tenths of an atom equivalent of deuterium.

That deuterium had entered the methyl group of the alanine during transamination in heavy water media, although unexpected, was not surprising. In view of the observations of Geib and Bonhoeffer (9) it is unlikely that the enolic form of pyruvic acid is responsible for this result. More probably deuterium enters the methyl group through a tautomeric form of the intermediate Schiff base. The —NH— group of the tautomer exhibits an exchangeable hydrogen atom. That deuterium has only partially replaced the methyl hydrogens may



likewise be due to differences in the relative reactivities of protons and deuterons. Although this would presumably be an equilibrium process, the extent of exchange will depend upon the speed of the over-all reaction, as well as on the rate of tautomeric shift.

The presence of a trace of deuterium in the benzaldehyde may be due to a slow exchange of the *alpha* hydrogen of the aminophenylacetic acid. The loss of fifteen to twenty-five percent of the deuterium when the *alpha* deuterio amino acid was employed may be explained in the same way. No exchange of ring hydrogen occurs, for no deuterium was present in the benzoic acid formed in the Cannizzaro reactions.

To confirm these results, α-deuterio-α-aminophenylacetic acid was prepared from the ordinary amino acid by exchange in heavy water solutions catalyzed by either hydrogen or hydroxyl ions. Moss and Schoenheimer (10) had shown the *alpha* hydrogen atoms of phenylacetic acid to be exchangeable in the presence of hydrogen ions. The results of a number of experiments (Table VI) indicated that exchange of the *alpha* hydrogen atom of aminophenylacetic acid proceeds at a negligible rate in the absence of catalysts, slowly in the presence of hydrogen

ions, and rapidly in the presence of hydroxyl ions. In no case was exchange of the ring hydrogen observed.

The reaction between deuterioaminophenylacetic acid and pyruvic acid was carried out in ordinary water. Alanine was isolated as such and found to be free of deuterium. The benzaldehyde formed was again subjected to a Cannizzaro reaction and both products isolated and analyzed as before. The absence of deuterium from the benzoic acid proved that deuterium was present only in the *alpha* position of the original deuterio amino acid and not in the aromatic ring. The benzyl 3,5-dinitrobenzoate in two experiments (Table III) contained 1.55 and 1.72 atom equivalents of deuterium, all of which must have been located in the methylene group.

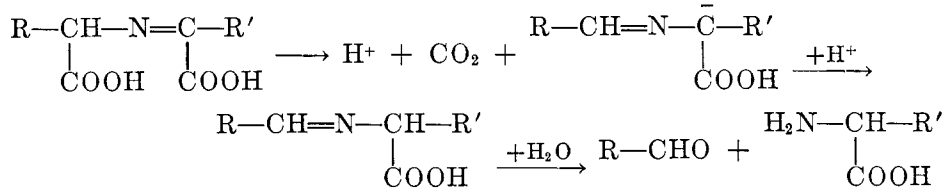
The results of experiments by two procedures indicated that the mechanism of the *in vitro* transamination reaction involves the decarboxylation of an inter-

TABLE III

REACTION OF α-DEUTERIO-α-AMINOPHENYLACETIC ACID AND PYRUVIC ACID IN ORDINARY WATER
DEUTERIUM CONTENT OF PRODUCTS

EXP. NO.	ALANINE AT. EQUIV. D	BENZALDEHYDE AS	
		BENZYL 3,5-DINITROBENZOATE AT. EQUIV. D	BENZOIC ACID AT. EQUIV. D
IX	0.03	1.55	0.02
X	.00	1.72	.00

mediate Schiff base-like compound, probably accompanied by a simultaneous shift of the double bond and followed by the addition to a carbonium ion of a proton from the medium.



Such a mechanism is perhaps more closely akin to the type of intramolecular change described by Lowry (11) as electrotopy, in which electrons move to new positions, than to the prototropic methyleneazomethine systems of Ingold (12) where the tautomeric change is due to the wandering of a proton.

Since the reactions were carried out in aqueous solutions at about *p*H 3, the assumption of proton addition during the reaction appears reasonable. In fact, earlier experiments (1) had shown that raising the hydroxyl ion concentration inhibited the reaction, whereas increasing the hydrogen ion concentration had only a slightly enhancing effect. These observations also indicate that carboxyl groups (COOH) rather than carboxylate ions (COO^-) are involved in the decarboxylation phase of the reaction.

It is interesting to note here that transamination with the esters of both the amino and the keto acid is inhibited by hydrogen ion but catalyzed by ethoxyl ion (13). This reaction bears a close relationship to the enzyme catalyzed biological transaminations. It appears likely that reactions of the enzyme catalyzed or negative ion catalyzed type proceed by a substantially different mechanism than the uncatalyzed *in vitro* transaminations, and that the former may proceed by a mechanism closely akin to the typical prototropic methyleneazomethine systems of Ingold.

An interesting observation for which no explanation is offered at this time is the failure of treatment with alkali, even when accompanied by ring opening, to remove completely the deuterium from the 5 position of 3-phenyl-5-methylhydantoin. The results of an investigation of the relationship between the mechanism of ring opening, racemization of optically active hydantoins, and exchange of hydrogen in the 5 position will be reported at an early date.

EXPERIMENTAL

Reactions between α-aminophenylacetic acid and pyruvic acid in heavy water solutions. A mixture of 4.53 g. (0.03 *M*) of α-aminophenylacetic acid, 7.9 g. (0.09 *M*) of pyruvic acid and 200 cc. of water (approximately 3.5 atom per cent deuterium) was boiled under reflux for three hours. A homogeneous solution was formed within a few minutes after the mixture began to boil. On completion of the reaction, benzaldehyde was removed by distillation through a declining condenser and extracted from the distillate with several small portions of chloroform. The aqueous portion of the distillate and the aqueous reaction mixture were reserved.

After drying the chloroform solution over sodium sulfate, the solvent was evaporated and the residual benzaldehyde converted into the phenylhydrazone by treatment with phenylhydrazine in 50% alcoholic solution. After recrystallization from 60% alcohol the yield of benzaldehyde phenylhydrazone (14) was 4.3–4.4 g., m.p. 155.5–157° for various preparations.[2]

After thorough chilling, the aqueous reaction mixture was filtered to remove a trace of aminophenylacetic acid which had separated. The filter was washed with the aqueous distillate from the benzaldehyde fraction. The entire filtrate was evaporated to a thick, syrupy consistency on the water-bath under reduced pressure, care being taken to recover the aqueous distillate as completely as possible. The residual syrup was taken up in about 100 cc. of ordinary water and the evaporation repeated. A second similar treatment with 100 cc. of water sufficed to remove easily exchangeable deuterium completely. The residual syrup was now taken up in 10 cc. of hot 95% alcohol, transferred to a small Erlenmeyer flask, and the distilling flask rinsed with four 5-cc. portions of hot 95% alcohol. Alanine crystallized spontaneously from the alcoholic solution on cooling; complete separation was ensured by the addition of 5 cc. of pyridine to the cold solution. After thorough chilling in the refrigerator, the alanine was filtered by suction, washed thoroughly with cold 95% alcohol, and dried in a vacuum desiccator. The yield of crude alanine varied from 1.4 g. to 1.8 g. in different experiments.

The crude alanine was converted into α-phenylureidopropionic acid by treatment with phenyl isocyanate in aqueous alkaline solution in the usual manner. A portion of the product was recrystallized from 50% alcohol, m.p. 162.5–163° with decomposition (15), while the remainder was converted into 3-phenyl-5-methylhydantoin by heating with 12% hydrochloric acid, m.p. 169–170° (16) after recrystallization from 30% alcohol.

Removal of the deuterium from the 5 position of the hydantoin was attempted in several

[2] The identity of all derivatives was established by the simultaneous determination of the melting point of the compound in question, an authentic specimen, and their mixture.

ways. (a) Part of the 3-phenyl-5-methylhydantoin (0.83 g.) was suspended in 75 cc. of cold water and treated with an equimolar amount of concentrated potassium hydroxide solution. The clear solution which resulted on shaking the mixture for a minute or two was acidified with concentrated hydrochloric acid after standing for twenty minutes at room temperature. The appearance of the product and its behavior on melting indicated that considerable conversion to the hydantoic acid had taken place. The ring was closed by treatment with acid as before and the product subjected to isotope analysis after suitable purification. (b) An aqueous solution 0.06 molar with respect to 3-phenyl-5-methylhydantoin and 0.004 molar with respect to potassium hydroxide was boiled under reflux for five hours, after which the solution was made strongly acid with hydrochloric acid and boiled for a few minutes to ensure ring closure of any hydantoic acid which may have been formed. The product, after recovery and purification in the usual way, was subjected to isotope

TABLE IV

ISOTOPE ANALYSES ON THE PRODUCTS OF THE REACTION BETWEEN α-AMINOPHENYLACETIC ACID AND PYRUVIC ACID IN HEAVY WATER

EXP. NO.	ATOM PER CENT DEUTERIUM[e]						
	WATER FOUND	ALANINE DERIVATIVES				BENZALDEHYDE PHENYLHYDRAZONE	
		α-PHENYLUREIDOPROPIONIC ACID		3-PHENYL-5-METHYL-HYDANTOIN			
		Calc'd[d]	Found	Calc'd[d]	Found	Calc'd[d]	Found
I	3.68	0.307	0.624	0.368	—	0.307	0.004
II	3.63	.303	—	.363	0.744 (.628)[c]	.303	.054
III	3.53	.295	.591	.353	.708 (.655)[a] (.646)[b]	.295	.004

[a] After attempt to remove deuterium by method (a).

[b] After attempt to remove deuterium by method (b).

[c] After attempt to remove deuterium by method (c).

[d] Calculated for the complete exchange of one hydrogen for deuterium at the concentration present in the water employed.

[e] Atom per cent deuterium in excess of the normal concentration.

analysis. (c) Fifty cc. of water containing 5 m*M* of the hydantoin and 2.5 m*M* of potassium hydroxide was boiled under reflux for 3.5 hours when further 2.5 m*M* of potassium hydroxide was added and boiling continued for 1.5 hours. The hydantoin was recovered as outlined in method (b) above.

The water recovered from the reaction was purified by successive distillations from potassium hydroxide, potassium hydroxide and potassium permanganate, and simple redistillation. The isotope content of the recovered water was then determined.

Isotope analyses were carried out on all products by the method of Keston, Rittenberg, and Schoenheimer (17) and the data are recorded in Table IV.

Apparent inability to remove deuterium completely from the 5 position of the hydantoin made advisable the use of different derivatives for determination of the isotope distribution in the various reaction products. In subsequent experiments the benzaldehyde was subjected to Cannizzaro reaction. Benzyl alcohol was removed from the reaction mixture by thorough extraction with ether and isolated as the 3,5-dinitrobenzoate (18), m.p. 112–114° for different preparations. Benzoic acid was recovered by acidification of the reaction mixture and recrystallization of the crude product, m.p. 122–123° for various preparations.

Alanine was obtained analytically pure[3] after one or two crystallizations from concentrated aqueous solution by the addition of alcohol. A portion of the alanine was oxidized to acetic acid with silver oxide (19). To avoid loss of acetaldehyde during the oxidation, this was carried out in a boiling water-bath with continuous stirring over a period of seven hours. After hot filtration from the excess silver oxide and silver, the reaction mixture was acidified with phosphoric acid and distilled in such a way as to carry the acetic acid into the distillate quantitatively. The distillate was made just alkaline to phenolphthalein with potassium hydroxide and evaporated to dryness. The residual potassium acetate was converted into *p*-nitrobenzyl acetate, m.p. 79–80° for various preparations, by treatment with *p*-nitrobenzyl bromide in the usual manner (20). The data for isotope analyses on products obtained by this modified technique are summarized in Table V.

Oxidation of alanine in heavy water solution. A solution of 0.89 g. (0.01 *M*) of ordinary alanine in 100 cc. of heavy water was oxidized with the silver oxide from 8.5 g. (0.05 *M*) of silver nitrate as described above. Isotope analysis of the water after completion of the

TABLE V

ISOTOPE ANALYSES ON THE PRODUCTS OF THE REACTION BETWEEN α-AMINOPHENYLACETIC ACID AND PYRUVIC ACID IN HEAVY WATER

EXP. NO.	ATOM PER CENT DEUTERIUM								
	WATER FOUND	ALANINE		*p*-NITROBENZYL ACETATE		BENZALDEHYDE AS			
						BENZYL 3,5-DINITRO-BENZOATE		BENZOIC ACID	
		Calc'd[a]	Found	Calc'd[a]	Found	Calc'd[a]	Found	Calc'd[a]	Found
IV	3.47	0.496	0.964	1.16[b]	1.70[b]	0.347	0.034	0.578	0.00
V	3.60	.51	0.854	0.40	0.284	.360	.014	.60	.006
VI	3.66	.523	1.014	.407	.516	.366	.037	.610	.017
VII	6.35	.91	1.55	.71	.829	—	—	—	—
VIII	6.30	.90	1.55	.70	.858	.630	.065	1.05	.002

[a] Calculated for the complete exchange of one hydrogen by deuterium at the concentration present in the water employed.

[b] Silver acetate.

experiment, and acetic acid as *p*-nitrobenzyl acetate, gave the following results: Water, 3.33 atom per cent D; *p*-nitrobenzyl acetate, 0.126 atom per cent D, equivalent to the exchange of 0.34 atom of hydrogen.

Exchange with silver acetate in heavy water solution. A solution of 3 g. of silver acetate in 150 cc. of heavy water was heated in a boiling water-bath for 6.5 hours. After filtration of the hot solution and taking care to recover the water employed, without dilution, acetic acid was isolated as potassium acetate and converted into the *p*-nitrobenzyl ester as described above. Isotope analyses gave the following results: Water, 3.44 atom per cent D; *p*-nitrobenzyl acetate, 0.346 atom per cent D, equivalent to the exchange of 0.90 atom of hydrogen in the methyl group of the acetic acid.

Preparation of α-deuterio-α-aminophenylacetic acid. Introduction of deuterium by exchange of the α-hydrogen of aminophenylacetic acid was studied under a variety of conditions summarized in Table VI. The products were isolated with care to wash out easily

[3] The decomposition temperature of alanine is not a satisfactory criterion of its purity. All alanine preparations were analyzed by the micro-Kjeldahl technique; nitrogen values checked closely with the calculated value.

replaceable deuterium and their purity was established by micro-Kjeldahl analyses. Nitrogen values in all cases agreed closely with the calculated values.

To determine the position of the deuterium in the amino acid, a portion of the product described in experiment 3 (Table VI) was oxidized with silver oxide as described above. Benzoic acid was isolated from the acidified reaction mixture by extraction with ether and was subjected to isotope analysis after suitable purification. The isotope content, 0.009 atom per cent D, was negligible.

TABLE VI

EXCHANGE OF α-HYDROGEN OF α-AMINOPHENYLACETIC ACID FOR DEUTERIUM IN HEAVY WATER SOLUTIONS

EXP. NO.	TIME, HOURS	TEMP., °C.	AMINO ACID, G.	CATALYST	WATER		α-DEUTERIO-α-AMINOPHENYLACETIC ACID		
					Vol., cc.	At. per cent D	Yield, g.	At. per cent D	Atom eq. D
1	24	BP	1	none	150	3.53	0.98	0.014	0.04
2	24	BP	1.51	H^+	20[a]	9.35	1.21	.170	.16
3	48	BP	6.0	H^+	58[a]	6.35	5.8	.314	.46
4[c]	6	120	7.5	OH^-	25[b]	3.66	7.15	.434	1.06
5[c]	15	115	7.5	OH^-	25[b]	22.7	6.1	2.28	0.90

[a] Hydrochloric acid made by diluting heavy water of twice the indicated isotope concentration to double its volume with concentrated hydrochloric acid.

[b] Four grams of sodium hydroxide added to the solution.

[c] Reaction carried out in a sealed tube.

TABLE VII

ISOTOPE ANALYSES ON PRODUCTS FROM THE REACTION OF α-DEUTERIO-α-AMINOPHENYLACETIC ACID WITH PYRUVIC ACID IN ORDINARY WATER

EXP. NO.	ATOM PER CENT DEUTERIUM						
	α-DEUTERIO-α-AMINOPHENYLACETIC ACID Found	ALANINE		BENZALDEHYDE AS			
				BENZYL 3,5-DINITROBENZOATE		BENZOIC ACID	
		Calc'd[a]	Found	Calc'd[a]	Found	Calc'd[a]	Found
IX	0.314	0.457	0.014	0.288	0.441	0.48	0.002
X	2.28	2.93	.001	2.05	3.53	3.42	.002

[a] Calculated on the basis of the replacement of one hydrogen by deuterium at the concentration present in the deuterio amino acid.

Reactions between α-deuterio-α-aminophenylacetic acid and pyruvic acid in ordinary water. The transaminations were carried out essentially as described above with such simplification as the use of ordinary water permitted. Benzaldehyde was subjected to Cannizzaro reaction and the products isolated as before. Alanine was isolated as such; the absence of deuterium from the compound obviated the necessity of oxidation to acetic acid. The data for isotope analyses of the products from several experiments are summarized in Table VII.

SUMMARY

1. The reaction between α-aminophenylacetic acid and pyruvic acid has been investigated in heavy water solutions.

2. It has been found that the α-hydrogen of the reacting amino acid is not involved in uncatalyzed *in vitro* transamination reactions.

3. α-Deuterio-α-aminophenylacetic acid has been prepared by exchange of the α-hydrogen for deuterium in heavy water solutions. The exchange is catalyzed slightly by hydrogen ion and markedly by hydroxyl ion.

4. The results of transaminations in heavy water solutions have been verified by experiments with α-deuterio-α-aminophenylacetic acid in ordinary water.

5. The mechanism of the *model* transamination reaction has been modified to include an electromeric intermediate.

6. During transaminations in heavy water media, deuterium enters the methyl group, *beta* carbon, of the alanine formed as the ultimate product. This observation is explained by postulating a tautomeric form of an intermediate Schiff base.

7. Deuterium appears in the methyl group of acetic acid formed by the oxidation of alanine with silver oxide in heavy water medium.

8. Hydrogen atoms in the methyl group of silver acetate exchange for deuterium when the salt is digested in water containing deuterium.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CINCINNATI]

SULFONIUM COMPOUNDS. III. THE REACTION OF ORGANIC SULFIDES WITH ORGANIC SULFATES[1]

FRANCIS EARL RAY AND JOSSELYN LISZNIEWSKA FARMER[2]

Received May 24, 1943

In a previous paper of this series (1), Ray and Levine proposed a new mechanism for the sulfonium reaction which offered a satisfactory explanation for the formation of trimethylsulfonium iodide when higher alkyl sulfides react with methyl iodide. The mechanism postulates the formation of the normally expected sulfonium compound as an intermediate. This may dissociate in one, two, or three ways, depending on the complexity of the salt, to give halides and sulfides, which in turn can combine to form the same or different sulfonium halides. Subsequent research (2, 3) has served to confirm this theory.

While there were numerous cases substantiating this mechanism in the literature, there is no report, so far as we are aware, of the formation of any but the expected product when organic sulfides are treated with methyl sulfate.

$$\text{I}\quad R_2S + (CH_3)_2SO_4 \rightarrow R_2CH_3S\cdot CH_3SO_4 \xrightarrow{H_2O} R_2CH_3SHSO_4 + CH_3OH$$

If rearrangement can occur in the case of the sulfonium sulfates it is certainly not easily observed. This might be due to either or both of two factors. (a) The reaction of organic sulfides with methyl or ethyl sulfate occurs so readily that long continued heating is unnecessary. (b) The methylsulfonium sulfate is so soluble and hygroscopic that it might well have escaped detection. In fact this latter compound has always been converted to some derivative for identification purposes (4).

Kehrmann and Duttenhöfer (5) in 1905 discovered that aromatic sulfides react with dimethyl sulfate to give sulfonium compounds. They did not isolate the sulfates, however. This almost universal tendency not to isolate the sulfates as such, led Rây and Rây (6) in 1927 to state that "sulfonium sulfates have not as yet been isolated." Although this was true of the aliphatic sulfonium sulfates with which they were working, Fichter and Sjöstedt (7) as early as 1910 had unmistakably isolated tribenzylsulfonium sulfate.

Even earlier Zincke and Glahn (8) had claimed the preparation of 2,6-dinitrophenol-4-dimethylsulfonium sulfate but gave no melting point or analytical data. In 1908 Smiles and Hilditch (9) reported the isolation of S-phenetyl-3,3′-dinitrophenazothionium sulfate and described it as bright green when dried in a vacuum and dark blue when dried at 100°. Kehrmann, Lievermann, and Frumkine (10), however, contended that Smiles' compound was impure, and that their preparation of it yielded light straw-yellow prisms. Neither of these

[1] Abstract of a thesis presented to the Graduate School of the University of Cincinnati in partial fulfillment of the requirements for the Ph.D. degree, June 1943.

[2] Laws Fellow in Chemistry 1942–43.

papers reported analyses of the sulfonium sulfate, but it was converted to other derivatives.

Richter (11) claimed the preparation of a triaryl-ortho-sulfurous acid but Libermann (12) showed that this was really *o,o',o''*-trihydroxytritolylsulfonium sulfate.

The neutral salts are less usual than the bisulfates. By treating the sulfonium chloride in acetic acid solution with the equivalent amount of dilute sulfuric acid, the neutral salt, bis-*p,p',p''*-trihydroxytriphenylsulfonium sulfate was obtained (13).

In their search for a suitable reagent for the identification of alkyl sulfides, Bost and Schultze (3) prepared a series of stable sulfonium sulfates from dialkyl-*p*-phenylphenacylsulfonium bromides with silver sulfate. All were bisulfates except that prepared from dimethyl sulfide.

Recently a number of patents have been issued for sulfonium sulfates. It is claimed that these are useful as wetting, foaming, and emulsifying agents; cleaning, dispersing, and stripping agents; disinfectants and fungicides (14).

The reaction between an organic sulfide and methyl sulfate gives first the methyl sulfate salt of the sulfonium compound (equation I). This on hydrolysis yields the sulfonium bisulfate and methyl alcohol.

The earliest isolation of a sulfonium methyl sulfate was accomplished by Auwers and Arndt (15). They treated *p*-thiocresol with dimethyl sulfate and obtained dimethyl-*p*-cresylsulfonium methyl sulfate. It was a solid melting at 97° and reportedly stable in water. The methyl sulfate obtained from the interaction of *p*-tolylethyl sulfide and dimethyl sulfate was an oil. Here is found the only indication in the literature of a rearrangement, for the oil, when subjected to distillation, gave *p*-tolyl*methyl* sulfide. Brand and Stallmann (16) observed that *o*-nitrophenyldimethylsulfonium methyl sulfate yellowed on long standing and supposed that *o*-nitrophenylmethyl sulfide was formed. It is possible that the volatile dimethyl sulfide was produced instead.

In none of these preparations, however, has any evidence been found for the rearranged sulfonium salts that are so commonly obtained in the synthesis of sulfonium halides. We felt, nevertheless, that a more careful search might enable us to isolate such rearranged products.

As the final product in the halide equilibrium is the trimethylsulfonium ion, we thought it likely that this ion might also be obtained in any sulfate rearrangement. But as previously remarked, trimethylsulfonium sulfate is too soluble and hygroscopic to be isolated. We sought, therefore, some derivative that could easily be analyzed and identified. The picrates used by Ray and Szasz (17) in an investigation of sulfonium salts of nitric and organic acids proved unsuitable as they could not be isolated in acid solution.

In 1917, Vanino and Mussgnug (18) prepared a double salt of trimethylsulfonium iodide with bismuth chloride which had a definite melting point. In the hope of obtaining a similar sulfate we treated a solution of trimethylsulfonium sulfate with an equivalent of bismuth chloride and obtained a crystalline compound melting at 245°. It was shown by analysis for carbon, hydrogen, bismuth,

sulfur, and chlorine to consist of three molecules of trimethylsulfonium chloride to two molecules of bismuth chloride, $3(CH_3)_3SCl \cdot 2BiCl_3$. When an excess of bismuth chloride was used, a compound melting at 121° was obtained in which trimethylsulfonium chloride and bismuth chloride were combined in a 1:1 ratio, $(CH_3)_3SCl \cdot BiCl_3$.

Blattler (19) claimed to have obtained a compound by treating trimethylsulfonium chloride with bismuth chloride. She gave no melting point and her analytical data were so inconclusive that she could not assign a formula to the product, which was probably contaminated with bismuth oxychloride. We repeated the preparation from trimethylsulfonium chloride and bismuth chloride and obtained the identical compounds, previously described.

No other bismuth chloride salts have been reported but Jörgensen (20) has described $3(C_2H_5)_3SBr \cdot 2BiBr_3$ but gave no analytical details. Kraut (21) reported that triethylsulfonium iodide combined in several ratios with bismuth iodide, but he gave no melting points for any of them. We obtained $(C_2H_5)_3SI \cdot BiI_3$ and found it to melt with decomposition at 218°. The early work on these double salts must, therefore, be considered unreliable as the possibility of contamination by bismuth oxyhalide was not guarded against.

In the present work it was decided to study the reaction between benzyl sulfide and dimethyl sulfate. Benzyl sulfide was selected because the high molecular weight of the benzyl radical should make its identification easy. In addition the well-known reactivity of the benzyl radical should favor rearrangement.

Benzyl sulfide and dimethyl sulfate in equimolar ratio in benzene solution were refluxed on the water-bath for thirty-six hours. Water was added and heating was continued until hydrolysis occurred. The aqueous layer was treated with bismuth chloride and a precipitate was obtained which on purification was found to be, not the normal dibenzylmethyl compound, but a benzyldimethyl derivative, $3(CH_3)_2C_7H_7SCl \cdot 2BiCl_3$. This may be expressed by the following series of reactions.

II
$$(C_7H_7)_2S + (CH_3)_2SO_4 \rightleftarrows (C_7H_7)_2CH_3SSO_4CH_3$$
$$\downarrow\uparrow$$
$$C_7H_7SCH_3 + C_7H_7SO_4CH_3$$
$$\downarrow$$
$$C_7H_7(CH_3)_2SSO_4CH_3 \xleftarrow{(CH_3)_2SO_4}$$

This then is the first case of a rearrangement to be reported in the preparation of a sulfonium sulfate.

In this experiment, however, either the reaction did not reach equilibrium or the trimethylsulfonium compound is not of predominant stability as it is in the sulfonium halide equilibrium. If the first assumption is correct, then a higher temperature should hasten the establishment of equilibrium with the concommitant formation of trimethylsulfonium sulfate. In the second, an excess of benzyl sulfide should displace the reaction in the direction of the normal product, dibenzylmethylsulfonium sulfate.

We, therefore, heated *two* moles of benzyl sulfide with *one* mole of dimethyl sulfate in glacial acetic acid. The main product of this reaction was tribenzylsulfonium sulfate. Here, indeed, the reaction had been displaced in the direction anticipated, but it was displaced further than had been expected.

III $(C_7H_7)_2S + (CH_3)_2SO_4 \rightleftarrows (C_7H_7)_2CH_3SSO_4CH_3$

$$\Updownarrow$$

$$C_7H_7SCH_3 + C_7H_7SO_4CH_3$$

$$(C_7H_7)_3SSO_4CH_3 \xleftarrow{(C_7H_7)_2S}$$

Sulfonium sulfates have also been prepared by the reaction of sulfides with alkyl hydrogen sulfates (or alcohols and sulfuric acid) (7). It seemed of interest to examine this reaction for evidence of rearrangement.

The reaction between dimethyl sulfide, benzyl alcohol, and sulfuric acid in glacial acetic acid resulted in the isolation of the normal product as $2C_7H_7(CH_3)_2SCl \cdot BiCl_3$. Due, possibly, to the low boiling point of the methyl sulfide no rearrangement occurred.

Benzyl sulfide, methyl alcohol, and sulfuric acid in glacial acetic acid, however, yielded tribenzylsulfonium sulfate. Rearrangement occurs, therefore, both with dimethyl sulfate and methyl hydrogen sulfate. It is possible that tribenzylsulfonium sulfate and benzyldimethylsulfonium sulfate are more stable than the other possible compounds, trimethylsulfonium sulfate and dibenzylmethylsulfonium sulfate, which were not isolated. These latter may have been present in small amounts in the gummy residues that could not be crystallized.

Due to the delitescent character of the sulfonium sulfate equilibrium our experiments are not as complete as they were with the sulfonium halides. They, nevertheless, leave no doubt that a similar series of equilibria exists. Limiting ourselves to the data secured we may summarize this as follows.

IV

$$\underset{A}{RSR} + \underset{B}{(CH_3)_2SO_4} \rightleftarrows R_2CH_3SSO_4CH_3 \quad (C)$$

$$\underset{D}{RSCH_3} + \underset{E}{RSO_4CH_3} \rightleftarrows R_2CH_3SSO_4CH_3 \quad (C)$$

The reaction of A with E can then give $R_3SSO_4CH_3$ while the reaction of D with B results in $R(CH_3)_2SSO_4CH_3$.

EXPERIMENTAL PART

Trimethylsulfonium sulfate. Six and seven-tenths grams (0.053 mole) of dimethyl sulfate was mixed with 4.4 g. (0.071 mole) of dimethyl sulfide and the solution was cooled in an ice-bath. The reaction was quite vigorous and in a short while the trimethylsulfonium methyl sulfate solidified. It was extremely deliquescent and could not be isolated in a pure state. It was converted to the sulfate by hydrolysis with water and a clear solution was obtained.

Tris-trimethylsulfonium chloride-bis-bismuth chloride. To 71 cc. of an aqueous solution of trimethylsulfonium sulfate (0.02 mole) was added 61.4 cc. (0.02 mole) of normal bismuth chloride. The mixture was stirred during the addition and a small precipitate of bismuth oxychloride was discarded. The filtrate on evaporation gave beautiful glistening white prisms. On recrystallization from dilute hydrochloric acid they decomposed at 245°. Analyses for carbon, hydrogen, sulfur, bismuth, and chlorine showed it to be $3(CH_3)_3SCl \cdot 2BiCl_3$.

Anal. Calc'd for $C_9H_{37}Bi_2Cl_9S_3$: C, 11.15; H, 2.79; S, 9.92; Bi, 43.17; Cl, 32.97.
Found: C, 11.3 (11.16[3]); H, 2.44 (2.75[3]); S, 10.03; Bi, 43.45; Cl, 32.75 (32.49[3]).

The identical compound was obtained when trimethylsulfonium chloride was treated with an equimolar amount of bismuth chloride. The trimethylsulfonium chloride was prepared from the iodide by treatment first with silver oxide followed by neutralization with hydrochloric acid.

Trimethylsulfonium chloride-bismuth chloride. When 0.15 mole of trimethylsulfonium sulfate was treated with 0.20 mole of bismuth chloride as described above, white crystals melting at 121–123° were obtained which proved to be $(CH_3)_3SCl \cdot BiCl_3$.

Anal. Calc'd for $C_3H_9BiCl_4S$: S, 7.48. Found: S, 7.24.

Equal moles of benzyl sulfide and dimethyl sulfate. A benzene solution of 21.4 g. (0.1 mole) of benzyl sulfide and 12.6 g. (0.1 mole) of dimethyl sulfate was heated on the water-bath for 14 hours. Water (100 cc.) was then added and the mixture was again heated for seven hours or until the hydrolysis was complete. The dark colored benzene layer was separated and on evaporation deposited crystals of benzyl sulfide. The clear, colorless aqueous layer was treated with bismuth chloride (100 cc. of 3 *N*). Hydrochloric acid was added until a clear solution was obtained, a total of 300 cc. of 6 *N* HCl being used. A small amount of gummy precipitate was discarded. The filtrate, on evaporation, gave a white precipitate which was recrystallized from diethyleneglycol monoethyl ether (Carbitol) by the addition of acetone. After several such purifications it melted constantly at 140° and decomposed at 145°. Analysis showed it to be $3(CH_3)_2C_7H_7SCl \cdot 2BiCl_3$.

Anal. Calc'd for $C_{27}H_{39}Bi_2Cl_9S_3$: S, 8.03; Bi, 34.94.
Found: S, 7.98; Bi, 35.2.

Two moles of benzyl sulfide to one of dimethyl sulfate. A solution of 21.4 g. (0.1 mole) of benzyl sulfide and 6.3 g. of dimethyl sulfate (0.05 mole) in 200 cc. of glacial acetic acid was heated for three hours, and then most of the acetic acid was removed under vacuum. The residual liquor was poured into water. An oil and a solid separated. The oil was soluble in benzene and was benzyl sulfide. The solid was recrystallized from very dilute sulfuric acid. It melted at 173° and proved to be tribenzylsulfonium sulfate. Fichter and Sjöstedt (7) give 170–175°. A mixed melting point with authentic material prepared by Fichter and Sjöstedt's method showed no depression.

Anal. Calc'd for $C_{21}H_{22}O_4S_2$: S, 15.92. Found: S, 16.03.

Benzyl sulfide, methyl alcohol, and sulfuric acid. A solution of 13.1 g. (0.06 mole) of benzyl sulfide in 150 cc. of glacial acetic acid was heated with 10 cc. of concentrated sulfuric acid and 2.5 cc. (0.06 mole) of absolute methyl alcohol for two hours. Most of the glacial acetic acid was removed in a vacuum and the residual liquor then separated into two layers. The upper layer proved to be benzyl sulfide. The lower layer was treated with water and a white solid precipitated. On recrystallization from very dilute sulfuric acid it melted at 174° and proved to be tribenzylsulfonium sulfate.

Methyl sulfide, benzyl alcohol, and sulfuric acid. A solution of 3.7 g. (0.06 mole) of methyl sulfide, 6.5 g. (0.06 mole) of benzyl alcohol, and 10 cc. of concentrated sulfuric acid in 150 cc. of glacial acetic acid was allowed to stand at room temperature for 12 days. The acetic acid was removed as described previously and the residue treated with water. An oil separated which was insoluble in ether. It was dissolved in acetic acid and bismuth chloride was added. The precipitate seemed to be a mixture, as it melted indefinitely between 89° and 130°. On recrystallization from dilute hydrochloric acid, however, a crystalline com-

[3] Analyses by Carl Tiedke.

pound was obtained that melted at 138°. On analysis it proved to be $2C_7H_7(CH_3)_2SCl \cdot BiCl_3$, showing that no rearrangement had occurred.

Anal. Calc'd for $C_{18}H_{26}BiCl_5S_2$: C, 31.2; H, 3.8; S, 9.25; Bi, 30.18.
Found: C, 31.06; H, 3.43; S, 9.00; Bi, 30.54.

Analytical notes. No difficulty was experienced in the analysis for C and H, or for sulfur by either the Carius or Parr bomb methods. Bismuth gave considerable trouble until the method of Myttenaere (22) was somewhat modified as follows. A sample of 0.5 g. was mixed with 4 g. of 1:2 potassium nitrate-potassium carbonate and 10 cc. of water in a platinum dish. This was carefully evaporated to dryness on the water-bath, cautiously heated and finally ignited at a temperature of 450–500°. The *cooled* melt should be yellow. When the cooled melt was orange in color, inaccurate results were obtained. Further heating was necessary. Water was then added to disintegrate the melt and the precipitate was filtered, washed until neutral and ignited. If filter paper was used, a few drops of nitric acid was added to convert any reduced bismuth to Bi_2O_3.

SUMMARY

The reaction between benzyl sulfide and dimethyl sulfate and between benzyl sulfide and methyl hydrogen sulfate has been shown to result in rearranged products, tribenzylsulfonium sulfate and benzyldimethylsulfonium sulfate. The latter was isolated as $3C_7H_7(CH_3)_2SCl \cdot 2BiCl_3 \cdot$

The mechanism proposed by Ray and Levine for the formation of sulfonium halides has been extended to the sulfonium sulfate.

No rearrangement was observed when dimethyl sulfide reacted with benzyl hydrogen sulfate.

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THE CONTIGUOUSLY SUBSTITUTED DIHYDROXYAMINOALKANES. I. THE SYNTHESIS OF 1-AMINO-2,3-DIHYDROXY-*n*-HEXANE AND 1,2-DIHYDROXY-3-AMINO-*n*-HEXANE[1]

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The contiguously substituted dihydroxyaminoalkanes of the type $RCHOHCHOHCH_2NH_2$, $RCHOHCHNH_2CH_2OH$, $RCHNH_2CHOHCH_2OH$, $RCOH(CH_2NH_2)(CH_2OH)$, and $RCNH_2(CH_2OH)_2$ are of interest because of their relationship to dihydrosphingosine (1), sphingosine (2), and other sphingosine-like compounds (3). For the past two years we have devoted our attention to preparing compounds of the above types, in order to develop model syntheses for dihydrosphingosine and its isomers, to utilize the compounds so prepared for studying reactions of structural interest, and to provide starting materials which could be converted into substrates suitable, from the standpoint of solubility, for *in vitro* enzymatic studies in aqueous media. This communication will be confined to a description of the synthesis of 1-amino-2,3-dihydroxy-*n*-hexane and 1,2-dihydroxy-3-amino-*n*-hexane and to a brief account of several reactions exhibited by these compounds, or their derivatives, which are of structural interest. The synthesis of 1,3-dihydroxy-2-amino-*n*-hexane will be described in a subsequent communication.

Propylvinyl carbinol, prepared from propylmagnesium bromide and acrolein by the method of Delaby (4), was oxidized with perbenzoic acid to give 1,2-epoxy-3-hydroxy-*n*-hexane. Ammonia was then added to the 1,2-epoxy-3-hydroxyalkane (5) to give the desired 1-amino-2,3-dihydroxy-*n*-hexane. As the alkylvinyl carbinols can be resolved (4b), the above synthesis appears to be an attractive one for the preparation of the isomeric and homologous 1-amino-2,3-dihydroxyalkanes although some difficulty is to be anticipated in preparing the higher molecular weight alkylvinyl carbinols (4a).

The 1,2-dihydroxy-3-aminoalkanes can be prepared by a variety of methods. Seydel (2c) has suggested three possible syntheses for 1,2-dihydroxy-3-amino-*n*-octadecane, *i.e.*,

I. $RCH_2OH \rightarrow RCH_2Br \rightarrow RCH_2CN \rightarrow RCH_2CO_2H \rightarrow RCHBrCO_2H \rightarrow RCHNH_2CO_2H \rightarrow RCH(NHCOCH_3)CO_2H \rightarrow RCH(NHCOCH_3)COCl \rightarrow RCH(NHCOCH_3)COCHN_2 \rightarrow RCH(NHCOCH_3)COCH_2OH \rightarrow RCH(NHCOCH_3)CHOHCH_2OH \rightarrow RCHNH_2CHOHCH_2OH$,

II. $RCH_2NO_2 + CH_2OHCHO \rightarrow RCHNO_2CHOHCH_2OH \rightarrow RCHNH_2CHOHCH_2OH$, and

[1] Taken in part from the Ph.D. Thesis of A. A. Benson, California Institute of Technology, June (1942).

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III. $RCHBrCO_2C_2H_5 + C_6H_5CH_2CH_2OCO_2C_2H_5 + Zn \rightarrow RCH(CO_2C_2H_5)$-$C(OC_2H_5)(ZnBr)CH_2OCH_2C_6H_5 \rightarrow RCH(CO_2C_2H_5)COCH_2OCH_2C_6H_5 \rightarrow RC(NOH)COCH_2OCH_2C_6H_5 \rightarrow RCHNH_2CHOHCH_2OH$, where R = $C_{15}H_{31}$.

Of these three syntheses only one, *i.e.*, II, was carried to completion by Seydel (2c). Synthesis I was not investigated beyond the formation of the acetamido acid chloride (2c) and synthesis III was but briefly considered.

Our first approach to the synthesis of 1,2-dihydroxy-3-amino-*n*-hexane was suggested by the work of Fischer, Baer, Pollock and Nidecker (6a) and was based upon the following reactions: $C_3H_7COCH{=}CH_2 \rightarrow C_3H_7COCHOHCH_2OH \rightarrow C_3H_7CHNH_2CHOHCH_2OH$. However the preparation of propylvinyl ketone in quantity, either by the oxidation of propylvinyl carbinol or by the method of Blaise (7), proved to be so unsatisfactory that the proposed synthesis was abandoned. Following this abortive attempt, 1,2-dihydroxy-3-amino-*n*-hexane was synthesized by the following series of reactions: $CH_2(OC_2H_5)CHO \rightarrow CH_2(OC_2H_5)CH(OC_2H_5)Cl \rightarrow CH_2(OC_2H_5)CH(OC_2H_5)(CN) \rightarrow CH_2(OC_2H_5)$-$CH(OC_2H_5)COC_3H_7 \rightarrow CH_2(OC_2H_5)CH(OC_2H_5)CHNH_2C_3H_7 \rightarrow C_3H_7CH$-$NH_2CHOHCH_2OH$, which were first applied to the synthesis of 2-hydroxy-3-amino-*n*-hexane in order to test certain steps of the synthesis with a more readily available starting material, *i.e.*, α-methoxypropionitrile.

The recent investigations of Seydel (2c), Niemann and Nichols (8), and Carter and co-workers (9) have shown that the structure proposed by Klenk and Diebold (10) for sphingosine and dihydrosphingosine is incorrect, although the assignment of the amino and hydroxyl groups to terminal and contiguous positions (2a, 10), which was based upon the oxidative degradation of sphingosine to myristic acid, and dihydrosphingosine to palmitic acid, is accepted.[3] The inertness of N-acetyldihydrosphingosine towards lead tetraacetate and periodate led Seydel (2c) to suggest that dihydrosphingosine was a 1,3-dihydroxy-2-amino-*n*-octadecane. This conclusion was subsequently substantiated by Carter and co-workers (9) who found that N-benzoyldihydrosphingosine was not oxidized by periodate.[4]

In view of the significance attached to the inability of periodate or lead tetraacetate to oxidize N-acyldihydrosphingosines it appeared to us to be worth while to study the action of these oxidizing agents upon compounds related to dihydrosphingosine and of known structure. It should be pointed out that in the case of the N-acyldihydrosphingosines it has been assumed that the acyl derivatives possess a normal structure.

The oxidation of 1-amino-2,3-dihydroxy-*n*-hexane by both periodate and lead tetraacetate was observed to proceed as expected (11), one mole of substrate

[3] Additional evidence as to the contiguous disposition of the amino and hydroxyl groups is to be found in the unpublished experiments of Dr. J. F. Mead who showed that dihydrosphingosine consumes two equivalents of lead tetraacetate.

[4] The inertness of N-acetyl- and N-bezoyl-dihydrosphinogosine towards periodate and lead tetraacetate has also been observed in this laboratory.

requiring two moles of periodate or tetraacetate. However, the yield of formaldehyde, isolated as the dimedon derivative, was never quantitative or even approximately so. The oxidation of the N-acetyl and N-carbobenzyloxy derivatives of 1-amino-2,3-dihydroxy-*n*-hexane and the N-carbobenzyloxy derivative of 1,2-dihydroxy-3-amino-*n*-hexane also proceeded as expected, one mole of substrate requiring one mole of periodate or tetraacetate.[5]

The results obtained in this study allow one to conclude that the N-acyl derivatives of 1-amino-2,3-dihydroxy-*n*-hexane and 1,2-dihydroxy-3-amino-*n*-hexane have normal structures and that the stoichiometry of the oxidation of these compounds by periodate and lead tetraacetate is normal and predictable. Although the above conclusions appear to provide additional and substantial evidence in favor of the 1,3-dihydroxy-2-amino-*n*-octadecane structure for dihydrosphingosine, suggested by Seydel (2c) and Carter (9), it should be emphasized that a structure of the type $RC(OH)(CH_2OH)(CH_2NH_2)$ has not been rigorously excluded, for it has been pointed out by Criegee (14) that glycols containing a tertiary alcohol group are very slowly oxidized by periodate or tetraacetate, and in some cases no apparent oxidation is observed.

EXPERIMENTAL[6]

n-*Propylvinyl carbinol* (4). A solution of 162 g. of acrolein in 500 ml. of ether was added, during the course of three hours, to a Grignard reagent prepared from 410 g. of *n*-propyl bromide, 77 g. of magnesium, and one liter of ether. Saturated aqueous ammonium chloride was added to the reaction mixture; the ethereal phase collected, dried over anhydrous potassium carbonate, and distilled to give 160 g. (55%) of propylvinyl carbinol, b.p. 90–94°/150 mm.

1,2-Epoxy-3-hydroxy-n-*hexane.* A chloroform solution containing 0.273 mole of perbenzoic acid (15) and 35 g. of propylvinyl carbinol was allowed to stand at 25° for two days. The chloroform was removed, the residue taken up in ether, the ethereal phase washed with aqueous potassium bicarbonate and water, and dried over anhydrous sodium sulfate. Distillation gave 16.0 g. (50%) of 1,2-epoxy-3-hydroxy-*n*-hexane, b.p. 87–90°/25 mm.

Anal. Calc'd for $C_6H_{12}O_2$ (116.2): C, 62.0; H, 10.4.
Found: C, 62.4; H, 10.5.

1-Amino-2,3-dihydroxy-n-*hexane.* A solution of 16 g. of 1,2-epoxy-3-hydroxy-*n*-hexane in one liter of conc'd aqueous ammonium hydroxide was allowed to stand for sixteen hours at 25°. Evaporation of the solution and distillation of the residue gave 14.6 g. (80%) of 1-amino-2,3-dihydroxy-*n*-hexane, b.p. 92°/0.06 mm., m.p. 53°.

Anal. Calc'd for $C_6H_{15}NO_2$ (133.3): N, 10.5. Found: N, 10.6.

Oxidation of 1-amino-2,3-dihydroxy-n-*hexane with sodium periodate.* One hundred milliliters of 0.1027 *M* sodium periodate (*p*H 5) was added to 0.4480 g. (0.00334 mole) of 1-amino-2,3-dihydroxy-*n*-hexane. Ten-milliliter aliquots were withdrawn at intervals varying from forty-five minutes to forty-eight hours, 10 ml. of borate-boric acid buffer solution (16) and excess potassium iodide added, and the liberated iodine titrated with standard arsenite solution. The ratio, mole IO_4^- consumed/mole subtrate was found to be 1.96 ± 0.03 in all cases.

Oxidation of 1-amino-2,3-dihydroxy-n-*hexane with lead tetraacetate.* Fifty milliliters of a 0.13 *N* glacial acetic acid solution of lead tetraacetate was added to 0.0859 g. of 1-amino-

[5] It is of interest to note that abnormal reactions have been observed in the case of acetylated derivatives of glucosamine (12, 13).

[6] Microanalyses by Dr. G. Oppenheimer and Mr. G. A. Swinehart.

2,3-dihydroxy-*n*-hexane, and the solution was allowed to stand for twenty hours at 25°. An excess of potassium iodide-sodium acetate solution was added, and the liberated iodine was titrated with standard thiosulfate solution. The amount of lead tetraacetate consumed was found to be 97% of that required for the oxidative cleavage of two —CHOHCHOH—(—CHOHCHNH$_2$—) groups.

N-Carbobenzyloxy-1-amino-2,3-dihydroxy-n-*hexane.* A solution containing equimolal quantities of 1-amino-2,3-dihydroxy-*n*-hexane, *N* sodium hydroxide, and carbobenzyloxy chloride (17) was shaken for one hour and the mixture allowed to stand overnight. The product was extracted with ether, the ethereal extract washed with aqueous pyridine, dilute hydrochloric acid, and water, and dried over anhydrous sodium sulfate. Evaporation of the solvent and recrystallization of the residue from either aqueous methanol or a mixture of methanol and isopropyl ether gave N-carbobenzyloxy-1-amino-2,3-dihydroxy-*n*-hexane, white prisms, m.p. 114–115°.

Anal. Calc'd for $C_{14}H_{21}NO_4$ (267.3): C, 62.9; H, 7.9; N, 5.4.
Found: C, 62.7; H, 7.9; N, 5.3.

Oxidation of N-carbobenzyloxy-1-amino-2,3-dihydroxy-n-*hexane with sodium periodate.* Ten milliliters of 0.1027 *M* sodium periodate was shaken with 0.1007 g. of N-carbobenzyloxy-1-amino-2,3-dihydroxy-*n*-hexane for eight and one-half hours, 10 ml. of borate-boric acid buffer solution (16) and an excess of potassium iodide added, and the liberated iodine titrated with standard arsenite solution. The ratio, mole IO_4^- consumed/mole substrate, was found to be 1.10. A second experiment with an elapsed time of thirteen hours gave the value 1.13 for the same ratio.

Oxidation of N-carbobenzyloxy-1-amino-2,3-dihydroxy-n-*hexane with lead tetraacetate.* Fifty milliliters of 0.156 *N* glacial acetic acid solution of lead tetraacetate was added to 0.4977 g. of N-carbobenzyloxy-1-amino-2,3-dihydroxy-*n*-hexane, the solution allowed to stand for twelve hours, an excess of potassium iodide-sodium acetate solution added, and the liberated iodine titrated with standard thiosulfate solution. The amount of lead tetraacetate consumed was found to be 97.5% of that required for the oxidative cleavage of one —CHOHCHOH— group.

1-Acetamido-2,3-diacetoxy-n-*hexane.* A solution of 6.2 g. of 1-amino-2,3-dihydroxy-*n*-hexane in 15 ml. of acetic anhydride and 30 ml. of dry pyridine was allowed to stand at 25° for ten hours. Water was added and the excess anhydride allowed to hydrolyze. The mixture was extracted with ether, the ethereal extract washed with water, dilute hydrochloric acid, and aqueous potassium bicarbonate, and dried over anhydrous sodium sulfate. Evaporation of the solvent and recrystallization of the residue from isopropyl ether gave 5.23 g. (43%) of 1-acetamido-2,3-diacetoxy-*n*-hexane, small colorless needles, m.p. 95.8–96.5°.

Anal. Calc'd for $C_{12}H_{21}NO_5$ (259.3): C, 55.6; H, 8.2; N, 5.4.
Found: C, 55.4; H, 8.0; N, 5.4.

1-Acetamido-2,3-dihydroxy-n-*hexane.* A solution of 3.50 g. of 1-acetamido-2,3-diacetoxy-*n*-hexane and 2 ml. of 7 *M* barium methoxide in 100 ml. of dry methanol was allowed to stand for ten hours at 25°. The solution was cooled to 0°, an equivalent amount of *N* sulfuric acid added, the precipitate removed with the aid of diatomaceous earth (Super-Cel), the solvent removed, and the residue distilled to give 2.0 g. (85%) of 1-acetamido-2,3-dihydroxy-*n*-hexane, a viscous colorless liquid, b.p. 140–125°/0.11 mm.

Anal. Calc'd for $C_8H_{17}NO_3$ (175.2): N, 8.0. Found: N, 8.1.

Oxidation of 1-acetamido-2,3-dihydroxy-n-*hexane with sodium periodate.* Ten milliliters of 0.1027 *N* sodium periodate was added to 0.0654 g. of 1-acetamido-2,3-dihydroxy-*n*-hexane, the solution shaken for thirty minutes, 10 ml. of borate-boric acid buffer solution (16) and an excess of potassium iodide added, and the liberated iodine titrated with standard arsenite solution. The ratio, mole IO_4^- consumed/mole substrate, was found to be 1.15. A second experiment with an elapsed time of nine hours gave the value 1.14 for the same ratio.

Oxidation of 1-acetamido-2,3-dihydroxy-n-*hexane with lead tetraacetate.* Fifty milliliters of 0.13 *N* glacial acetic acid solution of lead tetraacetate was added to 0.1109 g. of

1-acetamido-2,3-dihydroxy-*n*-hexane, and the solution was allowed to stand for twenty hours at 25°. An excess of potassium iodide-sodium acetate solution was added, and the liberated iodine was titrated with standard thiosulfate solution. The amount of lead tetraacetate consumed was found to be 96% of that required for the oxidative cleavage of one —CHOHCHOH— group.

Methyl α-chloropropionate (18). To a solution of 845 g. of methyl lactate in 740 g. of pyridine was added, with stirring and cooling, 1000 g. of thionyl chloride. The reaction mixture was heated for three hours on a steam-bath, cooled, the oily phase taken up in ether, the ethereal phase shaken with aqueous sodium carbonate, and dried over anhydrous potassium carbonate. Distillation gave 711 g. (71%) of methyl α-chloropropionate, b.p. 127–130°/748 mm.

Methyl α-methoxypropionate (19). A solution of 290 g. of methyl α-chloropropionate in 100 ml. of methanol was added slowly with stirring to 141 g. of sodium methoxide in 400 ml. of methanol. The reaction mixture was refluxed for three hours, filtered, the excess methanol removed by distillation, the residue taken up in water, and the solution extracted with ether in a continuous extractor. Distillation of the dried ethereal extract gave 177 g. (63%) of methyl α-methoxypropionate, b.p. 127–129°/747 mm.

α-Methoxypropionic acid (20). Methyl α-methoxypropionate, 200 g., was refluxed with 600 ml. of 25% sodium hydroxide until the ester layer disappeared. The hydrolysate was acidified, extracted with ether in a continuous extractor, the ethereal extract dried, and distilled to give 139 g. (79%) of α-methoxypropionic acid, b.p. 87–89°/10 mm., 105–108°/25 mm.

α-Methoxypropionyl chloride (20). Sixty grams of thionyl chloride was added dropwise at 40–50° to 44 g. of α-methoxypropionic acid, and the reaction mixture distilled to give 30 g. (58%) of α-methoxypropionyl chloride, b.p. 46–49°/52 mm. All attempts to prepare 2-methoxy-*n*-hexanone-3 by condensing the above acid chloride with *n*-propylzinc iodide (21) were unsuccessful.

α-Methoxypropionitrile (22). α-Chloroethyl methyl ether, 258 g., was carefully added to 260 g. of dry cuprous cyanide contained in a flask fitted with a mercury sealed stirrer. After the reaction had subsided an additional 100 g. of cuprous cyanide and 95 g. of chloro ether was added, as before, and the mixture refluxed for three hours. The product was then distilled to give 165 g. of crude nitrile, b.p. 110–118°. Fractional distillation of the crude nitrile gave 90 g. (28%) of α-methoxypropionitrile, b.p. 114–115°/747 mm.

*2-Methoxy-*n*-hexanone-3* (23). Seventeen grams of α-methoxypropionitrile in 17 ml. of et her was added to a Grignard reagent prepared from 37 g. of *n*-propyl bromide, 7.3 g. of magnesium, and 60 ml. of ether, at a rate compatible with adequate control. The reaction mixture was allowed to stand for sixteen hours, water was added, the solution acidified with dilute sulfuric acid, and extracted with ether. The ethereal extract was dried and distilled to give 19 g. (73%) of 2-methoxy-*n*-hexanone-3, b.p. 92–93°/100 mm. A portion of the ketone was converted into the semicarbazone, colorless needles (from water), m.p. 168.5–170°.

Anal. Calc'd for $C_8H_{17}N_3O_2$ (187.2): C, 51.3; H, 9.2; N, 22.5.
Found: C, 51.8; H, 9.2; N, 22.6.

*2-Hydroxy-3-amino-*n*-hexane.* Fifty grams of 2-methoxy-*n*-hexanone-3 was reduced with 38 g. of ammonium formate (24), the reaction product hydrolyzed with 30 ml. of conc'd hydrochloric acid, the acid hydrolysate extracted with benzene, the benzene phase discarded, the aqueous phase added to 40 g. of sodium hydroxide in 200 ml. of water, and the amine taken up in ether. The ethereal extract was dried and distilled to give 17 g. (34%) of 2-methoxy-3-amino-*n*-hexane, b.p. 95–98°/100 mm. Ten grams of 2-methoxy-3-amino-*n*-hexane was refluxed for four hours with 50 ml. of hydrobromic acid, sp. gr. 1.5. The hydrolysate was neutralized with sodium hydroxide, saturated with potassium carbonate, the oil taken up in ether, the ethereal extract dried over anhydrous potassium carbonate, and distilled to give 4 g. (45%) of 2-hydroxy-3-amino-*n*-hexane, b.p. 95°/20 mm. The hydroxy amine was condensed with 3,5-dinitrobenzoyl chloride to give the bis-3,5-dinitrobenzoate

of 2-hydroxy-3-amino-*n*-hexane, m.p. 207.2°, after repeated recrystallization from acetic acid.

Anal. Calc'd for $C_{20}H_{19}N_5O_{11}$ (505.4): C, 47.5; H, 3.8; N, 13.9.
Found: C, 47.8; H, 4.0; N, 13.6.

Ethoxyethanal (25). A Pyrex reaction tube 2 cm. in diameter and 140 cm. long, fitted with a Pyrex thermocouple well containing a Chromel P-Alumel thermocouple, was filled with 520 g. of copper oxide pellets about the size of a pea, and the charged tube placed in a vertical electric furnace. After the copper oxide had been reduced with hydrogen at 200°, a flask containing 2-ethoxyethanol (Cellosolve) was fitted to the lower end of the reaction tube and the temperature of the catalyst zone raised to 300–325°. Cellosolve was then distilled into the reaction tube at the rate of 2 liters per twenty-four hours and the products issuing from the upper end of the tube collected. The crude product was distilled through a short column and the low-boiling fraction redistilled through a nine-foot column, packed with one-turn glass helices, at a reflux ratio of 10:1. With fresh catalyst, 1400 ml. of Cellosolve gave 30 g. of azeotrope, b.p. 89–91°, 30 g. of a mixture, b.p. 91–104°, and 96.5 g. of ethoxyethanal, b.p. 104–106°/747 mm.

α-Chloro-β-ethoxyethyl ethyl ether. To 79 ml. of absolute ethanol was added 118 g. of ethoxyethanal at 0°. Dry hydrogen chloride was passed into the cold solution until 49 g. had been dissolved. The upper oily phase was collected and rapidly dried over anhydrous calcium chloride. The crude product was distilled to give 105 g. (51%) of colorless α-chloro-β-ethoxyethyl ethyl ether, b.p. 68–73°/30 mm.

Diethylglyceronitrile (22). Twenty-five grams of α-chloro-β-ethoxyethyl ethyl ether was added slowly with vigorous stirring to a suspension of 40 g. of powdered mercuric cyanide in 100 ml. of ligroin (60–70°) at refluxing temperature. Refluxing and stirring was continued for three hours after which the salt was removed and the product distilled to give 14 g. (60%) of diethylglyceronitrile, b.p. 96–98°/34 mm.

Anal. Calc'd for $C_7H_{13}NO_2$ (143.2): C, 58.7; H, 9.2.
Found: C, 58.7; H, 9.2.

*1,2-Diethoxy-*n*-hexanone-3* (22). To a solution of propylmagnesium bromide, prepared from 22 ml. of *n*-propyl bromide, 5.95 g. of magnesium and 100 ml. of dry ether, was added dropwise with vigorous stirring 23.3 g. of diethylglyceronitrile in 5 volumes of dry ether, and the mixture refluxed for thirty minutes. After the addition of saturated aqueous ammonium chloride the solution was extracted with ether and the ketimine, b.p. *ca.* 100°/10 mm. isolated by distillation. The ketimine was hydrolyzed in dilute sulfuric acid at 60°, the ketone taken up in ether, and the dried ethereal extract distilled to give 6.4 g. (21%) of 1,2-diethoxy-*n*-hexanone-3, b.p. 114–116°/30 mm.

Anal. Calc'd for $C_{10}H_{20}O_3$ (188.3): C, 63.8; H, 10.7.
Found: C, 61.8; H, 10.7.

*1,2-Diethoxy-3-amino-*n*-hexane.* A solution of 6.1 g. of 1,2-diethoxy-*n*-hexanone-3 in 100 ml. of methanolic ammonia was hydrogenated at 150 atmospheres and 150° with 4 g. of Raney nickel (26). The catalyst was removed and the solution distilled to give 4.07 g. (66%) of 1,2-diethoxy-3-amino-*n*-hexane, b.p. 85–87°/6 mm., 93–95°/10 mm.

Anal. Calc'd for $C_{10}H_{23}NO_2$ (189.5): C, 63.4; H, 12.2; N, 7.4.
Found: C, 63.6; H, 12.2; N, 7.6.

*1,2-Dihydroxy-3-amino-*n*-hexane.* 1,2-Diethoxy-3-amino-*n*-hexane, 3.95 g., was refluxed for three hours with 50 ml. of hydrobromic acid, sp. gr. 1.5. The excess hydrobromic acid was removed by repeated evaporation following the addition of water, and the aqueous solution of the residue extracted with ether. The ethereal phase was discarded, the aqueous phase freed of inorganic ions, and the basic solution distilled to give 1.0 g. (36%) of 1,2-dihydroxy-3-amino-*n*-hexane, b.p. 92–95°/0.1 mm.

*N-Carbobenzyloxy-1,2-dihydroxy-3-amino-*n*-hexane.* 1,2-Dihydroxy-3-amino-*n*-hexane was carbobenzyloxylated by shaking it with equimolal quantities of carbobenzyloxy chloride (17) and *N* sodium hydroxide. Recrystallization of the crude product from methanol-

isopropyl ether mixtures gave N-carbobenzyloxy-1,2-dihydroxy-3-amino-*n*-hexane, m.p. 109–110°.

Anal. Calc'd for $C_{14}H_{21}NO_4$ (267.3): C, 62.9; H, 7.9; N, 5.4.
Found: C, 63.1; H, 7.9; N, 5.6.

*Oxidation of N-carbobenzyloxy-1,2-dihydroxy-3-amino-*n*-hexane with sodium periodate.* To 10 ml. of 0.1027 *N* sodium periodate was added 0.0932 g. of N-carbobenzyloxy-1,2-dihydroxy-3-amino-*n*-hexane, the solution allowed to stand for ten hours, 10 ml. of borate-boric acid buffer solution (16) and an excess of potassium iodide added, and the liberated iodine titrated with standard arsenite solution. The ratio mole IO_4^- consumed/mole substrate was found to be 0.9.

*Oxidation of N-carbobenzyloxy-1,2-dihydroxy-3-amino-*n*-hexane with lead tetraacetate.* Twenty milliliters of 0.07 *N* glacial acetic acid solution of lead tetraacetate was added to 0.0870 g. of N-carbobenzyloxy-1,2-dihydroxy-3-amino-*n*-hexane, and the solution was allowed to stand for twenty hours at 25°. An excess of potassium iodide-sodium acetate solution was added, and the liberated iodine was titrated with standard thiosulfate solution. The amount of lead tetraacetate consumed was found to be 99% of that required for the oxidative cleavage of one —CHOHCHOH— group.

SUMMARY

1-Amino-2,3-dihydroxy-*n*-hexane and 1,2-dihydroxy-3-amino-*n*-hexane have been synthesized and the oxidative degradation of these compounds, and their N-acyl derivatives, by periodate and lead tetraacetate has been studied.

PASADENA, CALIF.

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

STUDIES IN THE BROMINATION OF STEROID KETONES

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It has been proposed by Butenandt *et alii* (1) that the structure of the dibromide, m.p. 174° (2), obtained by bromination of either cholestanedione-3,6 (I) or of cholestene-4-dione-3,6 (II) is represented by III below. The structure of the tribromide m.p. 195° (2) resulting from further bromination of III (or directly from I or II) is given as IV (1).

The evidence contributed by Butenandt supporting these structures is as follows:

1. The absorption spectra indicate the same conjugate unsaturation which is present in cholestene-4-dione-3,6 (II).

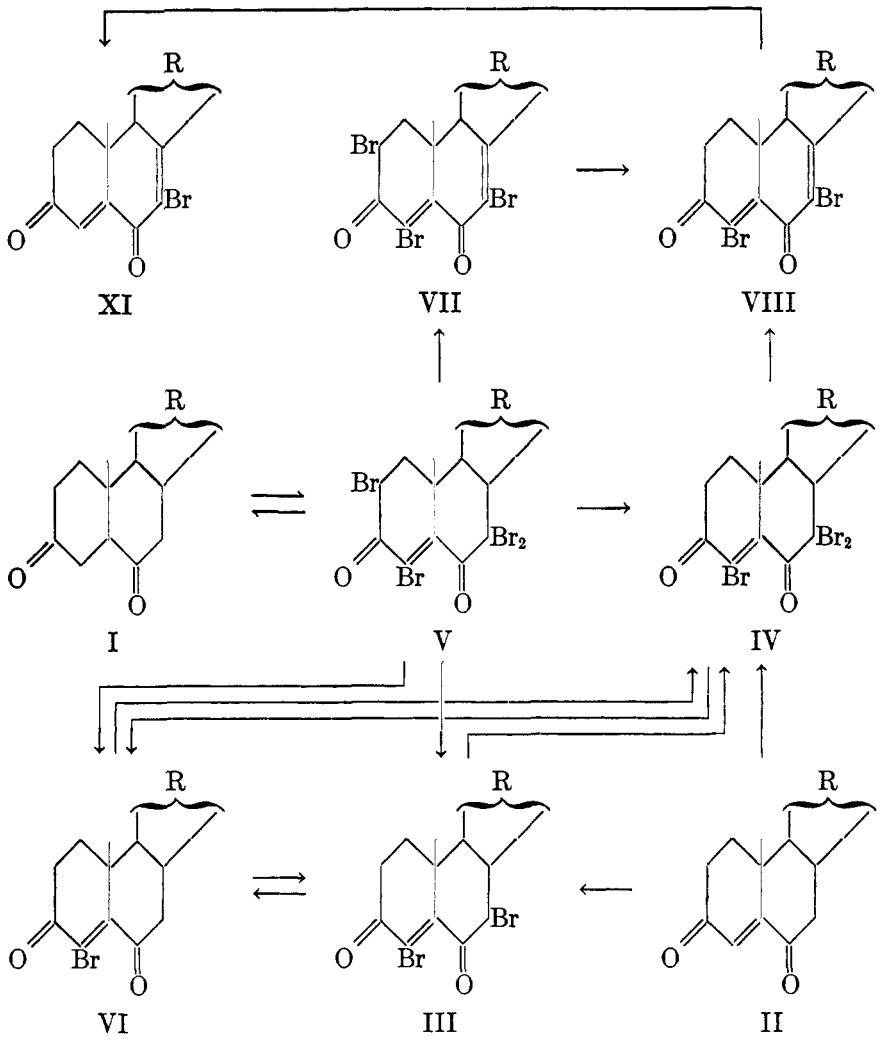
2. Compound III yields a diquinoxaline derivative on treatment with *o*-phenylenediamine, which is evidence for placing one Br at the C_7 position, and the second either at C_2 or C_4. That it is more probably at C_4 is suggested by analogy with the course of bromination of cholestene-4-one-3, the C_2 position of which is not attacked by bromine in the presence of hydrogen bromide (1). This supposition is supported also by the fact that coprostanedione-3,6 also yields compound III. In this latter compound rings A and B are *cis* and, therefore, favor orientation of entering bromine atoms at C_4 rather than at C_2.

3. Evidence that IV represents the tribromide is offered by its reaction with *o*-phenylenediamine to give the same diquinoxaline obtained from III.

In certain studies on the bromination of steroid ketones carried out in this laboratory it has been found that cholestanedione-3,6 on treatment with nine moles of bromine yields a white crystalline unsaturated tetrabromide (V), m.p. 190°. A 15% solution of hydrogen bromide in acetic acid reduces V quantitatively to IV (3). The latter reaction seems even in a high concentration of bromine to be irreversible. Neither has it been found possible to prepare V from cholestene-4-dione-3,6 or from 4,7-dibromocholestene-4-dione-3,6.

Absorption spectrum measurements indicate the presence in the tetrabromide of the conjugate unsaturation shown in formula V. Treatment with iron and alcohol reduces the tetrabromide to I through two isolable intermediates—III and VI. Treatment with silver nitrate and pyridine at room temperature gives a pale yellow tribromocholestadienedione (VII), m.p. 164°. The latter is readily reducible by the action of hydrogen bromide to 4,7-dibromocholestadiene-4,7-dione-3,6 (VIII), a compound previously obtained by Butenandt (1) directly by the action of pyridine and silver nitrate on IV, and to which he assigned the structure VIII.

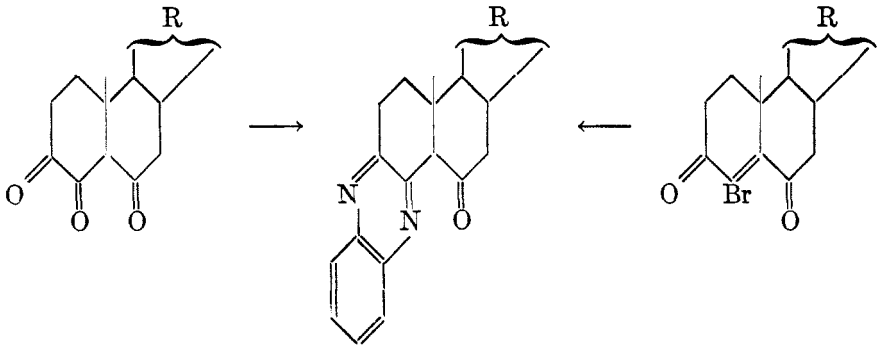
The presence of one bromine atom in the same position in III, IV, and V is apparent, since all are reducible to the monobromide VI under such mild conditions that the possibility of a rearrangement may be eliminated. Absorption



R = $C_{16}H_{30}$

spectrum measurements indicate that this compound is a monobromo derivative of II. That it is 4-bromocholestene-4-dione-3,6 is evident, since with *o*-phenylenediamine it condenses to the same quinoxaline (IX) obtained from cholestanetrione-3,4,6 (X). Efforts to hydrolyze VI directly to X proved unavailing. This is to be expected, since it is known that α,β-diketones are in general sensitive to rearrangement and oxidation in alkaline media.

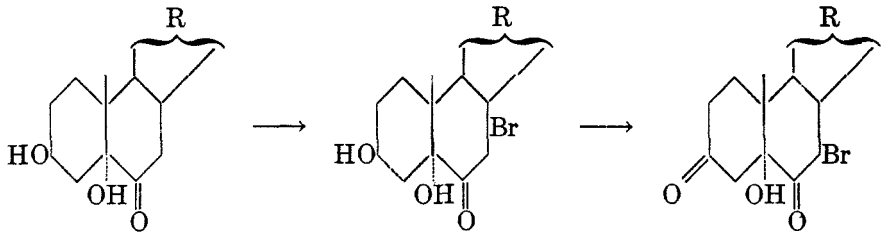
With the location of one bromine atom fixed at the C_4 position in III, IV, V, and VI, the formation of a diquinoxaline derivative from III is good proof that the second bromine atom in this compound is at C_7. With the hope of furnishing further proof for the structure of the dibromide (III), we undertook the synthesis of 7-bromocholestene-4-dione-3,6 (XII). For this purpose two methods im-



X IX VI

R = $C_{16}H_{30}$

mediately suggested themselves: (a) bromination of cholestanediol-3(β), 5(α)-one-6 (XIII), oxidation of the resulting 7-bromo derivative (XIV) to the corresponding diketone (XV), followed by splitting off of water at the C_4—C_5 positions; (b) hydrolysis of either 5,7- or 5′,7-dibromocholestanol-3-one-6 acetate (XVI), oxidation of the resulting alcohol (XVII) to 5,7- or 5′,7-dibromocholestanedione-3,6 (XVIII), followed by partial dehydrobromination at the C_4—C_5 positions.

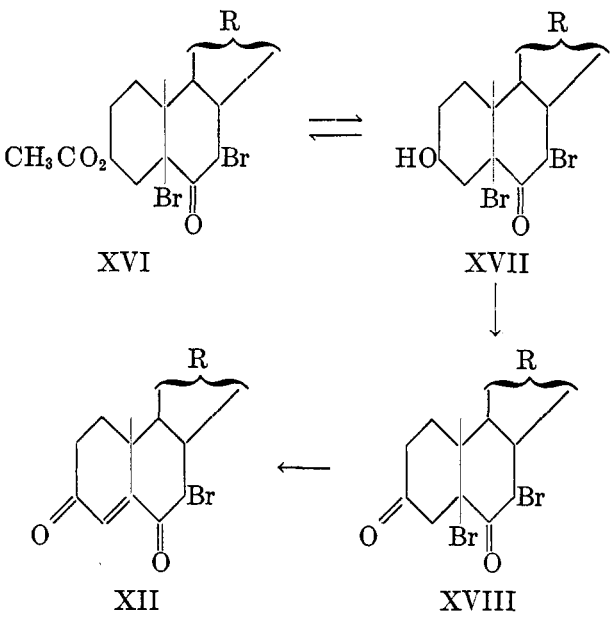


XIII XIV XV

R = $C_{16}H_{30}$

The first method failed because of the impossibility of finding a dehydrating agent which would be sufficiently strong to split the hydroxyl group in C_5, and not at the same time isomerize the product. See following page. The second method was successful only with 5(β),7-dibromocholestanol-3-one-6 acetate (XVI) designated as the 5′,7 derivative by Heilbron *et alii* (4).[1]

[1] The reason for assigning the β, or *cis*, configuration to the C_5 bromine in the so-called 5′,7-dibromocholestanol-3-one-6 acetate and the α configuration to its isomer, 5,7-dibromocholestanol-3-one-6 acetate is found in the fact that the latter compound has been shown to have the same configuration at C_5 as 5-bromocholestanol-3-one-6 acetate (4). This compound in turn yields on basic hydrolysis a cholestanediolone which is stereoisomeric about C_5 with cholestanediol-3(β),5(α)-one-6 [Ellis and Petrow, *J. Chem. Soc.*, 1078 (1939)] and is, therefore, cholestanediol-3(β),5(β)-one-6. As Ellis and Petrow have pointed out, an inversion must have occurred either during bromination or during hydrolysis of the 5-bromocholestanol-3-one-6 acetate. It has been demonstrated that nucleophilic attacks



R = $C_{16}H_{30}$

Attempted hydrolysis of the 5(α),7-dibromocholestanol-3-one-6 acetate led only to intractable gels. Acid hydrolysis of XVI went smoothly, however, giving a high yield of 5(β),7-dibromocholestanol-3-one-6 (XVII). The latter was readily oxidized by chromic oxide at room temperature to 5(β),7-dibromocholestanedione-3,6 (XVIII). This compound, on treatment with potassium acetate in dilute acetic acid at 100°, gave the desired product, 7-bromocholestene-4-dione-3,6, crystals of which melted at 130–131°, and were yellow, resembling cholestene-4-dione-3,6.

It was also found that this product was unstable toward mineral acids and to boiling neutral solvents. Consequently, in order to eliminate probable rearrangement or partial isomerization, further bromination of the compound XII had to be effected in the presence of acetate ion. When this was done, an unsaturated dibromo diketone, isomeric with III, was obtained. This compound should be either 2,7-dibromocholestene-4-dione-3,6 (XX) or 7,7-dibromocholestene-4-dione-3,6 (XXa). It exhibited the same instability toward hot unbuffered solvents as XII. It reacted with *o*-phenylenediamine very rapidly in alcohol solution to give a diquinoxaline derivative (XIX) isomeric with the corresponding diquinoxaline derivative obtained from III or IV. This fact would tend to show that the dibromide had the structure XX rather than XXa.

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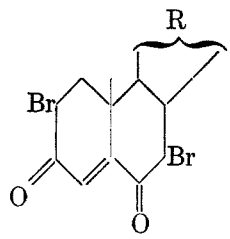
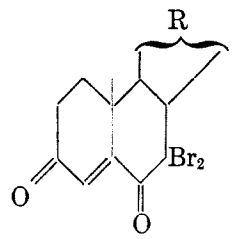
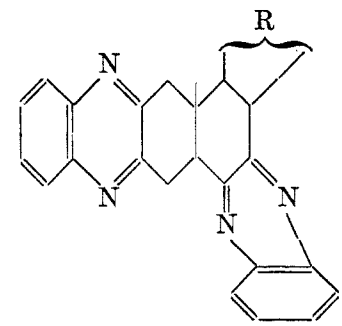
on carbon proceed almost without exception with inversion. [*Cf.* Hughes, *Trans. Faraday Soc.*, **34**, 202 (1938); **37**, 603 (1941)]. It is most likely, therefore, that the inversion occurred during the hydrolysis rather than the bromination. If this is true, then both the 5-bromo- and the 5,7-dibromo-cholestanolone acetates have the *trans* or α configuration. Hence the 5',7- compound is 5(β),7-dibromocholestanol-3-one-6 acetate.



XX



XXa



XIX

R = $C_{16}H_{30}$

This evidence cannot be considered conclusive, however, in view of the instability of the dibromide toward the solvent. Further bromination of XX (or XXa) in the presence of sodium acetate proceeded very slowly; from the mixture only starting material was isolated. It is also of interest in this connection that, although compound III reacted readily with one mole of bromine in the presence of sodium acetate, no crystalline product was isolated.

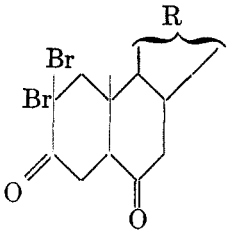
We have also made certain studies on the bromination of cholestanedione-3,6 (I) in the presence of acetate ion. Although in the reaction catalyzed by hydrobromic acid no homogeneous product may be isolated from the action of either one or two moles of bromine on I, when the reaction is carried out in the presence of sodium acetate a dibromocholestanedione is readily obtained. To this compound we have tentatively assigned the structure of 2,2-dibromocholestanedione-3,6 (XXI). Our reasons for this follow.

In view of the inertness of the 5 and 7 positions in cholestanol-3-one-6 acetate toward bromine in the presence of acetate ion it would appear that the locations of the two bromine atoms are limited to the C_2 and the C_4 positions.

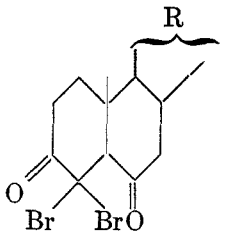
Windaus and Mielke (5) have shown that when an acetic anhydride solution of cholestanedione-3,6 is treated with sulfuric acid, sulfonation takes place at the C_2 position. Since in modern theories of substitution reactions, both sulfonation and bromination processes involve an electrophilic attack of the reagent, it is not improbable that in this particular case bromine has entered the steroid molecule at C_2.

Also we have found that the rate of bromination of the unisolable intermediate monobromide is much greater than that of cholestanedione itself; with one mole of bromine only the dibromide and starting material are obtained. This is a strong indication that the second molecule of bromine attacks the carbon atom to which the first bromine atom is attached.

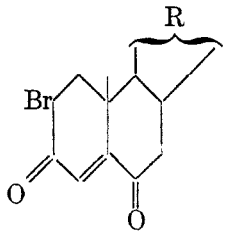
In addition, we have made the observation that when the dibromide in question is refluxed with pyridine, one molecule of hydrogen bromide is lost and a monobromocholestenedione (XXII) is formed. The latter is characterized by an absorption spectrum with a maximum at 257 μ. If for the saturated dibromo diketone the two most probable structures (XXI and XXIa) are considered,



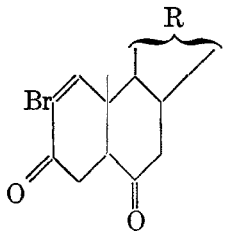
XXI



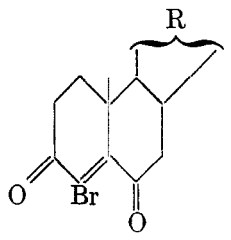
XXIa



XXII



XXIIa



VI

R = $C_{16}H_{30}$

it is seen that the possible products resulting from the loss of one molecule of hydrogen bromide are XXII, XXIIa, and VI. Since the properties of the monobromocholestenedione are different from those of VI, the formula XXIa may be eliminated as a possible structure for the dibromocholestanedione. For the latter compound then, XXI becomes the preferred formula. The absorption maximum of the corresponding monobromocholestenedione indicates, however, that the latter does not have the expected structure XXIIa. If XXIIa were the correct formula for the latter, an absorption maximum of not more than 240 μ would be expected, *i.e.* the approximate value for an α,β-unsaturated ketone with a halogen atom substituted in the α position (6). It would be expected, however, that the absorption maximum for the structure XII would be in the neighborhood of 257 μ, the sum of the value for cholestene-4-dione-3,6 (252 μ) and the positive increment due to the α substituted bromine atom (*ca.* 5 μ). Since this value is in good agreement with that experimentally found for the monobromocholestenedione, the latter compound is assigned structure XXII, 2-bromocholestene-4-dione-3,6. Hence, in the conversion of XXI to XXII a rearrangement occurred analogous to that observed by Ruzicka (7) in the pyridine dehydrobromination of 2-bromocholestanone-3.

Finally we should like to point out that a study of the observations outlined above on the bromination of cholestanedione-3,6 and cholestene-4-dione-3,6 seems to indicate that the respective reactions follow a different course.

In the case of cholestene-4-dione-3,6 (II), substitution of bromine proceeds directly at the C_4 and C_7 positions. It is our belief that in cholestanedione-3,6 (I), however, bromine substitutes initially in the C_2 position. That this is true is shown by the fact that from the bromination of cholestandione-3,6 compounds

containing a bromine atom at C_2 (V and XXI) may be isolated, whereas from the bromination of cholestene-4-dione-3,6 into brominated derivatives (III and VI) no compounds containing bromine in the C_2 position are formed.

The explanation of the formation of III and IV from cholestandione-3,6 lies in the fact that a further attack of bromine leads to the introduction of a double bond at the C_4—C_5 position. This conjugated system of unsaturation activates the bromine atom first introduced at C_2 so that over a period of time it becomes reduced by the hydrogen bromide present in the reaction mixture. Confirmation of this explanation lies in the experimental observations that hydrogen bromide irreversibly reduces V to IV.

EXPERIMENTAL PART

In the experiments described below on the absorption spectra of various compounds

$$\epsilon = \frac{1}{cd} \log \frac{I_0}{I}$$

where ϵ is the extinction coefficient, c is the concentration expressed in grams of solute per 100 cc. of solvent, d is the thickness in centimeters, and $\frac{I_0}{I}$ is the ratio of initial intensity to final intensity. The relationship between ϵ and E, the molecular extinction coefficient is:

$$E = \frac{M\epsilon}{10}$$

where M is the molecular weight.

All melting points in this paper have been recorded as observed and hence are uncorrected. All absorption spectra were taken in ethyl alcohol (95%). All rotations were taken in chloroform in a 1 dm. tube. (c = 1.0–1.2.)

Preparation of 2,4,7,7-tetrabromocholestene-4-dione-3,6 (V). Cholestanedione-3,6 (2.3 g.) in 10 cc. of dry chloroform was treated over a period of five minutes with a mixture of 2.5 cc. of bromine (9 moles) and 10 cc. of glacial acetic acid. The mixture was allowed to stand at room temperature for eighteen hours, was then diluted with chloroform, washed with water in a separatory funnel, then with a dilute solution of sodium sulfite, and finally again with water. After drying over anhydrous sodium sulfate the chloroform solution was evaporated to a small volume on the steam-bath and methanol added. White needles of 2,4,7,7-tetrabromocholestene-4-dione-3,6 precipitated, which after several recrystallizations from chloroform-methanol or benzene-methanol melted at 190°. $[\alpha]_D^{20}$ +22°; $\lambda_{max.}$ = 254μ; ϵ = 124; yield 2.4 g.

Anal. Calc'd for $C_{27}H_{38}Br_4O_2$: C, 45.40; H, 5.36; Br, 44.76.
Found: C, 45.9; H, 5.6; Br, 44.7.

Preparation of 4,7,7-tribromocholestene-4-dione-3,6 (IV). (a) 2,4,7,7-Tetrabromocholestene-4-dione-3,6 (20 mg.) in 1 cc. of chloroform was treated with a few drops of 15% solution of hydrogen bromide in acetic acid. A faint orange color was immediately produced due to the liberation of free bromine. Addition of a small amount of methanol precipitated the pale yellow 4,7,7-tribromocholestene-4-dione-3,6 in nearly quantitative yield, m.p. after one recrystallization from benzene-methanol 195°, not depressed by admixture with an authentic sample prepared from cholestene-4-dione-3,6 $[\alpha]_D^{20}$ +16°.

(b) A reaction mixture prepared as described in the preparation of (V) (*vide supra*) was allowed to stand for 48 hours. On working up the product, crystals of IV were obtained, m.p. 195°, $[\alpha]_D^{20}$ +16°.

(c) Five hundred milligrams of V was dissolved in a mixture of chloroform and acetic acid containing 9 moles of bromine and 2.5 moles of iodine. After standing 19 hours the reaction mixture was worked up in the usual manner. Crystals of IV were obtained, m.p. 195°.

Preparation of 4,7-dibromocholestene-4-dione-3,6 (III) from (V). Two and eight-tenths grams of V was dissolved in a mixture of 40 cc. of benzene and 1.2 cc. of alcohol, 2.0 g. of fine iron powder was added, and the mixture refluxed for 2 hours. The red solution was then decanted from the remaining iron, washed several times with water to hydrolyze the iron salts, filtered, and dried over anhydrous sodium sulfate. The clear yellow solution was then evaporated to a small volume. Addition of methanol caused a slow deposit of fine white needles, which after one recrystallization from chloroform-methanol melted at 175°; mixed m.p. with an authentic sample of 4,7-dibromocholestene-4-dione-3,6, 174–175°; $[\alpha]_D^{20}$ +82° (identical with the authentic material); yield 0.5 g.

Preparation of cholestanedione-3,6 (I) from compound (V). Three and seven-tenths grams of (V) in 200 cc. of alcohol was refluxed over 4.0 g. of finely divided iron powder for 5 hours. The resulting solution was worked up as usual. The product recrystallized from alcohol showed the melting point 171°, undepressed with an authentic specimen of cholestanedione-3,6; yield 1.1 g.

Preparation of 4-bromocholestene-4-dione-3,6. (VI). (a) One gram of compound V in 35 cc. of benzene and 1.0 cc. of alcohol was refluxed with 1.5 g. of finely divided iron powder for 2.2 hours. After working up the products by the usual method, 250 mg. of pure 4-bromocholestene-4-dione-3,6 was obtained, m.p. 169.5°. $[\alpha]_D^{20}$ −38°. $\lambda_{max.}$ = 254μ; ϵ = 190.

Anal. Calc'd for $C_{27}H_{41}BrO_2$: C, 67.89; H, 8.66; Br, 16.75.
Found: C, 67.8; H, 8.5; Br, 16.9.

(b) One gram of compound IV in 35 cc. of benzene and 3.0 cc. of alcohol was refluxed with 2 g. of iron powder for 6 hours. The solution after washing with water and drying was taken down on the steam-bath until all solvent was removed. Light petroleum ether was then added. The solution after standing at 0° for a day deposited 300 mg. of crude 4-bromocholestene-4-dione-3,6, which after several recrystallizations had the melting point 169.5°, which was not depressed when the compound was mixed with a sample of VI prepared by methods (a) or (c).

(c) Two and six-tenths grams of compound III in 70 cc. of benzene and 5.2 cc. of alcohol was refluxed for 6 hours with 3.5 g. of iron powder. Addition of methanol to the washed, dried, and concentrated solution precipitated white needles of VI, which after one recrystallization melted at 169.5°, undepressed in mixture with a specimen prepared by methods (a) or (b); yield 1.0 g.

Preparation of 2,4,7-tribromocholestadiene-4,7-dione-3,6 (VII). One gram of compound V was dissolved in 20 cc. of dry pyridine. To this solution was added a solution of 1.0 g. of silver nitrate in 10 cc. of dry pyridine. After standing for 48 hours at room temperature the product was taken up in ether, washed with water and dilute sulfuric acid, dried over anhydrous sodium sulfate, and evaporated to dryness on the steam-bath. The oily product was taken up in a small amount of chloroform, and methanol was added. Large yellowish plates of 2,4,7-tribromocholestadiene-4,7-dione-3,6 slowly deposited, which after two recrystallizations from chloroform-methanol melted at 164°, $[\alpha]_D^{20}$ −38°; yield 400 mg.; $\lambda_{max.}$ = 265μ; ϵ = 225.

Anal. Calc'd for $C_{27}H_{37}Br_3O_2$: C, 51.20; H, 5.89; Br, 37.86.
Found: C, 51.2; H, 6.1; Br, 37.68, 38.06.

Preparation of 4,7-dibromocholestadiene-4,7-dione-3,6 (VIII) from (VII). Twenty milligrams of compound XXV in 0.5 cc. of dry chloroform was treated with 4 drops of 15% solution of hydrogen bromide in acetic acid. After standing for 5 minutes, 2 cc. of methanol was added. Long needles of 4,7-dibromocholestadiene-4,7-dione-3,6 separated, which after one recrystallization from chloroform-methanol melted at 182° and were not depressed in melting point on admixture with an authentic sample; $[\alpha]_D^{20}$ −18°; yield 18 mg.

Preparation of 7-bromocholestadiene-4,7-dione-3,6 (XI) from VII. Five hundred milli-

grams of VII in 30 cc. of benzene and 3.0 cc. of alcohol was refluxed over 2 g. of iron powder for 6 hours. The product obtained after working up in the usual manner melted at 182° and gave no depression on mixture with an authentic sample of 4-bromocholestadiene-4,7-dione-3,6; $[\alpha]_D^{20}$ −141°; yield 250 mg.

Preparation of the quinoxaline derivative (IX). One and one-tenth grams of VI was dissolved in 170 cc. of absolute alcohol containing 1.1 g. of *o*-phenylenediamine. The mixture was refluxed for 7 hours, then taken up in ether, washed several times with dilute hydrochloric acid, dried over anhydrous sodium sulfate, and evaporated to dryness on the steam-bath. The product was then taken up in ethyl acetate and alcohol; after a few hours the red solution began to deposit the crystalline quinoxaline. After two recrystallizations from chloroform-alcohol, orange needles were obtained which melted at 143° to an opaque liquid, clearing sharply at 157°. On remelting, the solidified material showed the same melting behavior; yield 200 mg.

Anal. Calc'd for $C_{33}H_{46}N_2O$: C, 81.41; H, 9.53; N, 5.74.
Found: C, 81.0; H, 9.5; N, 5.8.

(b) Two hundred milligrams of cholestanetrione-3,4,6 was fused with 100 mg. of *o*-phenylenediamine for 45 minutes on the steam-bath. The product after working up as in (a) and recrystallizing once from chloroform-methanol melted partially at 143° and cleared sharply at 157°. The same behavior was observed with the resolidified material. The mixed melting point with the product prepared from VI showed no depression; yield 40 mg.

Preparation of 5(β), 7-dibromocholestanol-3-one-6 (XVII). One and one-tenth grams of 5(β),7-dibromocholestanol-3-one-6 acetate was refluxed for 30 minutes in a mixture of 50 cc. of alcohol and 4 cc. of 34% hydrochloric acid. On cooling, 850 mg. of XVII precipitated as white crystals, decomposition point about 140°. After two recrystallizations from ethyl acetate-methanol the compound had the decomposition point 117–119°; $[\alpha]_D^{20}$ −50°.

Reacetylation of XVII. Thirty milligrams of 5(β),7-dibromocholestanol-3-one-6 in 1 cc. of acetic anhydride was heated at 100° for 30 minutes, then refluxed for 15 minutes. On cooling, crystalline plates of the acetate m.p. 129° separated, showing no depression of mixed melting point with XVI.

Preparation of 5(β),7-dibromocholestanedione-3,6. (XVIII). One and eight-tenths grams of 5(β),7-dibromocholestanol-3-one-6 was dissolved in 150 cc. of glacial acetic acid by warming on the steam-bath. The solution was then cooled rapidly to room temperature, reprecipitating part of the dibromide. To this suspension was then added over a period of 30 minutes (with shaking) a solution of 900 mg. of chromium trioxide in 60 cc. of 97% acetic acid. After the mixture had stood at room temperature for 12–15 hours, water was added carefully, precipitating the diketone in the form of a gel which disintegrated into a white crystalline powder after a few hours. This was filtered off and recrystallized twice by dissolving in a large volume of acetone at 30°, adding water until crystallization began then chilling to 0°. In this manner there was obtained a dense white crystalline product which, when dry, decomposed at 100°. It also decomposed rapidly in boiling benzene evolving hydrogen bromide and giving a yellow oil. $[\alpha]_D^{20}$ −41°. Yield 1.1 g.

Anal. Calc'd for $C_{27}H_{42}Br_2O_2$: C, 58.08; H, 7.58; Br, 28.62.
Found: C, 57.8; H, 7.9; Br, 29.0.

Preparation of 7-bromocholestene-4-dione-3,6 (XII). Two and eight-tenths grams of 5(β),7-dibromocholestanedione-3,6 was suspended in 1 liter of glacial acetic acid at 30°. To this was rapidly added 200 cc. of 50% aqueous acetic acid solution containing 8.0 g. of potassium acetate. The mixture was then heated over a period of 15 minutes. When the temperature reached 95° the reaction was completed. The resultant bright yellow solution was then cooled to room temperature and water added until the precipitation of the product, 7-bromocholestene-4-dione-3,6, was complete. The latter was found to be remarkably sensitive to mineral acids and to boiling in benzene, chloroform, acetone, etc. It could, however, be recrystallized from dilute acetic acid containing a small amount of sodium acetate, from which it separated with reluctance as yellow plates, resembling cholestene-4-dione-3,6. For purposes of analysis it was recrystallized several times by this method and

finally by the rather inefficient method of dissolving in cold ethyl acetate, adding methanol, and chilling to −10°. The product melted at 130–131°; $[\alpha]_D^{20}$ −41°; $\lambda_{max.}$ = 259μ; ε = 152; yield 1.0 g.

Anal. Calc'd for $C_{27}H_{41}BrO_2$: Br, 16.75. Found: Br, 16.6.

Reduction of compound XII to cholestanedione-3,6. Twelve milligrams of XII in 2 cc. of alcohol was refluxed over 30 mg. of zinc dust for 45 minutes. The solution was then filtered free of zinc, and water was added. White needles of cholestanedione-3,6 slowly formed; melting point and mixed melting point 169°.

Preparation of 2,7-dibromocholestene-4-dione-3,6 (XX). One and nine-hundredths grams of XII in 5 cc. of chloroform was treated with 15 cc. of a solution of acetic acid containing 0.36 g. of bromine (1 mole) and 0.36 g. of anhydrous sodium acetate. Decolorization was complete in a few hours. The chloroform was then removed *in vacuo* at 0°, methanol added, and the solution chilled. Eight hundred milligrams of XX crystallized out in yellow needles, m.p. 119°. No completely satisfactory solvent was found from which to recrystallize the product. Several recrystallizations from a small volume of petroleum ether (b.p. 60–74°) did not raise the m.p. Warming in alcohol or other polar solvent lowered the m.p. and gave a less pure product; $[\alpha]_D^{26}$ +118°; $\lambda_{max.}$ = 260μ; ε = 183.

Anal. Calc'd for $C_{27}H_{40}Br_2O_2$: C, 58.26; H, 7.25; Br, 28.74.
Found: C, 58.3; H, 7.3; Br, 28.7.

Preparation of the quinoxaline derivative XIX. A mixture of 350 mg. of 2,7-dibromocholestene-4-dione-3,6 and 350 mg. of *o*-phenylenediamine in 85 cc. of absolute alcohol was refluxed for 90 minutes. The solution was taken up in ether, washed with water and dilute hydrochloric acid, and evaporated to a small volume. Addition of alcohol and a small amount of ethyl acetate caused a slow precipitation of the quinoxaline. After two recrystallizations from ethyl acetate and alcohol, 33 mg. of red crystals of m.p. 194° was obtained. Mixed m.p. with the diquinoxaline derivative of III (m.p. 208°) 179–181°.

Anal. Calc'd for $C_{39}H_{46}N_4$: C, 81.78; H, 8.45; N, 9.78.
Found: C, 81.7; H, 8.5; N, 9.7.

Bromination of compound XX. One hundred fifty-five milligrams of 2,7-dibromocholestene-4-dione-3,6 in 1 cc. of chloroform was treated with 3 cc. of acetic acid containing 51 mg. of anhydrous sodium acetate and 46 mg. of bromine (1 mole). After decolorization, which required about a week, a few cc. of methanol was added and the chloroform removed *in vacuo*. Chilling caused deposition of 80 mg. of starting material. The mother liquor slowly deposited a nearly colorless oil, which could not be crystallized.

Preparation of 7-bromocholestanediol-3(β),5(α)-one-6 (XIV). Three grams of cholestanediol-3(β),5(α)-one-6 in 50 cc. of chloroform was treated with 15 cc. of acetic acid containing 0.37 cc. of bromine (1 mole). The mixture was maintained at 35° until decolorization. It was then diluted with chloroform, washed thoroughly with water, dried over sodium sulfate, and evaporated to a volume of 25 cc. on the steam-bath. Addition of a few drops of dilute methanol induced crystallization. After several recrystallizations from alcohol and dilute acetone the product consisted of white needles which decomposed at 250°; $[\alpha]_D^{26}$ −24°; yield 2.0 g.

Anal. Calc'd for $C_{27}H_{45}Br_2O_3$: C, 65.17; H, 9.11; Br, 16.06.
Found: C, 65.0; H, 8.9; Br, 16.2.

Preparation of 7-bromocholestanediol-3(β),5(α)-one-6 acetate. Either by direct bromination of cholestanediol-3(β),5(α)-one-5 acetate under the conditions described for the preparation of XIV, or by the acetylation of XIV with boiling acetic anhydride, 7-bromocholestanediol-3(β),5(α)-one-6 acetate was formed, crystallizing in white fluffy needles containing solvent of crystallization. A sample crystallized several times from methanol melted at 172°. Reduction with zinc dust and boiling alcohol gave cholestanediol-3(β),5(α)-one-6, m.p. and mixed m.p. 234°; $[\alpha]_D^{25}$ +19°.

Anal. Calc'd for $C_{29}H_{47}BrO_4 \cdot CH_3OH$: C, 63.03; H, 8.99; Br, 14.00.
Found: C, 62.8; H, 9.1; Br, 14.1.

Preparation of 7-bromocholestanol-5(α)-dione-3,6 (XV). Four hundred milligrams of 7-bromocholestanediol-3(β),5(α)-one-6 was dissolved in 40 cc. of glacial acetic acid by warming on the steam-bath. The solution was then cooled to 15° and treated dropwise with 10 cc. of 90% acetic acid solution containing 200 mg. of chromium trioxide. After 3 cc. had been added the solution was permitted to warm to room temperature, the remainder then added, and the mixture permitted to stand for 21 hours. It was then diluted with water, extracted with ether, washed clean of chromic salts, dried over anhydrous sodium sulfate, and evaporated on the steam-bath. The partially solvated product was obtained with difficulty from warm dilute acetone as fluffy white needles. The compound had a strong tendency to give gels instead of crystals. It showed the melting point range 165–171° after drying at 100°. Reduction with zinc dust and boiling alcohol gave cholestanol-5(α)-dione-3,6, m.p. and mixed m.p. 232°. Attempted dehydration with 95% formic acid both at room temperature and 100°, also with dry hydrogen chloride and dry hydrogen bromide in chloroform, and hot acetic anhydride, led to uncrystallizable oils.

Preparation of 2,2-dibromocholestanedione-3,6 (XXI). Three and four-tenths grams of cholestanedione-3,6 in 25 cc. of chloroform was treated with 30 cc. of acetic acid containing 2 moles of bromine and 2.5 moles of sodium acetate. As the mixture decolorized, small hard needles of the dibromide deposited. When the reaction was complete, the crystals were filtered off and the mother liquor worked up for a further yield. After one recrystallization from chloroform-ethyl acetate, the product decomposed sharply at a temperature between 175° and 195° depending chiefly on the rate of formation of the crystals; the smaller crystals resulting from rapid cooling of the chloroform-ethyl acetate solution had the higher decomposition point. In the dry state the dibromide slowly decomposed at room temperature. The compound is insoluble in all the common organic solvents with the exception of chloroform and pyridine. Treatment with silver nitrate and pyridine at room temperature gave an oil. No crystalline quinoxaline derivative could be obtained. The dibromide had $[\alpha]_D^{24}$ +65°; $\lambda_{max.} < 230\mu$; yield 2.8 g.

Anal. Calc'd for $C_{27}H_{42}Br_2O_2$: C, 58.08; H, 7.58; Br, 28.62.
Found: C, 58.0; H, 7.6; Br, 28.6.

Preparation of 2-bromocholestene-4-dione-3,6 (XXII). A solution of 400 mg. of 2,4-dibromocholestanedione-3,6 in 15 cc. of dry pyridine was refluxed for 5 hours. It was then cooled, taken up in ether, washed with dilute hydrochloric acid, then with water, and finally taken down to a small volume on the steam-bath. A small amount of methanol was added and the solution left at 0° for several days. The small crop of crystals so obtained was recrystallized from chloroform-methanol and finally from ether. The compound then melted at 204–207°; $\lambda_{max.} = 257\mu$; $\epsilon = 146$.

Anal. Calc'd for $C_{27}H_{41}BrO_2$: C, 68.06; H, 8.46.
Found: C, 67.80; H, 8.69.

Preparation of 7-bromocholestanol-3-one-6. Three grams of 7-bromocholestanol-3-one-6 acetate was treated with 90 cc. of alcohol and 10 cc. of concentrated hydrochloric acid. After refluxing for 10 minutes water was added to turbidity and the solution left to deposit white needles of 7-bromocholestanol-3-one-6. After two recrystallizations from dilute acetone the product melted at 113°; $[\alpha]_D^{20}$ +51; yield 2.1 g. Reduction with zinc dust and alcohol gave cholestanol-3-one-6, m.p. and mixed m.p. 142°. Treatment with acetic anhydride at 100° for two hours gave 7-bromocholestanol-3-one-6 acetate, m.p. and mixed m.p. 145°.

Preparation of 7-bromocholestanedione-3,6. A solution of 600 mg. of 7-bromocholestanol-3-one-6 in 10 cc. of acetic acid was chilled to 15°. To this was added over a period of 15 minutes a chilled solution of 200 mg. of chromium trioxide in 15 cc. of 95% acetic acid. The mixture, after standing in an ice-bath for 1 hour, then at room temperature for 24 hours, on addition of water precipitated white crystals of the diketone. The latter on recrystallization from dilute acetone and from benzene and petroleum ether (b.p. 30–60°) melted at 135°; $[\alpha]_D^{20}$ +76°; yield 500 mg.

Anal. Calc'd for $C_{27}H_{43}BrO_2$: C, 67.62; H, 9.04; Br, 16.66.
Found: C, 67.7; H, 9.2; Br, 16.8.

Preparation of 5(α)-bromocholestanol-3-one-6. A solution of 1.8 g. of cholestanol-3-one-6 in 25 cc. of ether and 4.5 cc. of acetic acid was treated with 15.5 cc. of acetic acid containing 1 mole of bromine. When the bromine had reacted the solution was poured immediately into a dilute solution of potassium acetate, extracted with ether, washed, dried over anhydrous sodium sulfate, evaporated to a small volume on the steam-bath, and treated with light petroleum ether. After filtration of the powdery product it was recrystallized from methanol and from dilute acetone. The white needles so obtained melted with decomposition at about 150°. Reduction with zinc dust and alcohol gave cholestanol-3-one-6, m.p. and mixed m.p. 142°. Acetylation with acetic anhydride gave 5(α)-bromocholestanol-3-one-6 acetate m.p. and mixed m.p. 164°. The bromo alcohol had $[\alpha]_D^{25}$ −156°.

Anal. Calc'd for $C_{27}H_{45}BrO_2$: C, 67.34; H, 9.42; Br, 16.59.
Found: C, 67.3; H, 9.2; Br, 16.4.

Preparation of 5(α)-bromocholestanedione-3,6. The oxidation of 5(α)-bromocholestanol-3-one-6 was carried out in the same manner described above for the 7-bromo derivative except that twice the volume of acetic acid was used. The product was obtained as white needles in 84% yield. Recrystallization by dissolving in acetone at 30° followed by careful addition of water gave a product with the decomposition point 80–85°; $[\alpha]_D^{26}$ −140°. Boiling in pyridine for ten minutes gave cholestene-4-dione-3,6. The compound slowly decomposed with loss of hydrogen bromide at room temperature.

Anal. Calc'd for $C_{27}H_{43}BrO_2$: C, 67.62; H, 9.04.
Found: C, 67.7; H, 9.3.

We wish to take this opportunity to express our thanks to Merck and Company, Rahway, N. J. for the analyses and absorption data published in this paper.

SUMMARY

1. Various new brominated derivatives of cholestanedione-3,6 and cholestene-4-dione-3,6 have been prepared and the course of bromination suggested for certain of these compounds.

2. The structures of various of these brominated derivatives have been correlated with the structures of previously known derivatives.

PRINCETON, N. J.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TRINITY COLLEGE]

THE CONDENSATION OF AMINOANTIPYRINE. II. A NEW COLOR TEST FOR PHENOLIC COMPOUNDS

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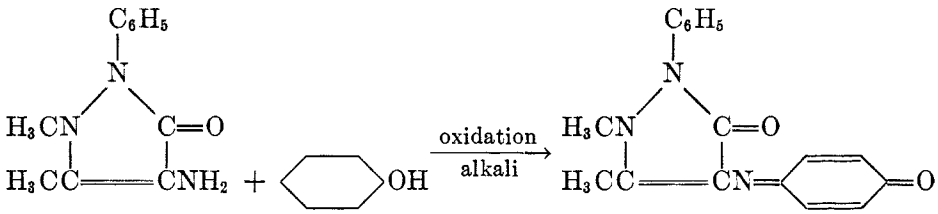
I. REACTIONS OF PHENOLS

Aminoantipyrine was found to condense with aromatic amines (1) in the presence of acid oxidizing reagents. The reaction is general for primary, secondary, and tertiary aromatic amines with the exceptions noted. Phenols do not react under the conditions described. However, when alkaline oxidizing agents are used, primary and secondary aromatic amines react with aminoantipyrine to form intensely colored compounds, and under these same conditions phenols also react.

Phenol and aminoantipyrine in an ammoniacal solution containing a trace of cupric ion form a dark red precipitate when air is blown through the solution (2).



This technique for the production of colored derivatives of phenols is not well suited for general laboratory procedure. Alkaline potassium ferricyanide is a better reagent because of its greater sensitivity. The reaction is analogous to that of *p*-aminophenol, *p*-phenylenediamine, *p*-methylaminoaniline, and *p*-dimethylaminoaniline with phenols.

Aminoantipyrine is a sensitive reagent for detecting phenols. Phenol can be detected in one part in over eight million, *o*-cresol in one part in two million, and *m*-cresol in one part in over six and one-half million. In addition to being sensitive, aminoantipyrine has the advantage of giving negative blanks. Alkaline solutions of this amine alone do not yield highly colored products when treated with oxidizing agents. The reaction with phenols is clean cut; any color, red to purple, is due to the reaction products of aminoantipyrine with the phenols, provided the alkalinity is sufficient to prevent the formation of antipyrine red. It must be understood that the hydroxy compound by itself does not produce colored oxidation products. Catechol, hydroquinone, and pyrogallol darken when treated with the oxidizing agent but where each test is completely controlled no confusion arises.

The phenols with only one OH group and no other acid groups form colored products soluble in chloroform. Introduction of these acid groups in the molecule prevent the dissolution of the colored products in chloroform. Thus the

sensitivity of the test for phenols producing chloroform-soluble colored products can be increased by concentration of the color in chloroform.

A study was made of numerous phenols[1] to determine the scope and limitations of the reaction. The results are shown in Table I.

On the basis of the results shown in Table I the following conclusions can be drawn:

1. There must be at least one free phenolic hydroxyl group in the molecule for a positive test.

2. Substituents in the position para to the hydroxyl group prevent the reaction except as follows: halogen, carboxyl, sulfonic acid, hydroxyl, and methoxyl. These groups are probably expelled.

3. A nitro group in the ortho position prevents reaction and a nitro group in the meta position inhibits the test but not completely.

4. Coupling of aminoantipyrine with the phenol takes place in the para position rather than in the ortho position.

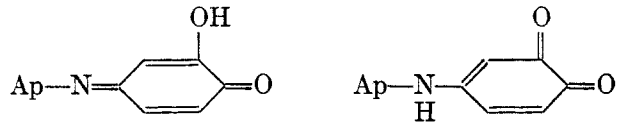
The fact that anisole and veratrole fail to give a positive test while phenol and guiacol do give one indicates that a free phenolic group is one of the prime requisites for a positive reaction.

That certain substituents are expelled from the para position may be deduced from information conveyed in Table I. *o*-Phenolsulfonic acid gives a positive test but the colored product formed is insoluble in chloroform. It is to be expected that a salt of an acid would be insoluble in chloroform. *p*-Phenolsulfonic acid also gives a positive test, but in this case the colored product formed is soluble in chloroform, a fact which indicates that the salt-forming group is no longer present in the molecule. Similar evidence is to be found in the series salicylic acid, *m*-hydroxybenzoic acid, and *p*-hydroxybenzoic acid. All three compounds give a positive test but only the colored product formed from the para compound is soluble in chloroform. Likewise, in the series catechol, resorcinol, and hydroquinone, the results are the same; only in the case of the para isomer is the colored product soluble in chloroform, a fact which indicates that the salt-forming group is expelled from the para position.

The results in the series of dihydroxybenzenes are not so conclusive as in the other two series. With hydroquinone no apparent coupling takes place if sodium hydroxide is used as an alkalizing agent. The stronger base seems to favor the oxidation of hydroquinone to quinhydrone and to quinone. When ammonium hydroxide is used there is a distinct positive test with the simultaneous formation of other colored oxidation products of hydroquinone. Alkalization with sodium bicarbonate results in a positive test obscured by very little color from other oxidation products of hydroquinone. It would seem from these facts that sodium bicarbonate is the best alkalizing agent to use. However, it is so weak

[1] The author expresses his thanks to the following firms which generously supplied samples: Calco Chemical Division of American Cyanamid, The Dow Chemical Company, Monsanto Chemical Company, the New York Quinine and Chemical Works, and Sharples Chemicals, Inc.

a base that it does not form salts with the free hydroxyl groups and consequently the colored products formed from catechol and resorcinol are also soluble in chloroform when this base is used. It is also to be noted that 4-tert.-butylcatechol gives a weak test and that the colored product is soluble in chloroform. It is soluble even if an excess of sodium hydroxide is used. In the catechol series the dyes might exist in one or both of the tautomeric forms.[2]



(I) (II)

Formula II would account for the solubility in chloroform of the dye even from an alkaline solution.

In the reaction of aromatic amines with aminoantipyrine no instance of expulsion has been observed when either alkaline or acid oxidizing agents are employed.

That the colored products are produced by aminoantipyrine coupling with the phenols in the para position may be deduced from the following facts. When the para position is blocked by an alkyl, aryl, ester, nitro, benzoyl, nitroso, or aldehyde groups, no color reaction takes place even though the ortho positions are unsubstituted. When the para position is substituted by carboxyl or sulfonic acid groups the colored products produced in the test are soluble in chloroform provided there is no other salt-forming group in the molecule. It is not likely that a group would be expelled from the para position followed by a coupling in an ortho position. If this were the case, then with 3,5-dibromo-4-hydroxybenzoic acid not only would the carboxyl group have to be expelled but also a bromine atom.

The test described can also be used to detect aminoantipyrine in small amounts. Amidopyrine does not interfere with the test and thus small amounts of aminoantipyrine present as an impurity in amidopyrine can be detected.

II. REACTIONS OF NAPHTHOLS

Just as there are two distinct series of naphthols, the alpha and the beta series, so also there are two distinct series of colors, red for the alpha series and green for the beta series. Unless there is an acid group in the molecule, the colored products formed when the naphthol is oxidized in the presence of aminoantipyrine are insoluble in water and soluble in chloroform.

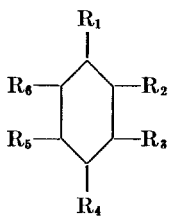
The red compounds are fairly stable in aqueous media and extremely so in chloroform, while the green ones are fugitive. In chloroform the green color disappears and on long standing changes to a yellow-red.

The results are indicated in Table II.

[2] Ap is used to denote the antipyryl radical.

TABLE I

THE RESULTS OF THE COLOR TEST OF AMINOANTIPYRINE WITH PHENOLS



COMPOUND	R_1	R_2	R_3	R_4	R_5	R_6	REACTION[a]
Anisole	OCH_3						0
Phenol	OH						3-S
o-Cresol	OH	CH_3					3-S
m-Cresol	OH		CH_3				3-S
p-Cresol	OH			CH_3			0
4-Hydroxy-1,3-dimethylbenzene	OH	CH_3		CH_3			0
4-Hydroxy-1,2-dimethylbenzene	OH		CH_3	CH_3			0
5-Hydroxy-1,3-dimethylbenzene	OH		CH_3		CH_3		3-S[b]
3-Hydroxy-1,4-dimethylbenzene	OH	CH_3			CH_3		3-S
Thymol	OH		CH_3			C_3H_7	3-S
Carvacrol	OH	CH_3			C_3H_7		3-S
p-tert. Amylphenol	OH			C_5H_{11}			0
p-tert. Butylphenol	OH			C_4H_9			0
p-tert. Butyl-*o*-cresol	OH	CH_3		C_4H_9			0
p-tert. Amyl-*o*-cresol	OH	CH_3		C_5H_{11}			0
o-Hydroxydiphenyl	OH	C_6H_5					3-S
p-Hydroxydiphenyl	OH			C_6H_5			0
o-Cyclohexylphenol	OH	C_6H_{11}					3-S

[a] The numbers refer to the strength of the test and the letters to the solubility of the colors in chloroform. Number 3 represents a strong test; 2, a moderate test; 1, a slight test; S, soluble; Ins, insoluble; SSl, slightly soluble.

[b] All positive tests produce varying shades of red except this one which is purple.

p-Cyclohexylphenol	OH			C_6H_{11}			0
Tyrosine	OH			CH_2NH_2COOH			0
o-Hydroxyacetophenone	OH	$COCH_3$					3-S
p-Hydroxyacetophenone	OH			$COCH_3$			0
2,4′-Dihydroxybenzophenone	OH	COC_6H_4OH					3-Ins.
4,4′-Dihydroxybenzophenone	OH			COC_6H_4OH			0
2-Chloro-5-hydroxytoluene	OH		CH_3	Cl			3-S
o-Chlorophenol	OH	Cl					3-S
p-Chlorophenol	OH			Cl			3-S
2,4-Dichlorophenol	OH	Cl		Cl			3-S
p-Bromophenol	OH			Br			3-S
2,6-Dibromophenol	OH	Br				Br	3-S
2,4,6-Tribromophenol	OH	Br		Br		Br	3-S
Veratrole	OCH_3	OCH_3					0
Guiacol	OH	OCH_3					3-S
Resorcinol monomethyl ether	OH		OCH_3				3-S
Hydroquinone monomethyl ether	OH			OCH_3			3-S
Eugenol	OH	OCH_3		$CH_2CH{:}CH_2$			0
iso-Eugenol	OH	OCH_3		$CH{:}CHCH_3$			0
Guiacol potassium sulphonate	OH	OCH_3				SO_3K	3-Ins.
o-Phenolsulphonic acid	OH	SO_3H					3-Ins.
p-Phenolsulphonic acid	OH			SO_3H			3-S
Salicylic acid	OH	COOH					3-Ins.
m-Hydroxybenzoic acid	OH		COOH				3-Ins.
p-Hydroxybenzoic acid	OH			COOH			3-S
Methyl *p*-hydroxybenzoate	OH			$COOCH_3$			0
Methyl salicylate	OH	$COOCH_3$					3-S
Salol	OH	$COOC_6H_5$					3-S
Salicylsalicylic acid	OH	$COOC_6H_4$ | $CO_2H(o)$					3-SSl
Salicylamide	OH	$CONH_2$					3-S
Salicylaldehyde	OH	CHO					3-S
p-Hydroxybenzaldehyde	OH			CHO			0

TABLE I—*Concluded*

COMPOUND	R_1	R_2	R_3	R_4	R_5	R_6	REACTION
Vanillin	OH	OCH_3		CHO			0
Vanillic acid	OH	OCH_3		COOH			3-S
3,5-Dibromo-4-hydroxybenzoic acid	OH	Br		COOH		Br	3-S
Catechol	OH	OH					3-Ins.
Resorcinol	OH		OH				3-Ins.
Hydroquinone	OH			OH			1-S
Orcinol	OH		OH		CH_3		3-Ins.
Hexylresorcinol	OH	C_6H_{13}			OH		
4-tert.-Butylcatechol	OH	OH			C_3H_7		1-S
Epinephrine	OH	OH			$HNCH_3$ | $CHOHCH_2$		3
Phloroglucinol	OH		OH		OH		3-Ins.
Pyrogallol	OH	OH	OH				3-Ins.
o-Nitrophenol	OH	NO_2					0
m-Nitrophenol	OH		NO_2				2-S
p-Nitrophenol	OH			NO_2			0
p-Nitrosophenol	OH			NO			0
o-Aminophenol	OH	NH_2					0
m-Aminophenol	OH		NH_2				3-S
p-Aminophenol	OH			NH_2			0

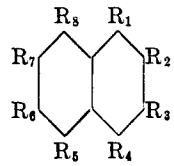
III. REACTIONS WITH HYDROXYPYRIDINES AND HYDROXYQUINOLINES[3]

(WITH HARRY H. BEACHAM[4])

Since many natural products and drugs are derivatives of pyridine and quinoline it seemed desirable to investigate the color reaction of aminoantipyrine

TABLE II

THE COLOR REACTIONS OF NAPHTHOLS WITH AMINOANTIPYRINE IN THE PRESENCE OF AMMONIACAL POTASSIUM FERRICYANIDE



SUBSTANCE	REACTION[a]	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
1-Naphthol	R—3—S	OH							
L Acid	R—3—Ins	OH				SO_3H			
Nevile and Winther's acid	R—3—S	OH			SO_3H				
Chromotropic acid	[b]	OH		SO_3H			SO_3H		OH
H Acid	[c]	OH		SO_3H			SO_3H		NH_2
Gamma Acid	R—1—Ins	OH		SO_3H				NH_2	
2-Naphthol	G—3—S		OH						
Schaeffer's acid	G—3—Ins		OH				SO_3H		
R Acid	G—3—Ins		OH	SO_3H			SO_3H		
G Acid, dipotassium salt	G—2—Ins		OH				SO_3K		SO_3K
3-Hydroxy-2-naphthoic acid	G—3—Ins		OH	COOH					
N-substituted 3-hydroxy-2-naphthamide	G—3—SSl		OH	CONHR[d]					

[a] The letters and numbers refer to the color of the solution, the strength of the test and to the solubility of the colored products in chloroform. R = red, G = green. The number 3 indicates a strong test, and 2 a moderate test. S = soluble, SSl = slightly soluble, and Ins = insoluble. Thus the designation G—3—SSl indicates that a strong green test was obtained and that the colored product is slightly soluble in chloroform.

[b] Brown changing to red-brown. Color insoluble in chloroform.

[c] Yellow-green turning to purple. Color insoluble in chloroform.

[d] R is C_6H_5, o-$CH_3C_6H_4$, or o-$CH_3OC_6H_4$. The anilide of 3-hydroxy-2-naphthoic acid gives only a weak test.

with hydroxy derivatives of these substances. In the series alpha, beta, and gamma hydroxypyridine, only the beta compound is unable to form a keto

[3] From part of the thesis of Harry H. Beacham submitted to the graduate faculty of Trinity College, in partial fulfillment of the requirements for the degree of Master of Science.

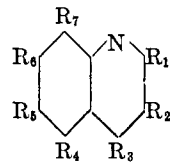
[4] Present address Eastman Kodak Company, Rochester, New York.

tautomer by the migration of the phenolic hydrogen to the nitrogen (3) and the beta compound is the only one which gives a positive test when treated with aminoantipyrine and alkaline potassium ferricyanide. The red solutions produced by this test are relatively stable compared to reddish-purple solutions produced when solutions of vitamin B_6 are tested.

When vitamin B_6 is tested, the color is extremely evanescent, appearing and disappearing in a matter of seconds. Only slight success toward stabilizing the color was achieved when the reaction was carried out in buffered solutions of

TABLE III

THE REACTION OF AMINOANTIPYRINE WITH HYDROXYQUINOLINES AND WITH HYDROXYQUINALDINES



COMPOUND	REACTION[a]	R_1	R_2	R_3	R_4	R_5	R_6	R_7
2-Hydroxyquinoline	0	OH						
3-Hydroxyquinaldine	G—1—Y	CH_3	OH					
4-Hydroxyquinaldine	0	CH_3		OH				
5-Hydroxyquinoline	R—2—R				OH			
6-Hydroxyquinoline	B—3—Y					OH		
7-Hydroxyquinoline	G—1—Y						OH	
8-Hydroxyquinoline	R—5—R							OH
7-Methyl-8-hydroxyquinoline	R—5—R						CH_3	OH
8-Hydroxyquinoline-5-sulfonic acid	R—4—R				SO_3H			OH

[a] The numbers in this column represent the strength of the test, 0 is negative and 5 represents a precipitate. The letters represent the colors of the solutions R, red; G, green; B, blue; Y, yellow. The colors of the aqueous solutions are represented by letters to the left of the numbers and the colors of the chloroform solutions are shown by letters to the right of the numbers. R—5—R indicates a very strong test in which the aqueous portion containing a precipitate is red. Extraction with chloroform produces a red chloroform layer.

varying *p*H. Just as the reaction of vitamin B_6 with quinonechloroimides is inhibited by borate ion, as reported by Scudi (4), so also do borates prevent the reaction of vitamin B_6 with aminoantipyrine.[5] Borates do not interfere with the aminoantipyrine test for phenols, naphthols, and 3-hydroxypyridine.

As might be expected, derivatives of 2- and 4-hydroxyquinolines fail to give

[5] If *p*-dimethylaminoaniline is used in place of aminoantipyrine in the test for vitamin B_6 the blue compound formed is soluble in chloroform in which solvent the color is stable for several hours. This test will detect vitamin B_6 in dilutions of between 1 part per million and 1 part per 10 million by visual methods.

the test because in both cases the position para to the hydroxyl group is blocked, in the 2-hydroxy compound by the fused benzene ring, and in the 4-hydroxy compound by the ring nitrogen.

The remaining hydroxy compounds give a positive test. It was expected that the 5- and 8-hydroxy compounds would give a red test in the same way that the 1-naphthols do and that the 3-, 6-, and 7-compounds would give a green test in the same way as the 2-naphthols. These expectations were realized. However, the 6-hydroxyquinoline gave a blue-green solution rather than the expected green. In general the test with compounds which produce green solutions is less sensitive than the test with compounds producing red solutions. Whereas the color of the red solutions is stable, the color of the green solutions fades rapidly to yellow. This change is hastened when the solution is shaken with chloroform. Attempts to capture the green color in chloroform always resulted in the appearance of a yellow chloroform layer.

It should be noted that the colored compound formed from 8-hydroxyquinoline-5-sulfonic acid is soluble in chloroform, a fact which indicates that the sulfonic acid group is expelled.

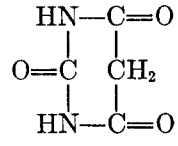
The results are summarized in Table III.

IV. REACTIONS WITH BARBITURATES, URACILS, HYDANTOINS, AND IMIDAZOLONS[6]

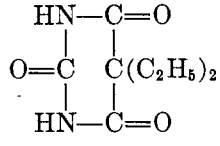
(WITH LINDLEY CLAIR BEEGLE[7])

An investigation was made of some barbiturates, uracils, hydantoins, and imidazolons in order to study further the scope and limitations of the aminoantipyrine color test.

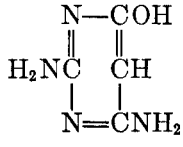
Barbituric acid (III) gives a positive test in which the red color formed is insoluble in chloroform. When the 5 position is substituted as in barbital (IV) no color is formed. Several commercial sedatives of the barbital type give a slight positive test, a fact which suggests that traces of barbituric acid may be present. When these compounds are purified they no longer give a positive test. The differences in the melting points of these commercial products and of the samples purified from them were not detectable by the usual laboratory procedure. The aminoantipyrine test would seem to offer a means of detecting traces of certain barbituric acids in sedatives which are derivatives of these acids.



(III)



(IV)



(V)

[6] From the thesis of Lindley Clair Beegle submitted to the Committee on Graduate Students at Trinity College in partial fulfillment of the requirements for the degree of Master of Science.

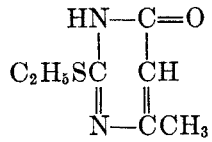
[7] Present address American Cyanamid Co., Stamford, Conn.

Apparently 5,5-disubstitution blocks the reaction of barbituric acid. In a similar manner substitution of a benzyl group in the 5 position inhibits the reaction. However, benzalbarbituric acid gives a positive test in which the red color formed is insoluble in chloroform. The apparent elimination of the benzal group finds no counterpart in any of the reactions previously studied although a similar reaction was noted in the pyrazolon series.

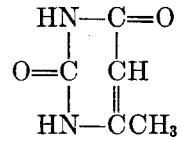
1,3-Diphenylbarbituric acid was prepared in order to determine the effect of large blocking groups on the nitrogen atoms. The compound gave a purplish-red test and the color formed was soluble in chloroform, a result which was to be expected since there was no longer a salt-forming group in the molecule.

If some of the carbonyl oxygen atoms of barbituric acid are replaced by imine groups the reaction still takes place. 2,4-Diamino-6-hydroxypyrimidine (V) couples with aminoantipyrine to give a red dye insoluble in chloroform. Instead of hydrolyzing readily in dilute acids, the dye takes on a blue-red color. The reaction also takes place in neutral or slightly acid solutions when ferric chloride is used as the oxidant. It seems likely that the reaction of this pyrimidine with aminoantipyrine is analogous to the reactions of the *m*-aminophenols (5).

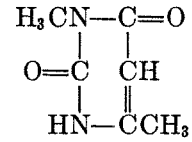
2-Ethylmercapto-4-methyluracil (VI), 4-methyluracil (VII), 1,4-dimethyluracil (VIII), and 1,3,4-trimethyluracil (IX) failed to react with aminoantipyrine.



(VI)

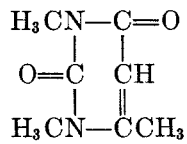


(VII)

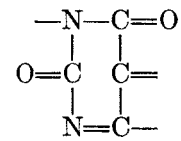


(VIII)

Compounds (VI) and (IX) are not capable of forming derivatives having a structure represented by formula (X) and were not expected to give the test. However, (VII) and VIII) theoretically are able to form derivatives of type (X). They failed to produce the least trace of color with aminoantipyrine and an oxidant. It may be that here we are dealing with a situation analogous to that encountered with 2-hydroxypyridine in which case no methylene derivative is possible, due either to the preference of the pyridone or zwitterion structure (3).



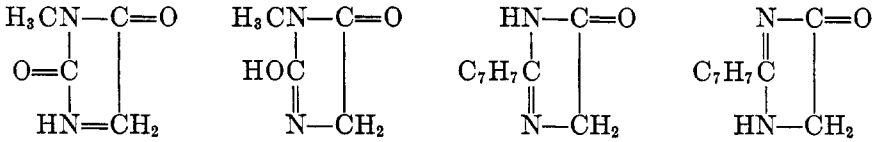
(IX)



(X)

It was believed that a compound should condense with aminoantipyrine to form highly colored products if there were alpha,beta double bonds on both sides of the coupling position as represented by the structure $=X-\underset{\|}{C}-Y=$ which must be in a ring system. Hydantoin and 3-methylhydantoin (XI)

might form this structure by tautomeric shift of the 1-hydrogen atom to the 2-carbonyl oxygen (XII).



(XI) (XII) (XIII) (XIV)

However, both compounds failed to give any trace of color when they were tested. Again it was thought that we might be dealing with an alpha-pyridone type of structure.

In order to avoid tautomerization of the group attached to the 2-carbon atom, the 2-hydroxy group was replaced by a benzyl radical. 2-Benzylimidazolon-5 (XIII) and 2-benzylimidazolon-4 (XIV) were prepared and tested. Neither one gave the least indication of a positive reaction.

While it appears that the ability of a compound to form the structure $=X-\overset{\|}{C}-Y=$ which must be included in a ring[8] is a necessary condition for a positive aminoantipyrine test, it is also apparent that this is not a sufficient condition. As yet no predictions can be made with any certainty as to which compounds will give the test.

EXPERIMENTAL

Compounds not commercially available were prepared according to directions found in the literature.

Procedure used for phenols and naphthols. All tests were carried out in the same general manner. A small quantity of the compound (about 10–20 mg.) was dissolved in 10 cc. of water to which 2–3 drops of 6 *N* ammonium hydroxide was added. If the substance did not dissolve in water or ammonium hydroxide it was dissolved first in a few drops of alcohol and then diluted with water to 10 cc. The solution was then divided into two equal portions and to one portion was added 2 drops of 2% aminoantipyrine solution, the other portion being kept as a control. Then to each of the tubes was added several drops of 8% potassium ferricyanide solution. A large excess of oxidizing agent is to be avoided because it may decolorize the dye formed. After the development of full color, 2 cc. of chloroform was added and the mixture shaken. The results are detailed in Tables I and II.

Determination of sensitivity of test. The general procedure used was as follows: a quantity of the phenol was weighed accurately on an analytical balance and dissolved in an equivalent amount of *M* NaOH solution and water added to make a solution of known volume. Then by a series of ten-fold dilutions a number of solutions were prepared and tested. Each test was carried out by the addition of 1 drop of 0.2% aminoantipyrine solution followed by 1 drop of 2% $K_3Fe(CN)_6$ in dil. NaOH [$K_3Fe(CN)_6$, 0.1395 g. + 0.30 ml. of *M* NaOH + 9.70 cc. water], to a 1-ml. portion. After the addition of the ferricyanide solution, 0.25 cc. of chloroform was added and the mixture shaken. By this method it was found that phenol could be detected in 1.2 parts per ten million. In the light of later work it seems probable that $NaHCO_3$ or Na_2CO_3 would be better to use than NaOH.

Procedure used in sections III and IV. A better procedure for testing the compounds was used in sections III and IV. Aqueous solutions of the compounds tested were made up

[8] Dibenzoylmethane, ethyl benzoylacetate, ethyl acetoacetate, diethyl malonate, and malonic acid give no test.

to 1 part in 10,000. To 2 ml. of each solution was added 1 drop of aminoantipyrine solution (13.6 g. per liter) followed by 1 drop of alkaline potassium ferricyanide (86.7 g. of $K_3Fe(CN)_6$, 18 ml. of conc'd NH_4OH and water to make 1 liter). After 5 minutes the color of the solution was noted, 0.5 ml. of chloroform added, the mixture shaken, and the color of the chloroform layer recorded.

Similar results were obtained when the oxidant was prepared with equivalent quantities of NaOH, Na_2CO_3, or $NaHCO_3$ in place of NH_4OH. Generally the sodium hydroxide was the least efficient alkali for color production.

The results obtained using other coupling amines instead of aminoantipyrine are recorded in the Chemistry Library of Trinity College (6).

Other compounds and mixtures tested. The following gave a positive test: 1-phenyl-3-methylpyrazolon-5, digitalis glucosides (Roche) (weak brownish test), urine, diketohydrindine,[9] and milk (very slight test).

The following gave a negative test: antipyrine, creatine, creatinine, 3,4-dimethyl-2-hydroxyfluorene, 1,4-dimethyl-2-hydroxyfluorenone, quinine, morphine, codeine, theobromine, uric acid, testosterone, theelol, thyroid (Schering), novatropine, benzedrine, thyroid gland emplets (Parke Davis), digilanid (Sandoz Chemical Works), ascorbic acid, dried blood plasma, saliva, aspirin, anthranol, anthrone, and thiophenol.

SUMMARY

1. A sensitive new color test for phenolic compounds is described. The color produced from vitamin B_6 is evanescent when aminoantipyrine is used but stable when *p*-dimethylaminoaniline is used.

2. Monohydric alpha-naphthols and the comparable hydroxyquinolines produce red colors while the monohydric beta-naphthols and the comparable quinolines produce green colors.

3. The probable structure of the colored products is discussed as well as the limitations of the reaction.

4. Aminoantipyrine as a reagent for phenolic compounds gives a well-defined test because alone it does not react with alkaline oxidizing agents to produce highly colored products as do the *p*-aminophenols and *p*-diamines.

HARTFORD, CONN.

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(5) EMERSON AND KELLY, unpublished work.
(6) BEACHAM, Master's Thesis, Trinity College (1943), BEEGLE, Master's Thesis, Trinity College (1943).

[9] This compound was prepared in this laboratory by Mr. Kenneth Kelly.

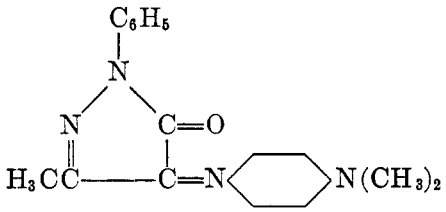
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TRINITY COLLEGE]

THE CONDENSATION OF AMINOANTIPYRINE. III. (1). THE SYNTHESIS OF METHYLRUBAZOIC ACID[1]

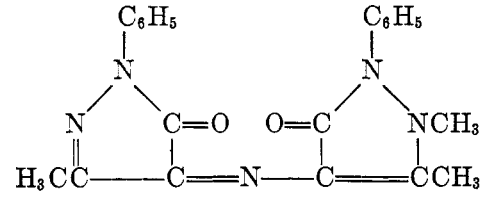
EDGAR EMERSON AND LINDLEY CLAIR BEEGLE[2]

Received June 29, 1943

It has been shown that aminoantipyrine in some of its reactions acts like the reducing amines, such as *p*-aminophenol, *p*-phenylenediamine, and *p*-dimethylaminoaniline (1a). Since *p*-dimethylaminoaniline reacts with 1-phenyl-3-methylpyrazolon-5 (2) to give compound (I) it was believed that aminoantipyrine should react with the pyrazolon to give a compound of analogous structure (II).



(I)



(II) Methylrubazoic Acid

Both compounds (I) and (II) have been prepared by condensing the pyrazolon with the corresponding nitroso compounds. Compound (I) was prepared by Sachs and Barschall (3) from nitrosodimethylaniline and 1-phenyl-3-methylpyrazolon-5 and (II) was reported by Pröscher (4) who made it from the pyrazolon and nitrosoantipyrine (IV). These reactions would seem to emphasize the apparent similarity of the condensation reactions of nitrosodimethylaniline and nitrosoantipyrine.

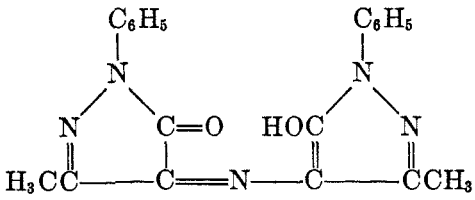
Many phenol-like compounds have been found to give the aminoantipyrine color test (1). The structures of the colored compounds formed in the test may be inferred from the data accumulated relating to the structures of the coupling components. However, it was felt necessary to prove the structure of a colored compound of this type by standard chemical means. For this purpose the reaction product formed by the oxidation of an equimolar mixture of aminoantipyrine and 1-phenyl-3-methylpyrazolon-5 was selected because it formed in good yield and presumably it had been prepared by another route (4).

An inspection of the formula for methylrubazoic acid (II) reveals the absence

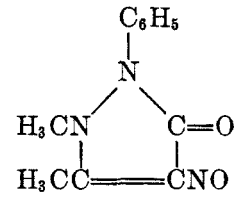
[1] From the thesis presented to the Committee on Graduate Students at Trinity College by Lindley Clair Beegle in partial fulfillment of the requirements for the Degree of Master of Science.

[2] Present address American Cyanamid Co., Stamford, Conn.

of any acid hydrogen in the molecule and, therefore, one would not expect the compound to be soluble in alkali; nor would one expect a deepening of color when the substance is treated with alkali since there is no salt-forming group present. However, Pröscher reported that methylrubazoic acid dissolves in ammonia and dilute alkalies with a change in color from red to purple. Pröscher also reported the compound to be insoluble in benzene. These properties are those of rubazoic acid (III), not of methylrubazoic acid. Moreover the empirical formula was incorrectly reported and the calculated composition agreed neither with the formula reported nor with the correct one.



(III) Rubazoic Acid



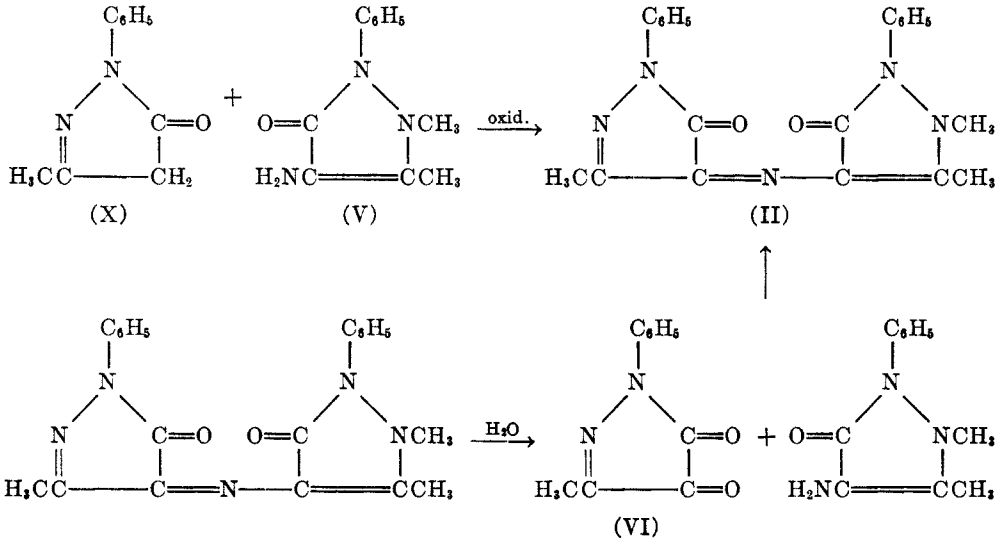
(IV) Nitrosoantipyrine

The work of Pröscher was repeated and the reaction took place in the manner he described. His statement that the reaction product could not be obtained in crystalline form was also verified. It was found that the reason for this was gross contamination of the desired product by other products of high molecular weight. The molecular weight of Pröscher's product varied and in some determinations attained a value of over 500 whereas the calculated value is 373. The Signer method (5) for molecular weights was used and found to be highly satisfactory. It is suggested that a reason for the somewhat anomalous condensation product(s) may be found in the structure of nitrosoantipyrine (IV).

The fixation of the 3,4 double bond and the influence of a nitroso group ortho to the 3-methyl group might activate this group in the same manner that the methyl groups in quinaldine and in 2,4-dinitrotoluene are activated. Polymerization by condensation of the nitroso group with the 3-methyl group of another molecule might take place to an undetermined extent and thus account for the high molecular weight observed in Pröscher's impure methylrubazoic acid. Methylrubazoic acid prepared by oxidizing an equimolar mixture of aminoantipyrine and 1-phenyl-3-methylpyrazolon-5 proved to be a product which was easily purified and obtained as crystals from methanol (mol. wt. 364; m.p. 175–176°).

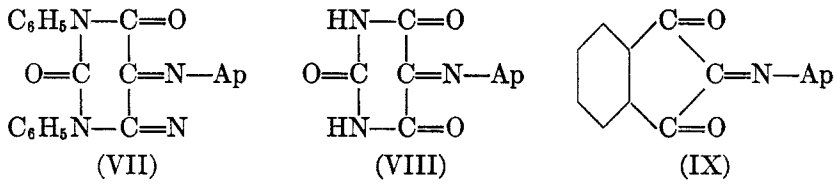
A quantitative hydrolysis of the crystalline material yielded equimolar quantities of aminoantipyrine (V) and 1-phenyl-3-methyl-4-ketopyrazolon-5 (VI).

Methylrubazoic acid was also prepared by the condensation of aminoantipyrine with 1-phenyl-3-methyl-4-ketopyrazolon-5. The purified condensation product melted at 174–176° and the melting point with the previously crystallized product was 174–176°.



(X) (V) (II) (VI)

These reactions serve to establish the structure of methylrubazoic acid and, by analogy, the structures of many of the other colored products formed in a positive aminoantipyrine test. The structure of the colored compound from 1,3-diphenylbarbituric acid, barbituric acid, and diketohydrindene are represented by (VII), (VIII), and (IX) where Ap- represents the antipyryl radical.



(VII) (VIII) (IX)

EXPERIMENTAL

Molecular weights. The molecular weights were determined in an apparatus modified from Signer (5). Ground glass caps were used on the filling tubes and to one of the caps a ground glass stopcock was sealed to permit evacuation after charging the apparatus. Chloroform was used as a solvent and the ground glass joints were lubricated with a manitol-glycerine mixture in which the solvent is insoluble. Carefully purified azobenzene was used as the reference compound. After charging the apparatus it was inclosed on the shelf of an ordinary steel locker until equilibrium was attained.

Preparation of methylrubazoic acid from nitrosoantipyrine (II). The procedure of Pröscher (4) was followed and it yielded a red amorphous powder soluble in dioxane, acetone, benzene, chloroform, ethanol, and methanol, insoluble in water, ligroin, and alkalies. It is hydrolyzed by mineral acids. Repeated extraction with methanol resulted in an unidentified white material. The "methylrubazoic acid" had a molecular weight of over 500.

Preparation of methylrubazoic acid from aminoantipyrine. Aminoantipyrine (10 g.) was dissolved in 350 cc. of distilled water and mixed with a solution of 1-phenyl-3-methylpyrazo-

lon-5 (8.8 g.) and sodium hydroxide (2.0 g.) in 50 cc. of distilled water. Potassium ferricyanide (66 g.) and sodium carbonate (7.8 g.) were dissolved in 200 cc. of distilled water and this solution was added to the first with good stirring over a period of 1–2 minutes. Stirring was continued for five minutes after which the copious red precipitate was separated at the pump. The product was suspended in 500 cc. of water and stirred for 30 minutes, after which it was separated by filtration. This process was repeated as long as the filtrate gave a test for ferrocyanide with ferric chloride. The yield of the crude product was 15 g. After crystallization from methanol, transparent garnet-red prisms having a slight green reflex were obtained. These melted at 175–176°; mol. wt. 364, calc'd 373. Soluble in dioxane, acetone, benzene, chloroform, ethanol, and methanol. Slightly soluble in ether and insoluble in water, ligroin, and alkalies. Soluble in mineral acids with decomposition.

Preparation of 1-phenyl-3-methyl-4-ketopyrazolon-5. This compound was prepared by the method of Sachs (3). Recrystallized from ligroin the bronze needles melted at 118–120° (lit. 119°).

Hydrolysis of methylrubazoic acid. Crystalline methylrubazoic acid (0.152 g.) was stirred for 1 hour with 2.5 cc. of 6 *N* sulfuric acid and 10 cc. of ether. This mixture was extracted continuously with ether until the extract was water-white. The extract was washed with water and dried over calcium chloride. When the ether was evaporated the residue was found to be 1-phenyl-3-methyl-4-ketopyrazolon-5 (0.076 g.). It was identified by the melting point and the melting point of a mixture of it with authentic material. The aqueous layer of the extract was made basic with sodium hydroxide and continuously extracted with benzene for 6 hours. Evaporation of the benzene extract left a residue of aminoantipyrine (0.071 g.) identified by the melting point, mixed melting point, and a derivative,—benzylidineaminoantipyrine.

Preparation of methylrubazoic acid from its hydrolytic products. Aminoantipyrine (1.0 g.) and 1-phenyl-3-methyl-4-ketopyrazolon-5 (0.9 g.) were each dissolved in 95% ethanol. The two solutions were mixed and warmed on a steam-bath for 10 minutes and after the mixture cooled to room temperature it was poured into 100 cc. of cold water. Yield of crude product 1.5 g. Recrystallized from methanol it melted at 174–176°. The mixed melting point with the previously described crystalline product was 174–176°.

SUMMARY

Methylrubazoic was found to be erroneously reported. It was prepared by two new methods and some of the properties are described.

The structures of some of the colored products formed from aminoantipyrine and phenol-like compounds have been verified.

HARTFORD, CONN.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TRINITY COLLEGE]

THE CONDENSATION OF AMINOANTIPYRINE. IV (1). A STUDY OF A NEW COLOR REACTION OF PYRAZOLONS

EDGAR EMERSON AND LINDLEY CLAIR BEEGLE[1]

Received June 29, 1943

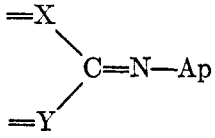
It has been shown that many kinds of ring compounds give the aminoantipyrine color test. All of the compounds which give a positive test have an enol-keto system incorporated in a ring structure, but not all such systems give a positive test (1b). While it was known that 1-phenyl-3-methylpyrazolon-5 gave a strong test[2] it remained to be determined which members of the pyrazolon series would or would not give the reaction.

In a previous article (1c) it was shown that coupling took place at the methylene carbon in the 4 position of the 5-pyrazolon. From this fact it is to be presumed that this position is analogous to the para position of phenols, the alpha position of beta-naphthols, and the 5 position of the barbiturates. In the phenol and barbituric acid series alkyl groups in the coupling position prevent a positive test. Alkyl groups in the 4 position of 5-pyrazolons likewise inhibit the color reaction; 1-phenyl-3,4-dimethylpyrazolon-5 and 1-phenyl-3-methyl-4-benzylpyrazolon-5 fail to give a positive test.

1-Phenyl-3-methyl-4-bromopyrazolon-5 coupled with aminoantipyrine, a reaction analogous to the coupling of *p*-bromophenol. The benzylidine and the isopropylidine derivative of the pyrazolon also reacted with aminoantipyrine in the same manner as did 5-benzalbarbituric acid. Contrary to expectations 4-isonitroso-1-phenyl-3-methylpyrazolon-5 gave a positive test. This latter reaction finds no counterpart in the phenol series where *p*-nitrosophenol failed to give any sign of color when it was tested with aminoantipyrine (1b).

The red colors formed from the pyrazolons previously mentioned were soluble in chloroform. This result was to be expected since there were no acid groups in the molecules. Compounds such as 1-*p*-sulphophenyl-3-methylpyrazolon-5, 1-phenyl-3-carboxypyrazolon-5 and 1-phenyl-3-hydroxypyrazolon-5 all produced red colors which were insoluble in chloroform.

Phenols, alpha-naphthols, beta-naphthols, barbituric acids, diketohydrindene, 3-methylisoxazolon-5,[3] and 5-pyrazolons after coupling all contain the structure (a)



(a)

[1] From the thesis of Lindley Clair Beegle presented to the Committee on Graduate Students at Trinity College in partial fulfillment of the requirements for the Degree of Master of Science.

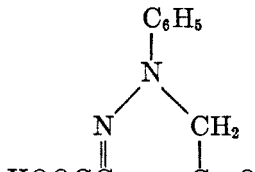
[2] Antipyrine does not give the test nor does it interfere with it; hence, small amounts of 1-phenyl-3-methylpyrazolon-5 can be detected in the presence of antipyrine by the aminoantipyrine test.

[3] This compound was made and tested by Beacham (2).

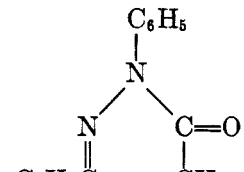
where the carbon, C, is in a ring and Ap- represents the antipyryl radical. It is to be noted that coupling with aminoantipyrine has taken place at a carbon atom on either side of which is an alpha,beta double bond system. It was believed that the ability of a substance to form derivatives of this type was a necessary condition for condensation with aminoantipyrine.

The investigation was then directed to a study of 4-hydroxypyrazols, which are tautomeric forms of 4-pyrazolons. Wolff (3) expressed the belief that these compounds existed entirely in the enol form, as indeed they may. However, on structural grounds they may be considered to form a keto tautomer containing a methylene group. We have depicted the formulas as methylene compounds not because we feel these necessarily represent the reacting forms but because the colored compounds are derivatives of them.

The keto form of 1-phenyl-3-carboxy-4-hydroxypyrazol is represented in formula I.

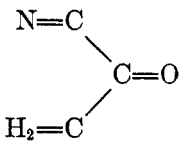


(I)



(II)

The compound contains in a ring the structure (b)

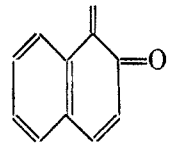


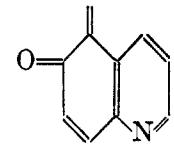
(b)

where the methylene carbon is the end of the system rather than the middle, as in structure (a). Thus it was confidently expected that this compound would fail to give the aminoantipyrine test. However, it did give a positive reaction, producing an intense green color which was insoluble in chloroform and very stable. The corresponding decarboxylated compound formed a similar stable green color, only in this case the color was transferable to chloroform. It will be recalled that all of the green colors previously noted (1b) quickly turned yellow in chloroform. The chloroform solution of this color was evaporated to dryness and the residual green pigment persisted for over a month without apparent change of depth or intensity of color.

It appeared that coupling of aminoantipyrine with structures of type (b) resulted in the formation of green compounds. Compounds such as 1-naphthol and 6-hydroxyquinoline, both of which produce green colors, have a keto structure represented by formulas III and IV respectively, and it is to be noted that structures analogous to both (a) and (b) are present in each molecule.

If the double bond common to both rings is considered apart from the ring in which coupling takes place, a rather arbitrary consideration, then the functional

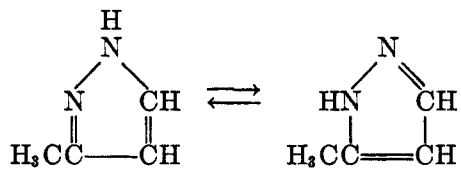

(III)


(IV)

grouping can be represented by form (b), which form is common to the green compounds and not to red ones.

Another point common to all the compounds producing green derivatives is the proximity of an aromatic ring to the coupling position, a fused benzene ring in the case of the naphthols and the N-phenyl group in the case of the 4-pyrazolon. An attempt was made to produce a green color by introducing a phenyl group on a carbon adjacent to the coupling position. 1,3-Diphenylpyrazolon-5 (II) fulfilled this condition but it produced a red color. However, models of 1-phenylpyrazolon-4 and 1,3-diphenylpyrazolon-5 constructed from Fisher-Hirschfelder atom models indicated interference with the coupling position by the phenyl group of the former compound. In order to avoid this interference, 3-carboxy-4-hydroxypyrazol (VIa) was prepared and tested. The color produced was red. Since this pyrazol contained an acid group it was expected that all of the color would be insoluble in chloroform. This was not the case. In the first chloroform extraction the color was almost equally divided between the two layers. Subsequent extractions of the aqueous portion with fresh portions of chloroform resulted in progressively less color in the chloroform until finally the aqueous layer remained red and the chloroform colorless. It must be concluded that coupling occurred with (VIa) or (VIc) to form a compound containing the carboxyl group which is insoluble in chloroform, while at the same time coupling occurred with (VIb) or (VId) to produce a compound soluble in chloroform and containing no carboxyl group.

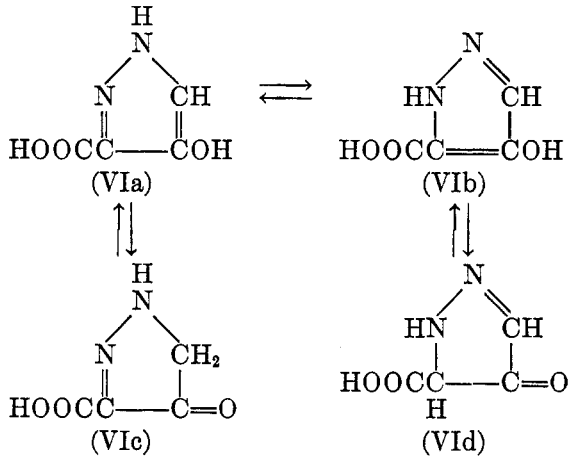
Knorr (4) proved the equivalence of the 3 and 5 position of N-unsubstituted pyrazols, formulas Va and Vb.


(Va) (Vb)

Our result from the color reaction of 3-carboxy-4-hydroxypyrazol with aminoantipyrine[4] not only furnishes another line of evidence in support of Knorr but it also affords at least visual evidence of the coexistence of activity in the 3 and 5

[4] Similar results were obtained when *p*-dimethylaminoaniline was used in place of aminoantipyrine. However, the results were not so clear because of the chloroform-insoluble color produced by the *p*-diamine alone. Similar results are to be expected by coupling reactions to produce azo compounds.

position, if not of the simultaneous presence of the two mobile tautomers[5] (VIa) and (VIb) and/or their keto modifications (VIc) and (VId).



This result is analogous to that obtained by Levine and Cole (5), who demonstrated the presence of an equilibrium mixture of the two Kekule forms of *o*-xylene by an entirely different technique.

Regardless of whether condensation takes place in the 3 or 5 position the red compounds formed are derivatives of (VIc) and (VId) and must be classified as belonging to structures of type (b), which type is, therefore, not peculiar to the green compounds.

The proximity of an aromatic group to the coupling position can scarcely be considered as the cause of the formation of green colors. The same proximity exists in the case of the alpha- and beta-naphthols. Nor can interference with the coupling position be considered as being related to the production of green colors, because phloroglucinol produces a red-brown, while beta-naphthol gives a green.

Two outstanding facts are to be noted common to all hydroxy compounds producing green colors. They are all derivatives of rings having fixed bond structures and within the coupling ring there are theoretically only two tautomeric forms possible. When the phenyl group of 1-phenyl-3-carboxy-4-hydroxypyrazol is removed, the bond structure is no longer fixed, four tautomers are structurally possible and the color produced is red.

Indene and fluorene both possess the requisite structure for coupling, but failed to do so, as did 3,5-dimethylpyrazol, 3,5-dicarboxypyrazol, and pyrazol. It therefore seems probable that at least one hydroxyl or amine group is necessary for coupling, as well as the requisite bond structure.

The question as to why some compounds couple and others, which apparently possess the prerequisites for coupling, fail to do so is still unanswered. Work on this problem is being continued in this laboratory and will be reported in a later paper.

[5] These statements are not meant to exclude the concept of resonance hybrids. There is at present no reason to believe that any one of the forms as such is capable of independent existence.

EXPERIMENTAL

All tests were made on samples at a dilution of 1:10,000 by the same technique as described in a previous article (1b).

Compounds not commercially obtainable were made according to directions found in the literature. The references to the preparations are listed:—4-benzylidine-1-phenyl-3-methylpyrazolon-5 (6); 4-isopropylidine-1-phenyl-3-methylpyrazolon-5 (7); 4-isonitroso-1-phenyl-3-methylpyrazolon-5 (8); 1-phenyl-3-methyl-4-bromopyrazolon-5 (9); 1-phenyl-3,4-dimethylpyrazolon-5 (10); 1,3-diphenylpyrazolon-5 (11); 1-phenyl-3-carboxypyrazolon-5 (12); 1-phenyl-3-hydroxypyrazolon-5 (13); 1-phenyl-3-carboxy-4-hydroxypyrazol (14); 1-phenyl-4-hydroxypyrazol (15); 3-carboxy-4-hydroxypyrazol (16); 4-hydroxypyrazol (17).

In addition to the compounds mentioned above, the following were tested with positive results:—3-methylpyrazolon-5 (18); tetronic acid (19); bromotetronic acid (19).

The following compounds were tested with negative results:—diketopiperazine; glycolide; N-phenylsuccinimide; nitrotetronic acid (19); 3,5-dimethylpyrazol (20); 3,5-dicarboxypyrazol (21); pyrazol (this compound was made from the previous compound by dry distillation).

SUMMARY

The aminoantipyrine reaction with 5-pyrazolons and 4-pyrazolons is described. Alkyl groups in the 4 position of 5-pyrazolons inhibit the reaction, whereas no inhibition is noted if the 4 position is substituted by bromine, nitroso, benzylidine, or isopropylidine radicals.

The suggestion is made that if the color reaction takes place, the color will be green if only two tautomeric forms are possible and red if three or more forms are possible.

A new means of detecting the presence of the two Kekule forms of N-unsubstituted 4-pyrazolons is given.

HARTFORD, CONN.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UNIVERSAL OIL PRODUCTS CO.]

THE ALKYLATION OF PARAFFINS WITH OLEFINS. THE IDENTIFICATION OF THE PARAFFINS FORMED[1]

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In our previous paper (1) we described a new catalytic reaction between paraffins and olefins, consisting of the direct addition of an olefin to a paraffin according to the equation

$$C_mH_{2m+2} + C_nH_{2n} \longrightarrow C_{m+n}H_{2(m+n)+2}$$

The identification of the reaction products is highly desirable *per se* and should give some very important information on the mechanism of the reaction. Their unambiguous identification is made difficult (a) because of the large number of possible isomers of the primary product; (b) because of their further alkylation to secondary products and (c) because of the possibilities of side reactions, such as auto-destructive alkylation (2).

It should be stressed that in catalytic reactions the lowering of the energy barrier of the desired reaction brought about by the particular catalytic mechanism, markedly increases also the probability of undesired reactions. This is particularly true for reactions among hydrocarbons. Furthermore the energy given off by the desired reaction stimulates the undesired reactions by providing the necessary activation energy. The cumulative effect is such that it is highly optimistic to expect the simple reaction mixture encountered in most inorganic or organic reactions. In the field of catalytic hydrocarbon reactions one can hope to surmount these difficulties only by picking the simplest hydrocarbons or developing highly selective catalysts and allowing them to work under carefully selected conditions.

In the reaction mentioned above the simplest hydrocarbon pair studied so far was *i-butane* and *ethylene*, leading by alkylation first to *hexanes*, which are then further alkylated to *octanes:* at the same time some autodestructive alkylation (2) to pentanes, heptanes, and nonanes also takes place.

The hexane fractions obtained both with a boron fluoride (1) and aluminum chloride (3) catalyst were investigated and found to consist mainly (in quantities of 90–70% of the total hexanes) of *2,3-dimethylbutane* and much smaller quantities (10–25%) of *2-methylpentane*. The presence of the expected reaction product *2,2-dimethylbutane* could be definitely established, but only in minute amounts (3% or less). The two other possible hexanes, 3-methylpentane and *n*-hexane, could not be detected and may have been present only in traces if at all. The identification proceeded by two independent but *parallel* methods, one

[1] Presented before the Petroleum Division of the American Chemical Society at its Rochester, N. Y., meeting, Sept. 1937; see "Papers presented before the General Meeting," pp. 1–12. A few additional data, particularly on the identification of 2,2-dimethylbutane, were added subsequently.

supporting the other, namely, preparation of chemical derivatives on one hand and comparison of Raman spectra of the hexanes (see Table V) on the other.

Possibilities of errors were ruled out by a detailed analysis of the chemical and physical properties of the other isomers and their derivatives.

The *2,3-dimethylbutane* was definitely identified by its Raman spectrum and the beautifully crystallizing needles of 2,3-dibromo-2,3-dimethylbutane, which could be obtained in yields corresponding to about 80% of the hexane fraction.

The presence of *2-methylpentane* was definitely proved by the preparation of its derivative, 2,3,3-trinitro-2-methylpentane, and checked by its Raman spectrum.

DISCUSSION

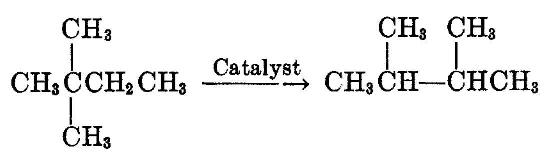
The presence of 2,3-dimethylbutane as the main reaction product is unexpected. In view of the presence of the tertiary C—H bond in i-butane, we expected (1) 2,2-dimethylbutane to be the primary product of the reaction:

$$(CH_3)_3CH + CH_2{:}CH_2 \longrightarrow (CH_3)_3CCH_2CH_3$$

2,2-Dimethylbutane

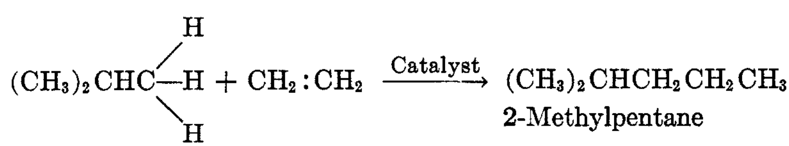
That this assumption is at least partly correct is shown by the presence of small quantities of this hexane (Experimental, part 3), and by the interesting experiments of Frey and Hepp (4). These workers were able to repeat our reaction of i-butane alkylation with ethylene, without the use of catalysts, by performing the reaction at much higher temperatures (*ca.* 500°) and pressures. Under their conditions the main portion of hexanes consisted of the expected 2,2-dimethylbutane.

The preponderance of 2,3-dimethylbutane in our product is most probably a result of the isomerization of the primary product according to the equation:



(either at the moment of formation or afterwards), similar to the isomerization of *n*-heptane into isomeric heptanes, *n*-pentane into i-pentane, or *n*-butane into i-butane (5).

Our second hexane, 2-methylpentane, is also an *a priori* not very probable product. It may be a primary product, according to the reaction



due to the greater availability (9:1) or the more efficient activation of the *primary* C—H bond by the catalyst or, although less likely, it may be a product of isomerization of the original 2,2-dimethylbutane.

The fruitful discussion of the reaction mechanism requires further experimental

material. It will be particularly important to study the isomerization of different hexanes in the presence of our catalysts.

EXPERIMENTAL PART

The hexane fractions from a set of alkylations made under identical conditions were combined and refractionated 2–3 times on a high-temperature Podbielniak column (at a reflux ratio of 5–10:1 and rate of 0.5–1.0 cc./min.) the fraction of a same starting boiling point being added to the still when the temperature of the distillate reached it. The distillates were all absolutely stable to nitrating mixture and potassium permanganate solution, proving the *absence* of *aromatic* and *unsaturated* hydrocarbons.

Two sets of hexane fractions (A-1, A-2, and B) were investigated. Set A was prepared according to our procedure by Dr. Carl B. Linn using boron fluoride (1) as a catalyst, set B by Dr. L. Schmerling using aluminum chloride (3) under the following specific conditions:

Set A-1: A batch of 350 g. of i-butane was alkylated in the presence of 35 g. of boron fluoride, 10 g. of nickel powder, and 30 g. of hydrogen fluoride under stirring at 0–5° during 10–12 hours with 170 g. of ethylene at a maximum pressure of 10 atmospheres. Yield of liquid product (separated from unreacted i-butane), 380 g. Yield of hexanes, 45% of total liquid product.

Set A-2: 341 grams of i-butane + 190 g. of ethylene, 10 g. of nickel powder, 35 g. of hydrogen fluoride and 35 g. of boron fluoride were used. Temperature −30° to −40°; 340 grams of product; hexanes, 20% of total liquid product. Maximum pressure, 6 atmospheres. Time, 20–22 hours.

Set B: A batch of 340 grams of i-butane was alkylated in the presence of 25 g. of aluminum chloride and 10–15 g. of hydrogen chloride under stirring at 25–35° during 4.0 hours with 90 g. of ethylene under a maximum pressure of 10 atmospheres. Yield of liquid product (separated from unreacted i-butane), 270 g. Yield of hexanes, 45% of total liquid product.

In all three cases the ethylene reacted completely.

The carbon and hydrogen analysis and molecular weight determinations of different fractions (Nos. 11 and 12 of Set A-1 and No. 8 of Set A-2, see Table II) prove that only *hexanes* are present (calc'd for C_6H_{14}: C, 83.61; H, 16.39; Molecular weight 86.1).

The results of fractionations are given in Table II; a typical result (of Set A-1) is further illustrated in Fig. 1.

These results indicate the probable presence of 2,3-dimethylbutane (b.p. 58.05°) and 2-methylpentane (b.p. 60.20°), whereas 3-methylpentane and particularly *n*-hexane seem to be absent. In the case of Set A-1 the presence of small quantities of 2,2-dimethylbutane (part 3, below) is indicated by the small hump at 49–51°.

The indices of refraction and especially the densities of (a) fractions 11–13 of Set A-1, (b) fractions 8 and 8a of Set A-2, and (c) fractions 7, 8, and 9 of Set B are consistent with values for a mixture of the two first named hexanes (compare with Table I).

1. *Identification of 2,3-dimethylbutane.* The identification, and also more or less quantitative determination of this hexane, is simple because it is the only isomer that forms a *solid* bromide on direct bromination of hexanes. Nitro derivatives, particularly the solid 2,3-dinitro compound, are difficult to prepare and the mononitro hexanes can hardly be separated and distinguished from one another.

The bromination of the pure hydrocarbon or mixtures rich in it takes place easily in the sunlight or in strong electric light at room temperature, with copious evolution of hydrogen bromide; every drop of bromine is decolorized in the course of a few seconds and soon colorless needles of *2,3-dibromo-2,3-dimethylbutane*, $CH_3CH(Br)\underset{\displaystyle CH_3}{\underset{|}{C}}H(Br)CH_3$, appear in feathery growths on the sides of the reaction flask until practically everything solidifies to a crystalline aggregate.

Our dibromide may be further brominated, but much less rapidly than the hexane, to the *1,2,3,4-tetrabromo-2,3-dimethylbutane* of melting point 130–131°.

Direct comparative experiments with a 1000-watt lamp, made by Dr. L. Schmerling showed that pure synthetic 2,2-dimethylbutane does not react with bromine, whereas pure synthetic 2-methylpentane absorbs bromine most rapidly, but that its reaction products are liquid even at −78°. The results with pure synthetic 2,3-dimethylbutane were identical with those obtained in sunlight.

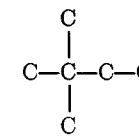
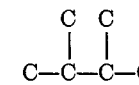
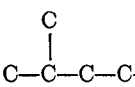
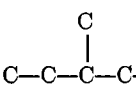
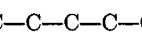
The *dibromide* has a strong characteristic odor; it is very easily soluble in ether, crystallizing in centimeter-long silky needles. It readily deteriorates in air (hydrolysis) and should be kept in a sealed tube or a phosphorus pentoxide desiccator.

Analysis showed 65.46% bromine; calculated for $C_6H_{12}Br_2$, 65.53%. The pure derivative sublimes without melting at 165–175° when heated in an open tube or capillary. In a sealed

TABLE I

PHYSICAL CONSTANTS OF THE HEXANES (14)

(Arranged in the Order of Increasing Boiling Point)

HEXANE	C-STRUCTURE	BOILING POINT °C. 760 MM.	d_4^{20}	n_D^{20}	OCTANE NUMBERS (RESEARCH METHOD 15)	U.O.P. DETERMINATION ON PURE SYNTHETIC SAMPLES. CFR MOTOR METHOD
2,2-Dimethylbutane		49.77	0.6491	1.3690	101	93.0
2,3-Dimethylbutane		58.00	.6615	1.3751	124	94.0
2-Methylpentane		60.20	.6536	1.3717	69	71.5
3-Methylpentane		63.20	.6643	1.3765	84	
n-Hexane		68.75	.6594	1.3751	29	

Average Values for Hexanes of:

$$\Delta t_{b.p.}/\Delta p = 0.042°/\text{mm. Hg}$$
$$\Delta n/\Delta t = -0.00055/°C$$
$$\Delta d/\Delta t = -0.00090/°C$$

capillary our purest crystals melted, with decomposition and gas evolution, at 166–168°; they showed no depression with an authentic sample of 2,3-dibromo-2,3-dimethylbutane prepared from the pure synthetic hexane. Evidently, in a sealed tube the small quantities of decomposition products, accumulating gradually, lower the melting point; the latter depends, therefore, also on the rate of heating, which explains the wide differences recorded in the literature,[2] for instance >140°, Pawlow (6) and 169–170°, Kaschirski (7). It was

[2] The melting point 192° given by H. L. Wheeler (8) for our derivative is identical with that of the isomeric pinacoline dibromide, $(CH_3)_3CC(Br_2)CH_3$; probably he had the latter compound in his hands, since it could readily form by "pinacoline rearrangement" from pinacone with hydrogen bromide in glacial acetic acid.

TABLE II

SET A-1. THIRD DISTILLATION OF HEXANES OBTAINED WITH BORON FLUORIDE AT 0–5°. ORIGINAL CHARGE, 350 cc. at 25°

FRACTION	BOILING RANGE, 760 MM.	VOLUME, IN CC., 25°	n_D^{20}	d_4^{20}	%C	%H	MOL. WT.	REMARKS
1	35.0–37.0	1.8	—					*n*-Pentane
2	37.0–39.0	3.0						
			1.3646					
3	39.0–41.0	3.4						
4	41.0–43.0	4.0						
			1.3675					
5	43.0–45.0	4.4						
6	45.0–47.0	4.8	1.3668					
7	47.0–49.0	4.4	1.3688					
8	49.0–51.0	16.0	1.3686					4% by Vol.
9	51.0–53.0	5.0	1.3693					
10	53.0–55.0	18.0	1.3709					
11	55.0–57.0	53.0	1.3722	0.6545	83.39	16.58		
12	57.0–59.0	81.0	1.3729	.6579	83.45	16.28	84	
13	59.0–61.0	90.0	1.3734	.6579				
14	61.0–63.0	7.0	1.3735					
15	63.0–65.0	3.4	1.3744					
16	65.0–67.0	2.0	1.3754					
Residue	>67.0	2	1.3819					Heptanes or Octanes
Total		307						
Losses during 3 distillations		43						

SET A-2. PROPERTIES OF SIMILAR CUTS OF HEXANES OBTAINED WITH BORON FLUORIDE AT −30 TO −40°. ORIGINAL CHARGE, 210 cc. at 25°

SECOND DISTILLATION

1	30.0–40.0	5.0	1.3546					
2	40.0–45.0	2.3	1.3566					
3	45.0–47.0	1.0	1.3627					
4	47.0–49.0	0.7	1.3621					
5	49.0–51.0	0.1	—					
6	51.0–55.0	2.9	1.3676					
7	55.0–57.0	14.5	1.3718					
8	57.0–58.8	147.0	1.3747	0.6600	83.42	16.39	83	
8a	58.8–59.0	22.5	1.3746	.6597				
9	59.0–61.0	15.0	1.3750					
10	61.0–70.0	2.0	1.3752					
Residue	>70.0	4	1.3790					
Total		197.0						
Losses during 2 distillations		1.3						

TABLE II—*Continued*

SET B. PROPERTIES OF HEXANES OBTAINED WITH ALUMINUM CHLORIDE AT 25–35°.
ORIGINAL CHARGE, 575 cc. at 25°
SECOND DISTILLATION

FRACTION	BOILING RANGE, 760 MM.	VOLUME IN CC., 25°	n_D^{20}	d_4^{20}	%C	%H	MOL. WT.
1	30.0–40.0	10.0	1.3546				
2	40.0–48.0	9.0	1.3622				
3	48.0–50.0	13.0	1.3655				
4	50.0–52.0	15.0	1.3670				
5	52.0–54.0	72.0	1.3693				
6	54.0–56.0	63.0	1.3708				
7	56.0–58.0	85.0	1.3724	0.655			
8	58.0–59.0	153.0	1.3743		83.51	16.49	84
9	59.0–60.0	44.0	1.3748				
10	60.0–61.0	50.0	1.3740				
11	61.0–62.0	12.0	1.3740				
12	62.0–63.0	5.0	1.3744				
13	63.0–70.0	12.0	1.3742				
Residue	>70.0	5.0	1.3821				
Total		548.0					
Losses during 2 distillations		27					

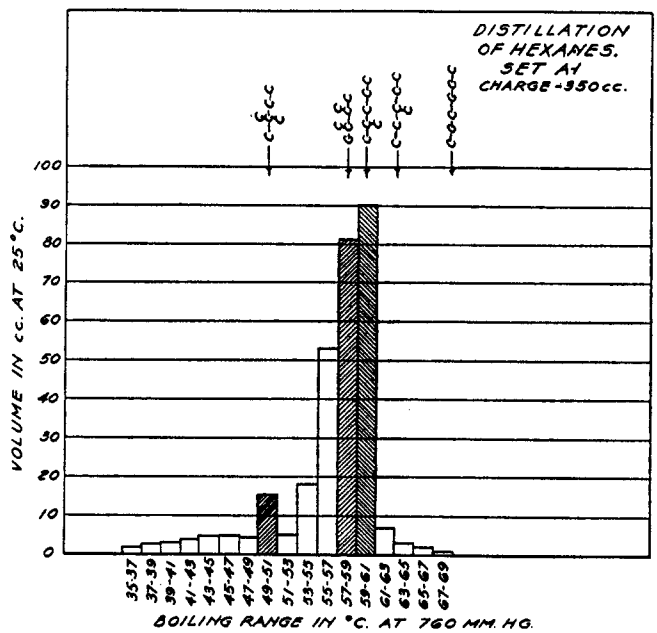


FIGURE 1. FRACTIONATION OF HEXANES

further identified by conversion into *tetramethylethylene*, of boiling point 72° at 760 mm. and n_D^{20} 1.4155, by boiling with zinc granules and 95% alcohol; this compound was converted by Thiele's method (9) into the volatile blue crystals of the *nitrosochloride*, $(CH_3)_2C—C(CH_3)_2$

NO Cl

melting point 121°.

The only other known *solid* mono- or dibromo-hexanes are: (a) the *monobromo derivative of 2,3-dimethylbutane*, $CH_3CH(Br)CH_2CH_3$ (with CH_3 on each of the two middle carbons), which seems to be much more readily brominated than 2,3-dimethylbutane itself (so that it does not accumulate in the bromination products of this hexane), and is more readily prepared by the addition of hydrogen bromide to tetramethylethylene; m.p. 24–25°, and (b) *3,3-dibromo-2,2-dimethylbutane*,

TABLE III

BROMINATION OF HEXANE FRACTIONS

SOURCE OF HEXANES	NO. OF BROMINATIONS	HEXANES USED, G.	HEXANES RECOVERED, G.	LIQUID BROMIDES, G.	CRYSTALLINE $(CH_3)_2CBrCBr(CH_3)_2$, G.	TOTAL YIELD OF $(CH_3)_2CBrCBr(CH_3)_2$, G.	ITS M.P. (IN SEALED TUBE), °C.	MIXED M.P. (WITH SYNTHETIC SAMPLE), °C.	ESTIMATED % OF 2,3-DIMETHYLHEXANE IN FRACTION
A-1 (BF_3 at 0°) Fractions 11, 12	I	100	55	17	93	168	165	165	>60
	II	55 ←	26	5	48		164	—	
	III	26 ←	5	2	23		162	—	
	IV	5 ←	0	0	4		160	—	
A-2 (BF_3 at −30°) Fraction 8	I	100	160		160	160	162	164	>50
B ($AlCl_3$ at 25–30°) Fractions 6, 7, 8, 9	I	100	32.5	33	128	142	163	164	>50
	II	32.5 ←	3.5	7	13		160	—	
	III	3.5 ←	0	0.5	1		160	—	

$CH_3C(CH_3)_2$—CBr_2CH_3 [printed as structural formula: $CH_3C—CCH_3$ with CH_3 above and below the first C and Br above and below the second C], mp. 191.5° (in sealed tube), prepared from pinacoline with phosphorus pentabromide and not by direct bromination of the hexane.

Our quantitative bromination took place at ordinary temperature, (25–35°) in the bright sunlight, in a flask fitted with a stirrer, reflux condenser, and burette with bromine. The hydrogen bromide fumes were absorbed in a trap containing water. At the beginning the rate of bromine addition was so adjusted that there was only a slight excess of bromine and it was usually stopped when the bromine absorption had slowed down to about one-tenth of its original value, to avoid overbromination. Between 10 and 100 g. of hexanes was used per batch. The product was then refluxed until all the bromine disappeared, the unreacted hexanes distilled off, the residue cooled, the crystals sucked dry on a porous filter plate, weighed and recrystallized from ether.

The results obtained with different fractions are correlated in Table III.

The *liquid bromides*, of Table III, still contained some dissolved 2,3-dibromo-2,3-dimethylbutane, but consisted mostly of *monobromides* having the boiling point 75–85° at 200 mm. and n_D^{20} 1.45. These remained liquid even on prolonged standing at −78° (solid carbon dioxide) and were free from the 25°-melting 2-bromo-2,3-dimethylbutane; evidently they represent monobromosubstituted 2-methylpentanes.

2. *Identification of 2-methylpentane.* The chemical identification of this hexane is much more difficult than that of the preceding one. Its bromine derivatives are not characteristic. Fortunately it is, besides 3-methylpentane, the only hexane that gives a crystalline trinitro derivative, on nitration by the method of Konowalow (10), although the yields are far from quantitative.

The two trinitro compounds[3] mentioned have the following properties: (a) *2,3,3-trinitro-2-methylpentane*, $CH_3C(NO_2)_2CH_2 \cdot CH_3$, colorless plates or needles, m.p. 96°, readily soluble in alcohol, insoluble in alkalies; (b) *2,2,3-trinitro-3-methylpentane*, $CH_3C(NO_2)_2CH_2CH_3$, m.p. 85°.

The results of our nitrations are given in Table IV. In every case the same crystalline trinitrohexane namely 2,3,3-trinitro-2-methylpentane, melting at 96.3–96.8° was obtained, besides some unreacted hydrocarbon and some yellow oily nitro compounds, probably mononitrohexanes. No crystalline derivative of 3-methylpentane could be found.

The nitrations of our fractions were carried out as follows: 20 cc. of the fraction was boiled under reflux (glass ground joints) with 60 cc. of 38% nitric acid for 6 hours. At the end of experiment the unreacted hydrocarbon was separated, the acid diluted with ice, any of the crystalline derivatives which usually appeared at this point were filtered off, the filtrate extracted with ether, the ether extract dried, and the ether allowed to evaporate slowly. Any crystals were separated from the oil and recrystallized from ethanol.

3. *Identification of 2,2-dimethylbutane.* At first, indications for the presence of this hexane were available in the form of a peak (4 vol. %) in the boiling point curve at 49–51° in the case of Set A-1, (see Fig. 1), and the value n_D^{20} 1.3686 coinciding with the properties of 2,2-dimethylbutane, b.p.$_{760}$ 49.75°, n_D^{20} 1.3690. This fraction was exceedingly resistant towards nitration (2,2-dimethylbutane is known to be the most difficult hexane to nitrate), and heating for 6 days with 37% nitric acid at 100° in a sealed tube failed to nitrate noticeable quantities of the hydrocarbon; at slightly higher temperatures explosions occurred.

Later, in working up another batch of $AlCl_3$-hexanes (obtained under similar conditions, as described under Set B), 3 vol. % (based on total hexanes) of a cut boiling at 49.2–49.9° at 760 mm. with d_4^{20} 0.6492 and n_D^{20} 1.3689, was obtained. Its analysis gave C, 83.55; H, 16.45. Nitration by Konowalow's method yielded colorless crystals of *3-nitro-2,2-dimethylbutane* (m.p. *ca.* +40°).

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[3] In this connection it should be mentioned that a third trinitro-2-methylpentane (with unknown positions of the nitro groups), m.p. 85°, registered in "Beilstein" (see Vol. I, p. 149) is evidently identical with the 2,2,3-trinitro-3-methylpentane mentioned below under (b). In the original article [Francis and Young, *J. Chem. Soc.*, **73**, 930 (1898)] no mention is made that specifically 2-methylpentane was used for nitration, but only "light petroleum fractions." The best yields of the above nitro derivative were obtained from a cut boiling from 62.6–63.1°. This range is very near the present reliable value for the b.p. of 3-methylpentane (63.20°). Evidently the *abstractor* assumed the cut to be 2-methylpentane.

Two cubic centimeters of hexane was heated with 6 cc. of 37% nitric acid in a sealed glass tube to 120° for 8 hours (in a rotating autoclave under 15 atmospheres nitrogen pressure). After the reaction, the tube was cooled in dry ice, the nitrogen oxides released, the tube resealed and again heated for 8 hours *at 120°*; at the end of the experiment a small quantity of colorless crystals floating at the surface between the two layers was observed. As the

TABLE IV

NITRATION OF HEXANE FRACTIONS

NITROHEXANE FROM (see Table II)		YIELD, % OF ORIGINAL FRACTION	MELTING POINT, °C.	%N	APPEARANCE	REMARKS
Set	Fraction					
A-1 (BF_3, 0–5°)	11	2	96.3		Colorless thin jagged plates	Some yellow oily nitro product obtained simultaneously. Mixed melting point of Cut 12 with 11 & 13. No depression.
	12	11	96.5	18.68		
	13	9	96.0			
Set B ($AlCl_3$, 25–30°)	8	5	96.8	18.61; 18.69	Mixed melting point with Set A-1, no depression	Larger quantities of oily nitro product.
2,3,3-Trinitro-2-methylpentane, from synthetic 2-methylpentane			96.8	18.99	Colorless plates	

TABLE V

RAMAN SPECTROSCOPIC RESULTS

SOURCE OF MATERIAL (see Table II)		HEXANES FOUND	APPROXIMATE AMOUNTS, %
Set	Fraction		
A-1 (BF_3)	12	2,3-Dimethylbutane	90–80
		2-Methylpentane	10–20
B ($AlCl_3$)	6	2,3-Dimethylbutane	100–90
		2-Methylpentane	≃0
B ($AlCl_3$)	8	2,3-Dimethylbutane	85–75
		2-Methylpentane	15–25

results of two such experiments, the tube contents were extracted with ether, separated from the acid layer, washed with water, dried with calcium chloride, and fractionally distilled. Discarding the fractions of ether and unreacted hexane, a colorless liquid came over at 168°/760 mm., leaving a small quantity of higher-boiling residue (dinitrohexanes). The fraction at 168° solidified to white crystals and represented 3-nitro-2,2-dimethylbutane. It dissolved completely in 5% solution of sodium ethoxide in ethanol, forming a

sodium salt; this remained in solution on adding an equal volume of water, and was precipitated as an oil on saturation with carbon dioxide, all characteristic properties of the *3-nitro* compound. The yield of crystals based on the hexane was 10–15%.

4. *Identification and quantitative estimation by means of Raman spectra.* The Raman spectroscopic work was carried out by one of us (A.V.G.) in conjunction with Dr. E. Rosenbaum at the University of Chicago. The method of investigation and details will be published separately (11). It is sufficient to mention here that first Raman spectra of the five *pure* synthetic hexanes (12) were taken. We owe these hexane samples to the kindness of Dr. P. L. Cramer of the General Motors Corporation (13). These spectra were compared with the spectra of our different fractions; from the correspondence of the Raman lines and their intensity the presence of a particular hexane and its approximate quantity could be determined. Some of the most important results are shown in Table V.

ACKNOWLEDGMENTS

The authors are indebted to Mr. R. W. Moehl for carbon and hydrogen analyses and to Drs. J. Mavity and L. Schmerling for their valuable help in various phases of the investigation.

SUMMARY

From the combined results of the chemical and Raman spectroscopic investigation it may be concluded with certainty that the hexanes formed by the catalytic alkylation of i-butane with ethylene, in the presence of boron fluoride or aluminum chloride, are *2,3-dimethylbutane* (90–70% of the total hexanes), *2-methylpentane* (10–20%), and traces of *2,2-dimethylbutane* (3% or less).

With both catalysts their relative amounts are approximately the same.

The identification has been accomplished (a) chemically through their bromo and nitro derivatives and (b) by their Raman spectra.

The two other hexanes can only be present in negligible amounts if at all.

RIVERSIDE, ILL.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SCHOOL OF PHARMACY, PURDUE UNIVERSITY]

IODINATED DERIVATIVES OF SOME SULFONAMIDO COMPOUNDS[1]

CARL J. KLEMME AND ERNEST L. BEALS

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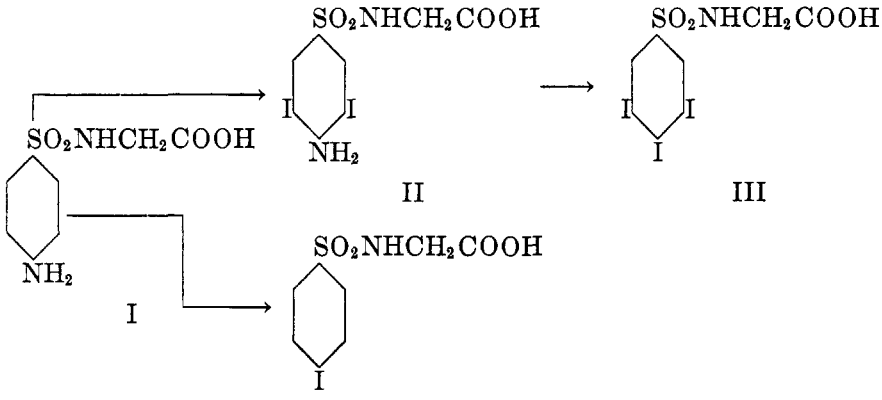
The synthesis of certain iodinated sulfonamido derivatives was undertaken with the object of obtaining compounds of high iodine content and containing solubilizing groups which might prove of value as contrast media for radiographic practice.

This report deals with the syntheses of a few of the above mentioned iodinated compounds. The investigations of the alkali salts as to solubility, toxicity, and suitability as contrast media are problems for subsequent study.

I. *Iodinated sulfanilylglycines.* N-Acetylsulfanilylchloride was coupled with glycine to give the starting material, N-acetylsulfanilylglycine. From this were prepared 3,5-diiodosulfanilylglycine, 3,4,5-triiodobenzenesulfonylglycine, and 4-iodibenzenesulfonylglycine as indicated in formulas I–IV.

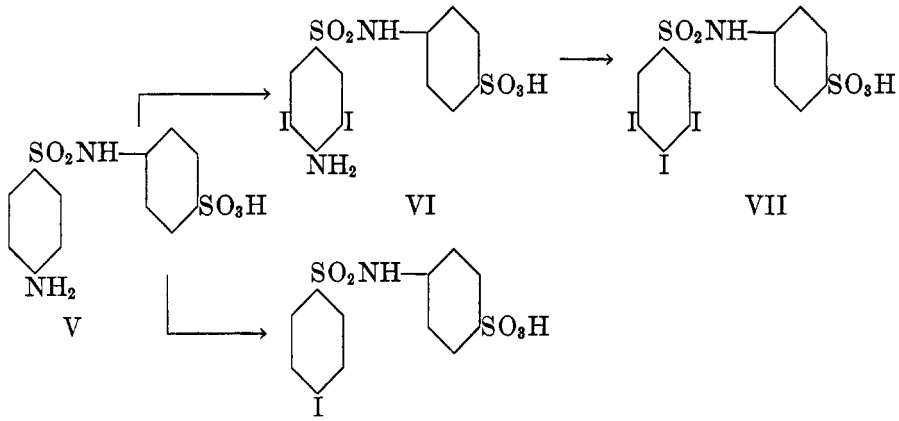


II. *Iodinated N-sulfanilylsulfanilic acids.* Synthesis of the precursors and the scope of the study of these iodinated derivatives are shown in formulas V–VIII.

N-3,5-diiodosulfanilylsulfanilic acid. The treatment of N-sulfanilylsulfanilic acid with iodine monochloride might be expected to yield a tetraiodo acid with substitution in the 3,5, 3′,5′ positions. However, no indication of the entrance of more than two atoms of iodine was obtained, even when a large excess of iodine monochloride was used. It appears probable that steric hindrance prevents the entrance of iodine at positions 3 and 5. Scudi (1) found that 3,5-diiodosulfanilamide could not be acetylated under a variety of conditions, the failure being attributed to spatial configuration. Conversely, it would be expected that iodination of N-sulfanilylsulfanilic acid in the 3,5 positions would likewise

[1] From a portion of a thesis submitted by Ernest L. Beals in partial fulfillment for the degree of Doctor of Philosophy, June 1940.

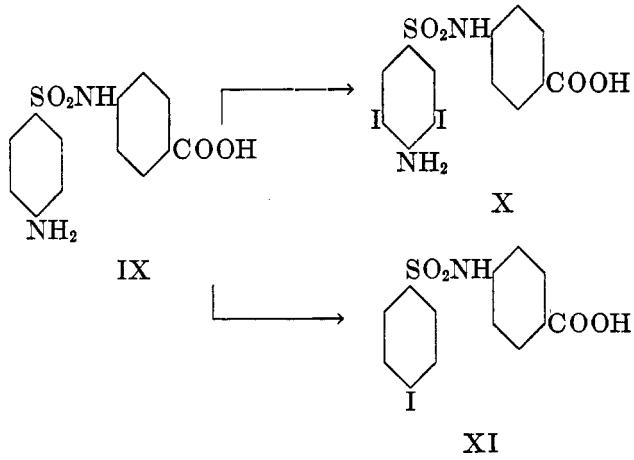
fail, because of the large substituent attached at position 4. It might be mentioned that unsuccessful attempts were made to acetylate the sodium salt of 3,5-diiodosulfanilic acid, although sodium sulfanilate reacts readily with acetic anhydride (2). From these facts it was concluded that the action of iodine monochloride on N-sulfanilylsulfanilic acid yielded the N-3,5-diiodosulfanilylsulfanilic acid.



N-3,4,5-triiodobenzenesulfonylsulfanilic acid. Attempts to prepare this acid led to a compound slightly deficient in iodine content, indicating either incomplete replacement of the amino group, or a tendency for the third iodine atom to be expelled. The relatively high solubility of the free acid in water makes a further study of this compound desirable.

N-4-iodobenzenesulfonylsulfanilic acid. Diazotization of N-sulfanilylsulfanilic acid and treatment with potassium iodide yielded only free iodine and the desired iodinated acid could not be isolated.

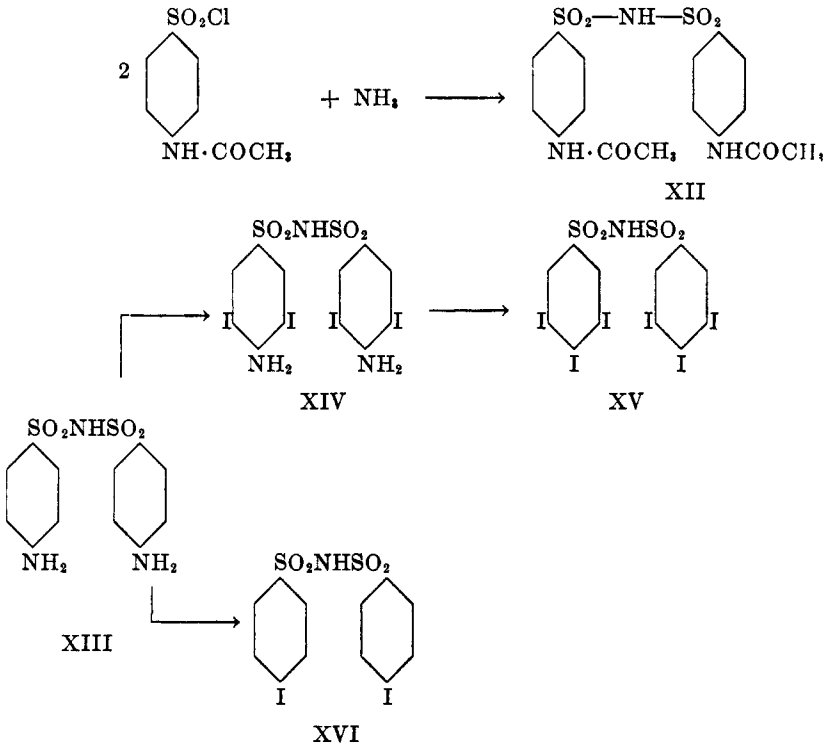
III. *Iodinated N-sulfanilyl*-p-*aminobenzoic acids.* This group of iodinated compounds and their precursor are shown in formulas IX–XI.



N-3,5(?)-diiodosulfanilyl-p-*aminobenzoic acid.* From a consideration of the spatial configuration of the parent acid, and the experimental results obtained on the iodination of N-sulfanilylsulfanilic acid, it was expected that a tetraiodo derivative would not be realized. This was confirmed by the experimental findings, only the diiodo acid being obtained. Attempts at hydrolysis of the sulfonamido linkage for the purpose of identification of the products were vitiated by decomposition of the acid with loss of iodine. However, it was concluded that iodination probably took place in the 3,5-sulfanilyl positions to give N-3,5-diiodosulfanilyl-*p*-aminobenzoic acid.

N-3,4,5-triiodobenzenesulfonyl-p-*aminobenzoic acid.* A limited yield of the necessary precursor (X) did not permit the synthesis of this acid which remains a problem for future investigation.

IV. *Iodinated disulfanilamides.* The precursors and iodinated derivatives of disulfanilamide were prepared as indicated in formulas XII–XVI.



3,3′,5-Triiododisulfanilamide was the unexpected product obtained upon direct iodination of disulfanilamide with iodine monochloride. Variation of acid strength, concentration of iodine monochloride used, and temperature failed to yield a tetraiodo derivative.

3,3′,5,5′-Tetraiododisulfanilamide. A mixture of the tetra- and tri-iododisulfanilamides was obtained by a reversed iodination process in which an acid solution of disulfanilamide was added dropwise to an excess of iodine monochlo-

ride contained in hot, dilute hydrochloric acid. Separation of the two was accomplished by taking advantage of the lower water solubility of the ammonium salt of the tetraiodo variety.

3,3',4,4',5,5'-Hexaiododibenzenesulfonamide. This derivative was not prepared due to the difficulty of separation of the tetraiodo precursor with very low yields of the pure compound. Work will be continued in an attempt to obtain this compound.

V. *Iodinated sulfapyridines.* The study of this group of iodinated sulfapyridines involved experimental difficulties such that only *3,5-diiodosulfanilyl-2-aminopyridine* was obtained in a pure state. *4-Iodobenzenesulfonyl-2-aminopyridine(?)* Diazotization of sulfapyridine and treatment with potassium iodide yielded a complex, iodinated, brick-red product the true identity of which has not been determined. *3,4,5-Triiodobenzenesulfonyl-2-aminopyridine.* Work is to be continued in an attempt to prepare this triiodo derivative of sulfapyridine.

Iodine was determined by electrical ignition in a Parr sulfur bomb. Silver iodate in the fusion filtrate was reduced with hydrazine sulfate and then precipitated as silver iodide. Sulfur was determined by the standard procedure using a Parr sulfur bomb.

EXPERIMENTAL

All melting points are corrected.

3,5-Diiodosulfanilylglycine. N-acetylsulfanilyl chloride was prepared according to Organic Syntheses (3). The crude, moist product was coupled at once with glycine by the method of Kolloff (4) giving a 70% yield of N-acetylsulfanilylglycine melting at 237.7° (Kolloff 237.5–238.5°). For removal of the acetyl group five grams of N-acetylsulfanilylglycine was gently refluxed with 50 cc. of 5 *N* hydrochloric acid for 45 minutes and then added dropwise, with mechanical stirring, to a hot solution of 10 g. of iodine monochloride in 50 cc. of 5 *N* hydrochloric acid. The mixture was heated on a water-bath for one and a half hours, precipitation of the iodo compound commencing within 10 minutes. The crude product was suspended in 4 liters of boiling water, made slightly alkaline with 5% sodium hydroxide, treated with charcoal, and filtered. The hot filtrate was acidified with dilute hydrochloric acid and allowed to stand overnight. (Note: Precipitation from more concentrated solutions yielded an amorphous, colloidal product.) The fine, white crystals were collected, washed with water, and dried. Yield: 6.73 g. (76%), melting with decomposition at 249.5°.

Anal. Calc'd for $C_9H_8I_2N_2O_4S$: I, 52.67. Found: I, 52.87.

3,4,5-Triiodobenzenesulfonylglycine. Two grams of 3,5-diiodosulfanilylglycine was suspended in 100 cc. of water and dissolved by the addition of 5% sodium hydroxide. After the addition of 6 cc. of 5% sodium nitrite the solution was chilled to 3° and added dropwise, over a period of 45 minutes, to 100 cc. of cold, 5 *N* hydrochloric acid. The resulting bright yellow solution gradually darkened and finally threw down a slight precipitate. A few minutes additional stirring caused the sudden appearance of a heavy bright yellow precipitate. The addition of an excess of cold potassium iodide solution caused an immediate evolution of nitrogen, the reaction being completed by warming to 50°. In order to obtain a crystalline product, an alkaline solution of the tan precipitate was diluted to 800 cc. with water, heated to boiling, and then acidified with 5 *N* hydrochloric acid. After slow cooling the pale yellow crystals were collected, washed with water, and again precipitated from a hot, dilute, alkaline solution with acid. The pale greenish-yellow, crystalline product weighed 1.05 g. (42.7%) and melted with decomposition at 279–280°.

Anal. Calc'd for $C_8H_6I_3NO_4S$: I, 64.22. Found: I, 64.09.

4-Iodobenzenesulfonylglycine. Two grams of N-acetylsulfanilylglycine was deacetylated by refluxing gently for one hour with 25 cc. of 5 *N* hydrochloric acid. The solution was diluted with 25 cc. of water, chilled to 3°, and diazotized by the addition of 10 cc. of 5% sodium nitrite over a period of 30 minutes. An excess of cold potassium iodide solution was then added and allowed to warm slowly to room temperature, nitrogen being evolved at about 5°. After warming to 50°, the mixture was cooled, the reddish-tan precipitate collected and repeatedly washed with water. The murky, yellow solution, obtained by dissolving the product in 100 cc. of water with the aid of 5 cc. of 10% potassium hydroxide, was treated with charcoal and filtered. Acidification of the solution with 5 *N* hydrochloric acid and chilling, yielded 1.52 g. of a buff colored powder (61%) melting with decomposition at 189–191°. Alkaline solutions of 4-iodobenzenesulfonylglycine exhibit a canary-yellow color.

Anal. Calc'd for $C_8H_8INO_4S$: I, 37.21. Found: I, 36.97.

Potassium N-3,5(?)-diiodosulfanilylsulfanilate. The starting material, N-sulfanilylsulfanilic acid was prepared in 83.5% yield according to the method of Crossley (5). Five grams of the acid was suspended in 50 cc. of 10% hydrochloric acid, warmed to 40–50° and 2 cc. of iodine monochloride added dropwise with mechanical stirring. At the end of two hours the mixture was chilled in ice, yielding a tan colored paste surmounted by a gelatinous layer. The insoluble product was filtered off and dissolved in a little warm water. Chilling of this solution in ice gave a clear jell which, when made slightly basic with 10% potassium hydroxide and warmed, was replaced by a mass of fine crystals on cooling. The potassium salt was recrystallized five times from hot water, yielding 2.0 g. of the anhydrous salt (21.4%). Potassium N-3,5(?)-diiodosulfanilylsulfanilate crystallized with two molecules of water and was rendered anhydrous when dried over sulfuric acid or heated to 100°.

Anal. Calc'd for $C_{12}H_9I_2KN_2O_5S_2$: I, 41.07; S, 10.37.
Found: I, 41.01; S, 10.44.

N-3,4,5-triiodobenzenesulfonylsulfanilic acid. One and sixty-nine hundredths grams of potassium N-3,5-diiodosulfanilylsulfanilate was suspended in 100 cc. of water. The addition of 5 cc. of hydrochloric acid gave a stiff jell which was thinned by the addition of 50 cc. of water. When chilled to 5° the gelatinous material consisted in part of fine, needle crystals. The addition of the theoretical amount of sodium nitrite solution over a period of 2.5 hours replaced the gelatinous material with a bright yellow precipitate. To this was added 1.0 g. of potassium iodide in 10 cc. of water, the yellow precipitate giving way to a clear, red solution which was allowed to warm slowly to room temperature and then heated to 50°. It was found necessary to evaporate the solution to a small volume on the steam-bath and chill in ice to obtain a paste of pale yellow material which was twice recrystallized from small volumes of water. The final product (0.93 g.) was in the form of extremely long crystals appearing as masses of microscopic hair. The material did not melt nor show signs of decomposition when heated to 310°.

Anal. Calc'd for $C_{12}H_8I_3NO_5S_2$: I, 55.11. Found: I, 51.40.

N-sulfanilyl-p-aminobenzoic acid. N-acetylsulfanilyl-*p*-aminobenzoic acid was prepared in 52% yield by the method of Kolloff (4). Kolloff found that deacetylation of the acid by boiling with a mixture of 4.9 *N* hydrochloric acid and ethyl alcohol resulted in partial esterification. To avoid this, hydrolysis was accomplished by refluxing with 5 *N* hydrochloric acid in the absence of alcohol.

The crude, powdered N-acetylsulfanilyl-*p*-aminobenzoic acid (41 g.) was refluxed with 400 cc. of 5 *N* hydrochloric acid. After five minutes most of the material had dissolved, when suddenly the solution set to an almost solid mass of crystals. The heat was withdrawn and 200 cc. more of the acid added to increase the fluidity of the mass. The mixture was then refluxed for one hour, cooled, chilled in ice, and the precipitate collected. The filter cake was dissolved in 200 cc. of 10% sodium carbonate, treated with charcoal, filtered, and the free acid precipitated by the careful addition of 10% hydrochloric acid. Final purification consisted of two crystallizations from 25% alcohol, yielding 23.2 g. (64.5%) of the crystalline acid melting at 201°. Kolloff (4) reports the melting point as 202°, while Crossley (5) lists it as 198–200.5°.

N-3,5(?)-diiodosulfanilyl-p-*aminobenzoic acid.* The addition of iodine monochloride contained in 10% hydrochloric acid to N-sulfanilyl-*p*-aminobenzoic acid dissolved in a large volume of hot 10% hydrochloric acid gave a product deficient in iodine content (35–37%). Reversing the order of mixing and using 5 *N* acid increased the iodine content to 44.0% (theory 46.66%). The desired derivative was obtained as follows: Five grams of N-sulfanilyl-*p*-aminobenzoic acid was dissolved in 100 cc. of glacial acetic acid by gently warming. The clear solution was added dropwise over a period of 1.5 hours to 10 cc. of iodine monochloride in 100 cc. of 10% hydrochloric acid maintained at 80–90°. The solution was stirred mechanically and heated for a total of 3 hours, precipitation being noted within 20 minutes. After standing overnight the mixture was again heated and stirred for 2 hours, the volume being maintained by the addition of more dilute hydrochloric acid. After cooling, the insoluble material was filtered off, washed with water, and dried, yielding 8.9 g. (93%) of a rose colored, sandy product. Repeated crystallization from hot alcohol failed to yield a pure compound. However, treatment with hot, dry acetone gave the desired product as the acetone-insoluble fraction. The white crystalline product melted with decomposition at 261.1°.

The acetone-soluble portion was reclaimed and recrystallized from water as the ammonium salt. Conversion to the free acid gave an additional yield of the diiodo derivative melting at 261.1°.

Anal. Calc'd for $C_{13}H_{10}I_2N_2O_4S$: I, 46.66. Found: I, 46.50.

N-4-iodobenzenesulfonyl-p-*aminobenzoic acid.* Two grams of N-sulfanilyl-*p*-aminobenzoic acid was suspended in 50 cc. of water and dissolved with the least amount of 10% potassium hydroxide. To this was added 0.53 g. of sodium nitrite, the solution chilled to 0°, and added, over a period of one hour, to 100 cc. of ice-cold, 2.5 *N* hydrochloric acid. An excess of cold potassium iodide solution was then added and, after warming slowly to room temperature, the mixture was heated to 50°, yielding 2.83 g. of a tan product. Partial purification resulted when the acid was twice precipitated from alkaline aqueous solution with dilute hydrochloric acid. The material was then dissolved in hot alcohol, treated with charcoal, and filtered. The filtrate was heated to boiling under reflux and sufficient hot water added to produce a distinct cloudiness. The precipitate which formed as the solution cooled was collected and the process repeated three times, yielding 1.5 g. (54%) of a buff colored powder melting with decomposition at 265–267°.

Anal. Calc'd for $C_{13}H_{10}INO_4S$: I, 31.49. Found: I, 31.40.

3,3',5-Triiododisulfanilamide. Using Crossley's method (6), $N^4,N^{4'}$-diacetyldisulfanilamide was prepared (78%) and deacetylated to N^1-sodium disulfanilamide in 90% yield.

Five grams of N^1-sodium $N^4,N^{4'}$-diacetyldisulfanilamide was boiled for 3 hours with 40 cc. of 10% sodium hydroxide, the volume being maintained by the addition of water. The solution was cooled, the deacetylated product filtered off and heated to 80° with 60 cc. of 25% hydrochloric acid. In an attempt to obtain complete solution, 5 cc. more acid was added, causing the separation of fine, needle crystals. To this suspension was added a solution of 4 cc. of iodine monochloride in 15 cc. of 25% hydrochloric acid. The mixture was stirred mechanically and maintained at 80° for two hours. At the end of this time 1 cc. of iodine monochloride was added directly and the stirring continued for one hour. The heavy white precipitate was washed several times by decantation with 25-cc. portions of 25% hydrochloric acid, collected on a filter, and washed with water; yield: 7.6 g.

The crude material was converted to the sodium salt by warming with 3 cc. of 10% sodium hydroxide in 15 cc. of water, digested with charcoal, and filtered hot. Well-defined crystals were obtained when the filtrate was chilled in the ice-box overnight. The crystalline material was collected and recrystallized three times from small volumes of hot water. When dried for one hour at 110° the crystals effloresced and became opaque; yield: 4.1 g. (50%).

Anal. Calc'd for $C_{12}H_9I_3N_3NaO_4S$: I, 52.38; S, 8.22.
Found: I, 52.67; S, 8.63.

A small amount of the sodium salt of triiododisulfanilamide was dissolved in water and converted to an insoluble, amorphous substance by the addition of 10% hydrochloric acid.

The triiododisulfanilamide was filtered off, washed thoroughly with water and dried. Melting point 249.2°, with decomposition.

3,3',5,5'-Tetraiododisulfanilamide. Two grams of N^1-sodium disulfanilamide (99.92% by nitrite assay) was treated with 50 cc. of water. A trace of insoluble material dissolved only on boiling and reappeared on cooling. The insoluble fraction was filtered out in the belief it might be unhydrolyzed diacetyldisulfanilamide. Sufficient hydrochloric acid was then added to give a final acid strength of 10%, and the clear, cold solution added dropwise over a period of one hour to 5 cc. of iodine monochloride contained in 50 cc. of hot 10% hydrochloric acid. The mixture was cooled, the precipitate collected and washed with 10% hydrochloric acid and with water; yield: 4.0 g. of lavender powder (84.5%).

The powder was suspended in 200 cc. of water and made alkaline with 28% ammonium hydroxide. The reddish solution obtained on boiling was treated with charcoal and filtered hot, the lavender filtrate throwing down fine needle crystals on cooling. These were collected and twice recrystallized from 100-cc. portions of boiling water, yielding 0.75 g. of N^1-ammonium 3,3',5,5'-tetraiododisulfanilamide.

Anal. Calc'd for $C_{12}H_{12}I_4N_4O_4S_2$: I, 59.87. Found: I, 59.70.

A small amount of ammonium tetraiododisulfanilamide was dissolved in boiling water, precipitated with 10% hydrochloric acid, washed with water, and dried. Tetraiododisulfanilamide darkened gradually at 230° and melted with decomposition at 259–260°.

The mother liquor from the crystallization of ammonium tetraiododisulfanilamide gave a bulky precipitate upon acidification with hydrochloric acid. This material was repeatedly recrystallized from hot water as the ammonium salt, decomposed with dilute hydrochloric acid, collected, washed with water, and dried. About 0.1 g. of amorphous material was obtained which assayed 54.05% iodine, and melted with decomposition at 248.6–249.6°, values in good agreement with those found for triiododisulfanilamide.

N^1-potassium 4,4'-diiododibenzenesulfonamide. Two grams of N^1-sodium $N^4,N^{4'}$-diacetyldisulfanilamide was boiled into solution with 50 cc. of 5 *N* hydrochloric acid, requiring 1.5 hours. The solution was treated with charcoal and filtered, the clear filtrate cooled to 0°, and a slight excess of sodium nitrite solution added dropwise, yielding a water-white solution. The addition of an excess of potassium iodide solution gave a greenish-black precipitate which changed to yellow on warming to 50°. After standing overnight the yellow, insoluble material was filtered off, washed with water, and dissolved in 25% alcohol. The hot solution was treated with charcoal, filtered, and made alkaline with 10% potassium hydroxide. On cooling, the potassium salt separated as a pale yellow precipitate which was twice recrystallized from 300-cc. portions of boiling water. The nearly white product weighed 0.5 g. (18.5%).

Anal. Calc'd for $C_{12}H_8I_2KNO_4S_2$: I, 41.95. Found: I, 41.45.

3,5-Diiodosulfanilyl-2-aminopyridine. Two grams of sulfapyridine (Calco) dissolved in 10 cc. of 10% hydrochloric acid was added dropwise over a period of 45 minutes to 2 cc. of iodine monochloride contained in 50 cc. of 10% hydrochloric acid. The mixture was stirred mechanically and kept at a temperature of 80–90°. At the end of one hour the mixture was chilled, the tan precipitate filtered off and washed with water. The product was purified by precipitation from hot alkaline 50% alcohol solution by the addition of dilute hydrochloric acid. This process was repeated twice, the hot alkaline solutions being digested with charcoal and filtered. A yield of 2.7 g. (78%) of white, crystalline product was obtained which melted with decomposition at 269–272°.

Anal. Calc'd for $C_{11}H_9I_2N_3O_2S$: I, 50.67. Found: I, 50.57.

SUMMARY

1. Three new iodinated derivatives of sulfanilylglycine, *viz.*, 3,5-diiodosulfanilylglycine, 3,4,5-triiodobenzenesulfonylglycine, and 4-iodobenzenesulfonylglycine have been prepared.

2. N-3,5(?)-diiodosulfanilylsulfanilic acid has been prepared and described as its potassium salt.

3. N-3,5(?)-diiodosulfanilyl-*p*-aminobenzoic acid and N-4-iodobenzenesulfonyl-*p*-aminobenzoic acid, iodinated derivatives of N-sulfanilyl-*p*-aminobenzoic acid have been prepared and described.

4. A study of the action of iodine monochloride upon disulfanilamide has been made. 3,3′,5-Triiododisulfanilamide has been obtained by the addition of an acid solution of iodine monochloride to disulfanilamide dissolved in hot dilute hydrochloric acid. A reverse iodination process yielded both the triiodo- and 3,3′,5,5′-tetraiodo-disulfanilamide, which were separated and identified as their ammonium salts.

A method for the preparation of the potassium salt of 4,4′-diiododibenzenesulfonamide has been given.

5. 3,5-Diiodosulfanilyl-2-aminopyridine, a diiodo derivative of sulfapyridine, has been obtained in good yield.

LAFAYETTE, IND.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

REACTIONS OF TETRAHYDROPHENANTHRENE. II

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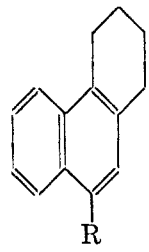
In continuation of work on the reactions of 1,2,3,4-tetrahydrophenanthrene (1), the hydrocarbon has been subjected to bromination, chloromethylation, benzoylation (Perrier reaction), and a modified Friedel-Crafts reaction with acetyl chloride and with propionyl chloride. From the products so obtained various derivatives of tetrahydrophenanthrene have been prepared. In all cases, substitution was predominantly in the 9 position.



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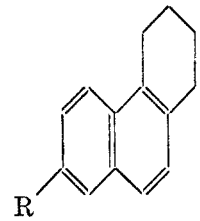


II

By means of the Friedel-Crafts reaction between 1,2,3,4-tetrahydrophenanthrene and acetyl chloride in nitrobenzene, in addition to the 9-acetyltetrahydrophenanthrene (I, R = $COCH_3$) which had been obtained previously, the 7 isomer (II, R = $COCH_3$) was isolated; the ratio of the 9 to the 7 isomer was about 2:1. The structure of the isomer was proved by reduction to 7-ethyl-1,2,3,4-tetrahydrophenanthrene (II, R = CH_2CH_3) followed by dehydrogenation to 2-ethylphenanthrene. Further proof for the location of the acetyl group in the 7 position in this isomer was obtained by conversion to the previously identified β-7-(1,2,3,4-tetrahydrophenanthroyl)propionic acid (II, R = $COCH_2CH_2COOH$) (2). When a mixture of tetrachloroethane and carbon bisulfide was used as solvent for the acetylation in such a proportion that an aluminum chloride addition complex of the product precipitated, the 9-acetyl derivative was obtained free from the 7 isomer.

Propionyl chloride was employed in this same manner to yield 9-propionyl-1,2,3,4-tetrahydrophenanthrene (I, R = $COCH_2CH_3$). This was reduced by the Clemmensen method to 9-propyl-1,2,3,4-tetrahydrophenanthrene (I, R = $CH_2CH_2CH_3$) which was converted to the known 9-propylphenanthrene by dehydrogenation.

The product obtained by benzoylation of 1,2,3,4-tetrahydrophenanthrene by the Perrier modification of the Friedel and Crafts reaction proved to be 9-benzoyl-1,2,3,4-tetrahydrophenanthrene. Beckmann rearrangement of its oxime gave the anilide of 1,2,3,4-tetrahydrophenanthrene-9-carboxylic acid

[1] From the Ph.D. dissertation of M. W. Cronyn.

(I, R = $CONHC_6H_5$) which was identical with the anilide of the acid obtained by hypochlorite oxidation of 9-acetyl-1,2,3,4-tetrahydrophenanthrene.

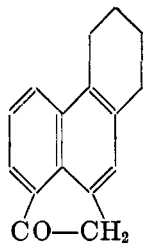
Bromination of 1,2,3,4-tetrahydrophenanthrene yielded 9-bromo-1,2,3,4-tetrahydrophenanthrene, (I, R = Br), which was converted to 9-cyano-1,2,3,4-tetrahydrophenanthrene (I, R = CN) in 80% yield by reaction with cuprous cyanide. Hydrolysis of the resulting nitrile gave the 9-carboxylic acid (I, R = COOH).

Chloromethylation of 1,2,3,4-tetrahydrophenanthrene by the procedure employed by Grummitt and Buck (3) on naphthalene gave a crystalline monochloromethyl derivative, which was identified as 9-chloromethyl-1,2,3,4-tetrahydrophenanthrene (I, R = CH_2Cl) by its reaction with malonic ester to give the 9-propionic acid (I, R = CH_2CH_2COOH). This acid was identical with the propionic acid obtained by sodium amalgam reduction of the acrylic acid (I, R = CH=CHCOOH) produced from the reaction between malonic acid and the aldehyde (I, R = CHO) derived from the 9-acid anilide by the Sonn-Müller method. In addition, reaction of the 9-chloromethyl derivative with sodium cyanide and hydrolysis of the resulting nitrile gave 1,2,3,4-tetrahydrophenanthrene-9-acetic acid (I, R = CH_2COOH) identical with the acid obtained by means of the Willgerodt reaction from 9-acetyl-1,2,3,4-tetrahydrophenanthrene.

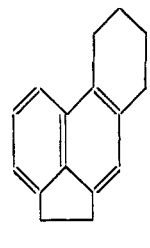
Beckmann rearrangement of the oxime of 9-acetyl-1,2,3,4-tetrahydrophenanthrene gave 9-acetylamino-1,2,3,4-tetrahydrophenanthrene which was hydrolyzed to 9-amino-1,2,3,4-tetrahydrophenanthrene (I, R = NH_2). A small amount of the 7-amino-1,2,3,4-tetrahydrophenanthrene (II, R = NH_2) was prepared in a similar manner by hydrolysis of the corresponding acetylamine which was separated from the mixture of acetylamines obtained by rearrangement of a mixture of the oximes of the 7- and 9-acetyl derivatives.

1,2,3,4-Tetrahydrophenanthrene-7-acetic acid (II, R = CH_2COOH) was obtained by the Willgerodt reaction from the 7-acetyl derivative. 1,2,3,4-Tetrahydrophenanthrene-7-carboxylic acid (II, R = COOH) was separated from a mixture of the 7- and 9-acids resulting from hypochlorite oxidation of a mixture of 7- and 9-acetyl derivatives.

By cyclizing the acid chloride of 1,2,3,4-tetrahydrophenanthrene-9-acetic acid with aluminum chloride, 4-keto-7,8,9,10-tetrahydroacephenanthrene (III) was obtained. Clemmensen reduction converted the ketone to 7,8,9,10-tetrahydroacephenanthrene (IV). Fieser and Peters (4) prepared this hydrocarbon from acenaphthene.



III



IV

EXPERIMENTAL

Preparation of 1,2,3,4-tetrahydrophenanthrene. A mixture of γ-(1- and 2-naphthyl)-butyric acids (208 g.), prepared as described (1) and 222 g. of phosphorus pentachloride in 900 cc. of dry benzene was allowed to stand at room temperature for one hour and then warmed for five minutes on a steam-cone. To the solution, cooled to 5° in an ice-salt bath, a cold solution of 240 cc. of stannic chloride in 240 cc. of benzene was added with stirring at such a rate that the temperature did not rise above 10° (twenty-five minutes). After an additional thirty-five minutes of stirring, the mixture was hydrolyzed by stirring it cautiously into crushed ice and dilute hydrochloric acid. Vacuum distillation of the product gave 162 g. (85%) of a mixture of 1- and 4-ketotetrahydrophenanthrene. Reduction of 225 g. of the mixture of the cyclic ketones by the method described (1) gave 188 g. (90%) of 1,2,3,4-tetrahydrophenanthrene (b.p. 118–120° at 0.1 mm.), which crystallized on cooling.

9-Acetyl-1,2,3,4-tetrahydrophenanthrene. To a suspension of 16.5 g. of anhydrous aluminum chloride in 200 cc. of carbon bisulfide was added 10 g. of acetyl chloride and the mixture was then stirred for fifteen minutes. After the addition of 130 cc. of *sym*-tetrachloroethane, the solution was stirred for another fifteen minutes, then warmed for about five minutes up to 45–50° until all the aluminum chloride had dissolved to give a clear, greenish-yellow solution. The solution was cooled to 15°, and 11 g. of 1,2,3,4-tetrahydrophenanthrene dissolved in 20 cc. of carbon bisulfide was added. Before addition of the hydrocarbon had been completed, hydrogen chloride was evolved, the solution became dark, and within a few seconds it was filled with a thick gelatinous precipitate of the aluminum chloride-ketone addition complex. Stirring was continued for half an hour at room temperature and then the mixture was placed in a refrigerator for twenty-four hours. The cold mixture was filtered and the canary-yellow crystalline complex (23–24 g.) was washed with carbon bisulfide, and then spread out on filter paper for a few minutes to allow the carbon bisulfide to evaporate. The solid was added in portions with stirring to 5% hydrochloric acid solution and crushed ice, and the cream colored lumps of ketone were broken up, filtered, washed thoroughly with water, and dried; yield 11.8–12.2 g. (87–90%); m.p. 52–55°. This was sufficiently pure for most reactions. A purer product was obtained by distilling the ketone under reduced pressure (b.p. 163–166° at 0.1 mm.) and recrystallizing from ethanol; yield 10.6–11.0 g. of colorless prisms; m.p. 56.5–58°. An additional 0.5–0.7 g. of pure ketone was recovered from the carbon bisulfide solution, bringing the total yield to 83–86%.

7-Acetyl-1,2,3,4-tetrahydrophenanthrene. After dissolving 30 g. of anhydrous aluminum chloride in 150 cc. of nitrobenzene cooled to 5°, 12 g. of acetyl chloride was added, the solution was cooled further to −15°, and a solution of 20 g. of 1,2,3,4-tetrahydrophenanthrene in 25 cc. of nitrobenzene was added dropwise with good stirring. The stirring was continued for half an hour at −15°, and for two hours up to 0°, and the mixture then placed in a refrigerator for forty-eight hours. Vacuum distillation of the residue after hydrolysis and steam distillation of the nitrobenzene yielded 21.3 g. of a mixture of the 7- and 9-acetyl derivatives and some tetrahydrophenanthrene. This oily product was dissolved in 175 cc. of absolute methanol, the solvent was removed with a current of air until the first drops of oil appeared, and the solution then seeded with 9-acetyl-1,2,3,4-tetrahydrophenanthrene and placed in a refrigerator for twenty-four hours. After removing the first crop of large prisms of the 9-acetyl derivative (7.2 g., m.p. 55–57°), a current of air was passed over the solution until crystals of the 7-acetyl derivative separated in the form of stubby needles. In one run these separated spontaneously in the filtrate from the first crop. After standing in the cold several days, a total of 4.7 g. was obtained, m.p. 85–89°. Further crystallization gave another 2 g. of the 9-acetyl derivative. Although more crystalline product could not be obtained, the residue was suitable for reactions in which the isomeric products could be separated, such as hypochlorite oxidation of the ketones and Beckmann rearrangement of the oximes. Two recrystallizations from ethanol of 7-acetyl-1,2,3,4-tetrahydrophenanthrene gave fine colorless needles, m.p. 90.5–91.5°.

Anal. Calc'd for $C_{16}H_{16}O$: C, 85.7; H, 7.2.
Found: C, 85.8; H, 7.3.

7-Ethyl-1,2,3,4-tetrahydrophenanthrene. A mixture of 1 g. of 7-acetyl-1,2,3,4-tetrahydrophenanthrene, 5 g. of amalgamated zinc, 10 cc. of acetic acid, 10 cc. of hydrochloric acid, and 4 cc. of toluene was refluxed for twenty-four hours with the addition of 6 cc. of hydrochloric acid during that time. The product after evaporative distillation at low pressure was a colorless oil; yield 0.9 g.

Anal. Calc'd for $C_{16}H_{18}$: C, 91.4; H, 8.6.
Found: C, 91.1; H, 8.7.

The *picrate* was obtained as light yellow needles from ethanol; m.p. 90–91°.

Anal. Calc'd for $C_{22}H_{21}N_3O_7$: N, 9.6. Found: N, 9.7.

A 0.27-g. sample of the above hydrocarbon was heated with 0.04 g. of palladium-charcoal catalyst (5) for one hour at 300–320°. After benzene extraction, filtration, and removal of the benzene, the residue was crystallized from ethanol; yield 0.23 g. (87%) of pearly leaflets; m.p. 64–65°. Two recrystallizations from ethanol raised the melting point of the 2-ethylphenanthrene to 65–66°. The picrate was obtained as yellow needles from ethanol; m.p. 93.5–94.5°. Previously reported values for the hydrocarbon and picrate respectively are 67–68° and 95.5–96° (6), and 64–65° and 92–93° (7).

ω-Bromo-7-acetyl-1,2,3,4-tetrahydrophenanthrene. To 1 g. of 7-acetyl-1,2,3,4-tetrahydrophenanthrene dissolved in 40 cc. of absolute ether cooled to −15° was added 0.74 g. of bromine in 20 cc. of ether. After one and one-half hours at −5° to −10°, a colorless crystalline product had separated. The ether was partially removed and the product collected; yield 0.95 g. (70%); m.p. 114.5–116°. After two recrystallizations from methanol a sample formed colorless needles; m.p. 115.5–116.5°.

Anal. Calc'd for $C_{16}H_{15}BrO$: Br, 26.4. Found: Br, 26.5.

β-7-(1,2,3,4-Tetrahydrophenanthroyl)propionic acid. After refluxing a mixture of 0.05 g. of sodium, 0.5 cc. of malonic ester, and 10 cc. of dry benzene for twenty-four hours, 0.39 g. of ω-bromo-7-acetyl-1,2,3,4-tetrahydrophenanthrene was added and the mixture was refluxed for twenty-four hours. The substituted malonic ester was hydrolyzed with 3 cc. of 40% potassium hydroxide solution, and the dicarboxylic acid was decarboxylated at 180° for half an hour. The warm melt was dissolved in benzene, the acid extracted with dilute potassium hydroxide, and the solution acidified after treatment with Norit. Two recrystallizations from acetone-petroleum ether gave clusters of colorless prisms; yield 0.22 g. (60%); m.p. 155.5–157°, alone and unchanged when mixed with an authentic sample (m.p. 158–159°) (2).

9-Benzoyl-1,2,3,4-tetrahydrophenanthrene. After warming 8 g. of benzoyl chloride and 7.5 g. of anhydrous aluminum chloride over a free flame for a few minutes, the melt was cooled somewhat and dissolved in 42 cc. of warm carbon bisulfide; then a solution of 10 g. of tetrahydrophenanthrene in 10 cc. of carbon bisulfide was added carefully in portions in order to avoid vigorous evolution of hydrogen chloride. After remaining in a refrigerator for twenty-four hours, a current of air was passed over the solution for a few minutes until the entire mass had solidified. The mixture was returned to a refrigerator for two hours, and then the brick-red complex was filtered, washed with cold carbon bisulfide, spread out to dry for a few minutes and then added to a 15% hydrochloric acid solution and cracked ice. The mixture was stirred until the complex was completely hydrolyzed and the colorless solid ketone was then filtered. Recrystallization from benzene-petroleum ether, after decolorization with Norit, gave 13.5 g. (86%) of thin colorless rectangular prisms; m.p. 119.5–121°. Two recrystallizations of a sample from ethanol gave prisms with the melting point 120–121°.

Anal. Calc'd for $C_{21}H_{18}O$: C, 88.1; H, 6.3.
Found: C, 87.9; H, 6.4.

9-Benzoyl-1,2,3,4-tetrahydrophenanthrene oxime. To a suspension of 20 g. of 9-benzoyl-1,2,3,4-tetrahydrophenanthrene in 300 cc. of absolute alcohol and 100 cc. of pyridine was added 20 g. of hydroxylamine hydrochloride and the mixture was refluxed for forty-eight hours; at no time did the solution become clear. After removing most of the solvent and pouring the residue into water, the oxime was filtered and crystallized from methanol; m.p. 225–227°; yield quantitative. Two recrystallizations of a sample from anhydrous ethyl acetate gave colorless prisms; m.p. 228–229°.

Anal. Calc'd for $C_{21}H_{19}NO$: N, 4.6. Found: N, 4.6.

1,2,3,4-Tetrahydrophenanthrene-9-carboxylic acid anilide. After refluxing 6.5 g. of the 9-benzoyl oxime and 5 g. of phosphorus pentachloride in 35 cc. of benzene for 15 minutes, the solution was poured into cold water with vigorous stirring until the anilide crystallized. After filtering the anilide from the benzene-water mixture, the benzene was washed with water, dried over anhydrous sodium sulfate, and evaporated to give further amounts of the anilide. The total yield amounted to 5.5 g. of fine needles; m.p. 238–241°, (85%). Two recrystallizations from anhydrous ethyl acetate gave colorless needles; m.p. 240–241°. The same compound resulted when the acid chloride of the 9-carboxylic acid (obtained by hypochlorite oxidation of the 9-acetyl derivative) prepared from the acid and phosphorus pentachloride was treated with aniline.

Anal. Calc'd for $C_{21}H_{19}NO$: N, 4.6. Found: N, 4.6.

9-Propionyl-1,2,3,4-tetrahydrophenanthrene. Only ten minutes stirring was required and no heating was necessary to effect solution of 8.5 g. of anhydrous aluminum chloride in 100 cc. of carbon bisulfide, 50 cc. of *sym*-tetrachloroethane and 5.7 g. of propionyl chloride. To this solution was added slowly with stirring a solution of 5.5 g. of 1,2,3,4-tetrahydrophenanthrene in 25 cc. of carbon bisulfide. An additional 25 cc. of carbon bisulfide was added and after a few minutes the addition complex started to separate. Stirring was continued for half an hour at room temperature and then the mixture was placed in a refrigerator for twenty-four hours. The canary yellow complex (9–10 g.) was worked up in the same manner as for the 9-acetyl derivative and gave 6 g. (83%) of ketone; m.p. 40–43°. Two recrystallizations from ethanol after distillation under reduced pressure (b.p. 160–162° at 0.05 mm.) gave colorless prisms; m.p. 43–44°.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.7; H, 7.6.
Found: C, 85.5; H, 7.8.

9-Propyl-1,2,3,4-tetrahydrophenanthrene. A mixture of 2 g. of 9-propionyl-1,2,3,4-tetrahydrophenanthrene, 10 cc. of toluene, 10 g. of amalgamated zinc, 15 cc. of hydrochloric acid, and 15 cc. of acetic acid was refluxed for twenty-four hours with the addition of 9 cc. of hydrochloric acid during this time. The product after evaporative distillation under reduced pressure crystallized from acetone-methanol in colorless needles; yield 1.75 g. (93%); m.p. 25–25.5°.

Anal. Calc'd for $C_{17}H_{20}$: C, 91.0; H, 9.0.
Found: C, 91.0; H, 9.0.

The *picrate* was obtained in orange needles from ethanol; m.p. 106–107°.

Anal. Calc'd for $C_{23}H_{23}N_3O_7$: N, 9.3. Found: N, 9.4.

A 0.25-g. sample of the above hydrocarbon was treated with 0.04 g. of palladium-charcoal catalyst for one hour at 300–320°. After benzene extraction, filtration, and removal of the benzene the *9-propylphenanthrene* crystallized from ethanol in colorless needles; yield 0.20 g. (81%); m.p. 58.5–59.5°. Two recrystallizations failed to raise the melting point. The picrate was obtained from ethanol as yellow needles; m.p. 95.5–96°. Previously reported values for the hydrocarbon and picrate respectively are 57.5–58° and 98–99° (8), and 59° and 99° (9).

9-Bromo-1,2,3,4-tetrahydrophenanthrene. To a stirred ice-cooled solution of 5 g. of tetrahydrophenanthrene in 25 cc. of dry, thiophene-free benzene containing 0.5 g. of reduced iron powder as catalyst was added dropwise 5 g. of bromine in 10 cc. of dry benzene. The solution was kept cold for thirty minutes with stirring and then placed in a refrigerator for twelve hours, after which it was warmed for fifteen minutes on a steam-bath. The filtered solution was washed with dilute sodium carbonate and with water and dried. After removal of the solvent, the product was distilled under reduced pressure; b.p. 142–145° at 0.05 mm.; yield 6.4 g. (88%) of colorless liquid.

Anal. Calc'd for $C_{14}H_{13}Br$: Br, 30.6. Found: Br, 30.5.

The *picrate* was obtained from ethanol as light yellow needles; m.p. 102–103°.

Anal. Calc'd for $C_{20}H_{16}BrN_3O_7$: N, 8.6. Found: N, 8.7.

9-Cyano-1,2,3,4-tetrahydrophenanthrene. An intimate mixture of 3 g. of anhydrous cuprous cyanide, 2 cc. of pyridine, and 6.4 g. of 9-bromo-1,2,3,4-tetrahydrophenanthrene was heated at 215–225° for eighteen hours. The mixture was cooled somewhat, and poured

into 50 cc. of 15% ammonium hydroxide, and the dark lumps were mashed and stirred until a powder was obtained. The mixture was diluted and filtered, and the nitrile was evaporatively distilled at 190° and 0.1 mm. and then crystallized from acetone-petroleum ether from which it separated in colorless prisms; yield 4.1 g. (81%); m.p. 120–123°. After two recrystallizations from anhydrous ethyl acetate, it formed large prisms; m.p. 124–125°.

Anal. Calc'd for $C_{15}H_{13}N$: N, 6.8. Found: N, 6.8.

1,2,3,4-Tetrahydrophenanthrene-9-carboxylic acid. A mixture of 1 g. of 9-cyano-1,2,3,4-tetrahydrophenanthrene, 15 g. of potassium hydroxide, and 50 cc. of methanol was refluxed on a steam-cone for seven days. The alcohol was evaporated, the residue dissolved in water, and the solution filtered and acidified. In order to remove the silica, the acid was dried, dissolved in dilute bicarbonate solution, the solution filtered, and the acid reprecipitated; yield 1 g.; m.p. 206–210°. Sublimation and two recrystallizations from acetone gave colorless needles; m.p. 215–216°.

Anal. Calc'd for $C_{15}H_{14}O_2$: C, 79.6; H, 6.2.
Found: C, 79.4; H, 6.2.

The *methyl ester* obtained by means of diazomethane crystallized from methanol in colorless needles; m.p. 70.5–71°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7.
Found: C, 79.9; H, 6.7.

The acid and ester obtained by hypochlorite oxidation of the 9-acetyl derivative melted at 214–216° and 69–70° respectively, alone and when mixed with the acid and ester obtained from the nitrile.

9-Chloromethyl-1,2,3,4-tetrahydrophenanthrene. A mixture of 9 g. of tetrahydrophenanthrene, 2.8 g. of paraformaldehyde, 6.5 cc. of acetic acid, 9.1 cc. of hydrochloric acid, and 4.1 cc. of 85% phosphoric acid was stirred vigorously and heated for six hours at 80–85°. The product was poured into a separatory funnel, the lower acid layer was withdrawn and washed with ether, the ether was returned to the organic layer, more ether was added, and the ethereal solution was then washed twice with portions of cold water and dried with anhydrous potassium carbonate. After removal of the ether, the residue was distilled under reduced pressure; b.p. 163–165° at 0.05 mm.; yield 7 g. of colorless oil which crystallized after several hours. One recrystallization from acetone-ethanol gave thin flat needles; m.p. 60.5–61°. Two more recrystallizations failed to raise the melting point.

Anal. Calc'd for $C_{15}H_{15}Cl$: Cl, 15.4. Found: Cl, 15.5.

1,2,3,4-Tetrahydrophenanthrene-9-acetonitrile. To a solution of 2 g. of 9-chloromethyl-1,2,3,4-tetrahydrophenanthrene in 30 cc. of acetone was added a solution of 2 g. of potassium cyanide in 6 cc. of water and the mixture was refluxed for forty-eight hours. Ether and water were then added and the ether layer was separated, washed with water, and evaporated. The residue, after evaporative distillation under reduced pressure, crystallized from acetone in colorless prisms; yield 1.3 g.; m.p. 89–90°. After two more recrystallizations a sample melted at 89.5–90°.

Anal. Calc'd for $C_{16}H_{15}N$: N, 6.3. Found: N, 6.2.

1,2,3,4-Tetrahydrophenanthrene-9-acetic acid. (*a*) *From the nitrile.* A mixture of 1 g. of the 9-acetonitrile, 20 cc. of acetic acid, 9 cc. of hydrochloric acid, and 2 cc. of water was refluxed for twenty-four hours and then poured while hot into 30 cc. of hot concentrated hydrochloric acid. On cooling, the solution deposited 1 g. of colorless needles; m.p. 151–153°. Two recrystallizations from acetic acid raised the melting point to 153–153.5°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7.
Found: C, 80.3; H, 6.5.

(*b*) *From 9-acetyltetrahydrophenanthrene.* Using the Willgerodt method in the manner suggested by Fieser and Kilmer (10) except that the time of heating was twenty-four hours and the temperature 170°, 1.2 g. (56%) of 1,2,3,4-tetrahydrophenanthrene-9-acetic acid amide (m.p. 211–212°) was obtained from 2 g. of 9-acetyltetrahydrophenanthrene. After two recrystallizations from xylene the amide was obtained in colorless needles; m.p. 211.5–212.5°.

Anal. Calc'd for $C_{16}H_{17}NO$: N, 5.9. Found: N, 6.0.

The amide was hydrolyzed in the same manner as the corresponding nitrile. From 1.2 g. of the amide, 1.1 g. of acid (m.p. 144–149°) was obtained. After sublimation and two recrystallizations from acetone, the acid melted at 153–153.5° alone and when mixed with the acid obtained in part (a).

1,2,3,4-Tetrahydrophenanthrene-9-aldehyde. After an intimate mixture of 5 g. of the 9-acid anilide, 3.5 g. of finely powdered phosphorus pentachloride, and 4 cc. of dry benzene had been stirred until most of the mass had reacted to give a bright yellow oil, it was heated on a steam-bath for fifteen minutes. The benzene and phosphorus oxychloride were removed at 12–15 mm. by gradually heating the mixture to 140° and maintaining this temperature for 10–15 minutes. A cooled solution of the product in 8 cc. of ethylene dichloride was added to an ice-cold solution of 13 g. of anhydrous stannous chloride in 50 cc. of dry ether saturated with dry hydrogen chloride. The mixture was placed in a refrigerator; after an hour an orange crystalline solid started to separate. After forty-eight hours the complex (7.5 g.) was filtered from the solution and was hydrolyzed by hot dilute hydrochloric acid; yield 3.2 g. of tan powder; m.p. 125–129°. One recrystallization of the aldehyde from carbon tetrachloride-petroleum ether after treatment with Norit in the carbon tetrachloride gave 2.9 g. of long thin needles; m.p. 127–129°. After two recrystallizations from acetone-ethanol a sample melted at 128.5–129°. In addition 0.2 g. of anilide was recovered from the ethereal residue from the reaction.

Anal. Calc'd for $C_{15}H_{14}O$: C, 85.7; H, 6.7.
Found: C, 85.9; H, 6.7.

1,2,3,4-Tetrahydrophenanthrene-9-β-acrylic acid. A mixture of 2.5 g. of the 9-aldehyde, 2 g. of malonic acid, and 3 cc. of pyridine was heated on a steam-bath for eight hours. After a few hours, crystals of the product began to separate from the clear solution. The product was dissolved in 20 cc. of 5% sodium carbonate, the diluted solution was treated with Norit and the filtered solution was acidified; yield 2.75 g. (91%); m.p. 225–227°. After two recrystallizations from acetone a sample formed short colorless needles; m.p. 226.5–227.5°.

Anal. Calc'd for $C_{17}H_{16}O_2$: C, 80.9; H, 6.4.
Found: C, 80.7; H, 6.4.

1,2,3,4-Tetrahydrophenanthrene-9-β-propionic acid. (*a*) *From the acrylic acid.* A solution of 0.5 g. of the acrylic acid in 10 cc. of 10% potassium hydroxide was shaken vigorously with 15 g. of 2% sodium amalgam for several hours; the filtered solution was then acidified. One crystallization from benzene-petroleum ether gave 0.46 g. of the reduced acid; m.p. 158–162°. After two more recrystallizations from acetic acid the acid was obtained in fine colorless needles; m.p. 168–169°.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1.
Found: C, 80.4; H, 6.9.

The *methyl ester* prepared with diazomethane crystallized from methanol in long slender colorless needles; m.p. 49–50°.

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5.
Found: C, 80.4; H, 7.4.

(*b*) *From 9-chloromethyltetrahydrophenanthrene.* To a solution of sodium ethoxide prepared from 0.3 g. of sodium and 1.5 cc. of absolute alcohol and 1.3 cc. of benzene was added 3 g. of malonic ester and then 2 g. of 9-chloromethyl-1,2,3,4-tetrahydrophenanthrene in 3 cc. of benzene. After standing at room temperature for twelve hours the mixture was refluxed for twenty-four hours; 8.2 g. of potassium hydroxide, 5 cc. of alcohol, and 10 cc. of water were added and heating was continued for two hours. The benzene was evaporated and the residual solution heated another hour, diluted, filtered, and acidified. The dry dicarboxylic acid was decarboxylated at 180–190° for half an hour, the product was dissolved in benzene, the solution was extracted with 5% potassium hydroxide and the alkaline solution was acidified, whereupon the propionic acid precipitated; yield 1.7 g.; m.p. 158–162°. Two recrystallizations from acetic acid gave fine needles; m.p. 168–169°, alone and when mixed with the acid obtained in part (a). The methyl ester was obtained in needles; m.p. 49–50°, alone and when mixed with the ester obtained in part (a).

9-Acetyl-1,2,3,4-tetrahydrophenanthrene oxime. A mixture of 17.7 g. of 9-acetyl-1,2,3,4-tetrahydrophenanthrene, 14 g. of hydroxylamine hydrochloride, 70 cc. of absolute alcohol, and 23 cc. of pyridine was refluxed four hours on a steam-bath, most of the alcohol was distilled, and the residue was stirred with cold water until the oxime solidified. The oxime was crystallized from alcohol; yield 14.3 g.; m.p. 152–156°. Two recrystallizations from ethanol gave colorless prisms; m.p. 157–158°.

Anal. Calc'd for $C_{16}H_{17}NO$: N, 5.9. Found: N, 5.8.

9-Acetylamino-1,2,3,4-tetrahydrophenanthrene. After refluxing a mixture of 15.5 g. of the aforementioned oxime and 15.5 g. of phosphorus pentachloride in 300 cc. of dry benzene for fifteen minutes, the mixture was poured into cold water and stirred vigorously for several hours while the product precipitated. After standing for twelve hours, 9.2 g. of the acetylamine was filtered from the mixture, the benzene and aqueous layers were separated, and the benzene solution was washed with water, dried, and evaporated. On trituration with ether the residue yielded 2.3 g. of crude acetylamine, which was recrystallized to give an additional 1.5 g. of the pure compound; total yield 10.7 g.; m.p. 186–188°. Hydrolysis of the residue by refluxing it with 100 cc. of alcohol and 5 cc. of hydrochloric acid for twenty-four hours gave 1.2 g. of amine. The over-all yield of products amounted to 79%. A sample of the acetylamine recrystallized twice from ethanol formed fine colorless needles; m.p. 191–192°.

Anal. Calc'd for $C_{16}H_{17}NO$: N, 5.9. Found: N, 5.9.

9-Amino-1,2,3,4-tetrahydrophenanthrene. A solution of 13 g. of the 9-acetylamine derivative in 500 cc. of alcohol and 30 cc. of hydrochloric acid was refluxed for twenty-four hours. The alcohol was distilled and the residual amine hydrochloride was dissolved in a liter of boiling water and the solution was decolorized with Norit and filtered. The filtrate was cooled rapidly with crushed ice and the amine was precipitated with ammonium hydroxide. When the hot acid solution was allowed to stand in contact with the air and cooled slowly, fine needles of the amine hydrochloride separated, and both the solution and crystals became discolored. Yield of amine, 9.0 g.; m.p. 73–75°. After two recrystallizations from ethanol-methanol it formed clusters of colorless needles; m.p. 76.5–77°.

Anal. Calc'd for $C_{14}H_{15}N$: N, 7.1. Found: N, 7.2.

The *amine hydrochloride* after sublimation and two recrystallizations from alcohol formed stout colorless needles; m.p. 263–264°.

Anal. Calc'd for $C_{14}H_{16}ClN$: Cl, 15.2. Found: Cl, 15.3.

7-Acetylamino-1,2,3,4-tetrahydrophenanthrene. By treating a mixture (10.5 g.) of the 7- and 9-acetyltetrahydrophenanthrenes in the same manner as the 9-acetyltetrahydrophenanthrene, except that the oximes were not crystallized from alcohol, a mixture of acetylamines was obtained from which the 9-acetylamino-1,2,3,4-tetrahydrophenanthrene was separated by crystallization from the benzene-water mixture (4.4 g.; m.p. 184–188°). The residue, after evaporation of the benzene, was recrystallized from methanol and gave 2.8 g. of impure acetylamine; m.p. 130–140°. Two recrystallizations from methanol gave 2 g. of colorless needles of the 7-acetylamino-1,2,3,4-tetrahydrophenanthrene; m.p. 136–137°.

Anal. Calc'd for $C_{16}H_{17}NO$: N, 5.9. Found: N, 5.8.

7-Amino-1,2,3,4-tetrahydrophenanthrene hydrochloride. The 7-amine was obtained as an oil upon hydrolysis of the 7-acetylamine in the same manner as for the corresponding 9 derivative. The amine hydrochloride was precipitated by passing hydrogen chloride into a benzene solution of the amine; after sublimation it was obtained in colorless needles by two recrystallizations from ethanol; m.p. 238–239°.

Anal. Calc'd for $C_{14}H_{16}ClN$: Cl, 15.2. Found: Cl, 15.1.

1,2,3,4-Tetrahydrophenanthrene-7-carboxylic acid. Using the hypochlorite method employed by Newman and Holmes (11), 7.5 g. of a mixture of the 7- and 9-acetyl derivatives was oxidized to the carboxylic acids; yield 6.5 g. of crude acids; m.p. 155–175°. By fractional crystallization from benzene-petroleum ether, one gram each of acids melting at 211–214° and 179–182° were obtained. Recrystallization of the former from acetone gave pure 9-acid (identical with the compound prepared from 9-cyanotetrahydrophenanthrene

above) melting at 214–215°; recrystallization of the latter gave colorless needles of the 7-acid, melting at 184–186°.

Anal. Calc'd for $C_{14}H_{15}O_2$: C, 79.6; H, 6.2.
Found: C, 79.3; H, 6.2.

The *methyl ester* obtained by the action of diazomethane crystallized from methanol in colorless prisms; m.p. 114–115°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7.
Found: C, 79.9; H, 6.7.

1,2,3,4-Tetrahydrophenanthrene-7-acetic acid amide. This compound was obtained in the same manner as the corresponding 9 isomer from 7-acetyltetrahydrophenanthrene by the Willgerodt reaction. Two grams of the 7-acetyl derivative gave 1.4 g. (66%) of the 7-acetic acid amide; m.p. 205–210°. After sublimation under reduced pressure and two recrystallizations from acetone the amide was obtained in colorless needles; m.p. 210–211°.

Anal. Calc'd for $C_{16}H_{17}NO$: N, 5.9. Found: N, 5.9.

1,2,3,4-Tetrahydrophenanthrene-7-acetic acid. The acid was obtained by hydrolysis of the amide using acetic acid and hydrochloric acid as for the 9 isomer. Two recrystallizations from acetone gave fine colorless needles; m.p. 150–151°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7.
Found: C, 79.6; H, 6.8.

4-Keto-7,8,9,10-tetrahydroacephenanthrene (III). To 0.5 g. of the 9-acetic acid and one drop of pyridine in 3 cc. of dry ether was added 0.5 cc. of thionyl chloride, and the solution was allowed to stand for half an hour at room temperature. The excess thionyl chloride was removed under reduced pressure at room temperature and the crystalline acid chloride was dissolved in 15 cc. of anhydrous benzene. To this solution was then added 0.7 g. of anhydrous aluminum chloride in small portions with stirring and cooling in ice. After half an hour the mixture was kept at room temperature for thirty minutes and then hydrolyzed with ice and dilute hydrochloric acid. The product was evaporatively distilled at 160° and 0.05 mm. and crystallized from acetone-petroleum ether; yield 0.3 g. (67%); m.p. 157–159°. After two recrystallizations from acetone a sample was obtained in colorless fine needles; m.p. 158.5–160°.

Anal. Calc'd for $C_{15}H_{14}O$: C, 86.4; H, 6.4.
Found: C, 86.5; H, 6.3.

7,8,9,10-Tetrahydroacephenanthrene (IV). To 3 g. of amalgamated zinc, 5 cc. of acetic acid, and 5 cc. of hydrochloric acid was added a solution of 0.5 g. of the aforementioned ketone, in 3 cc. of toluene; the mixture was refluxed for twenty-four hours with the addition of 3 cc. of hydrochloric acid. The toluene layer was separated, the aqueous layer was washed with benzene, and the combined solutions were washed with water. After evaporative distillation under reduced pressure, the hydrocarbon crystallized from ethanol in colorless plates; yield 0.30 g. (63%); m.p. 88–89°. After two more recrystallizations it melted at 89–90°. The picrate formed red needles which melted at 111–112°. Fieser and Peters (4) reported 92.5° for the melting point of the hydrocarbon and 112° for its picrate.

SUMMARY

The reactions of several reagents with 1,2,3,4-tetrahydrophenanthrene have been studied and various new derivatives of the hydrocarbon have been prepared.

7,8,9,10-Tetrahydroacephenanthrene has been synthesized from 1,2,3,4-tetrahydrophenanthrene.

ANN ARBOR, MICH.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

FORMATION AND PROPERTIES OF AZLACTONES OBTAINED FROM VANILLIN SUBSTITUTION PRODUCTS

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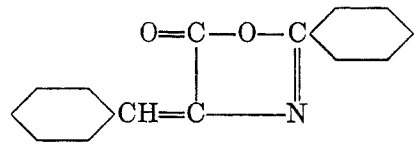
The condensation of aromatic aldehydes with hippuric acid under the influence of acetic anhydride, first noted by Plöchl (1), was studied more intensively by Erlenmeyer and students (2) who established the structures of the products. With benzaldehyde they obtained the inner ester of α-benzoylamidocinnamic acid, designated in the current edition of Beilstein (3) as 2-phenyl-4-benzaloxazolone-5, but more commonly known as an azlactone (4). When a hydroxy

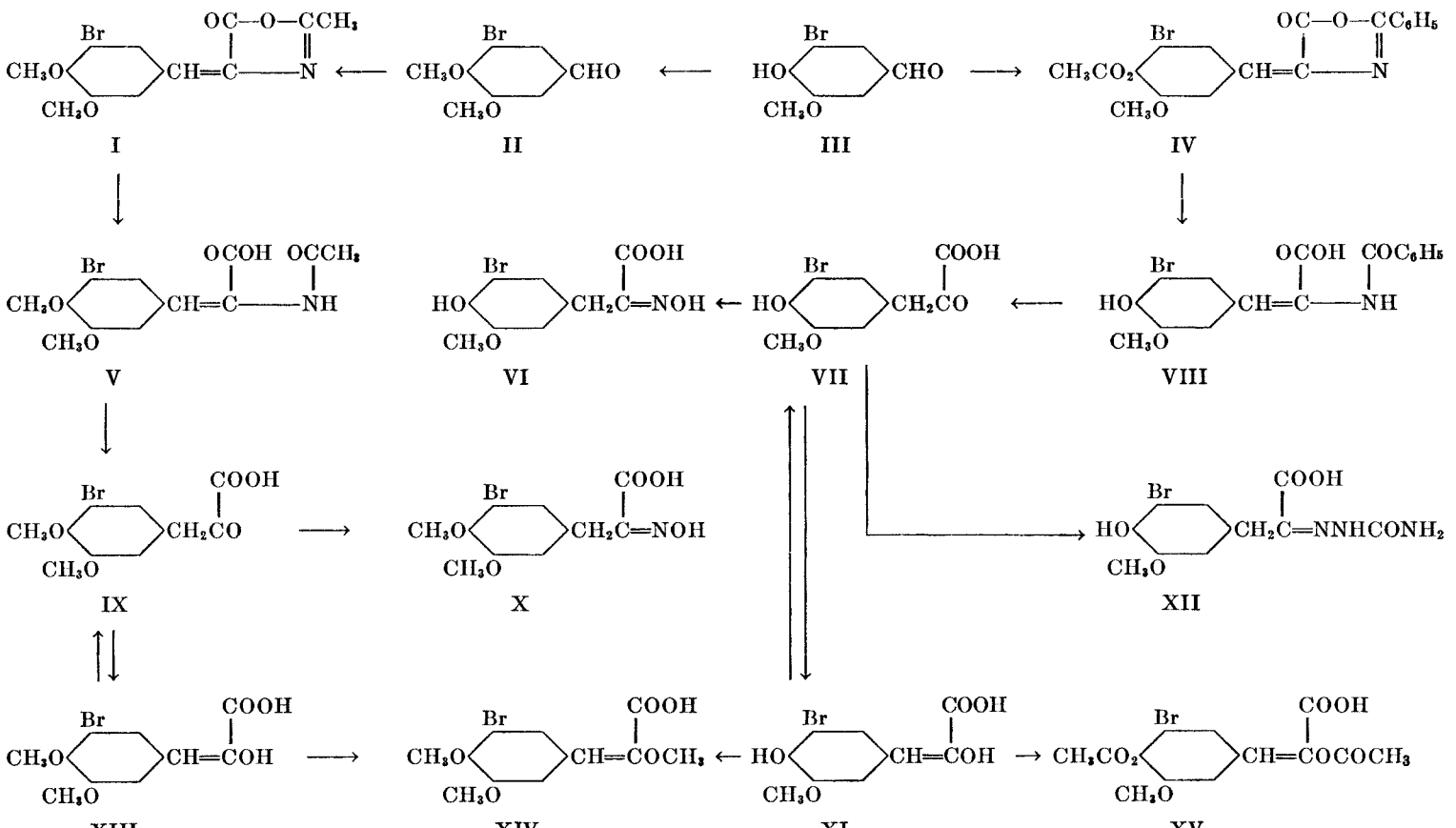


aldehyde is used as starting material the corresponding acetyl derivative is obtained.

These azlactones undergo a number of interesting reactions. Warming the compound with caustic alkali solution for a short time opens the ring to give the related α-acylamidocinnamic acid. Heating the latter with acetic anhydride closes the ring to give the azlactone once more. Heating an alcoholic solution of the azlactone with sulfuric acid opens the ring and gives the ester of the acylamidocinnamic acid. Heating the ester with acetic anhydride does not give the azlactone.

Prolonged treatment of these azlactones with boiling caustic alkali solution not only opens the ring but decomposes the α-acylamidocinnamic acid to give ammonia, the acid represented in the acyl radical and the pyruvic acid related to the aldehyde used in preparing the azlactone. In the case of compound IV, Figure 1, obtained from 5-bromovanillin and hippuric acid, the final products obtained were ammonia, benzoic acid, and 3-methoxy-4-hydroxy-5-bromophenylpyruvic acid, VII. The last-named product, like the mother substance, first obtained by Plöchl (1) and studied further by Wislicenus (5), by Erlenmeyer (6), and by Dieckmann (7), was found to exhibit tautomerism. In the present work the keto form was identified by conversion of the acid into an oxime, VI, and a semicarbazone, XII, respectively. Warming the acid with acetic anhydride gave a diacetyl derivative, XV, which was strongly acidic to litmus and soluble in cold dilute sodium carbonate solution, indicating an exposed carboxyl group, thus characterizing enolic form XI. This form was further identified by its reaction with dimethyl sulfate which introduced two alkyl groups to give a trimethyl derivative, XIV, which was also obtained by another route that proved its structure. Following the suggestions of Erlenmeyer and Frühstück (8) 5-bromoveratraldehyde, II, was condensed with aceturic acid, prepared and purified as directed by Radenhausen (9), to give azlactone I, which was

FIGURE 1



treated with alkali solution, as explained above for the hippuric acid derivative. The resulting α-acylamidocinnamic acid was converted into pyruvic acid IX. Treatment of the latter with dimethyl sulfate introduced one methyl group and gave product XIV. The relations are shown in Figure 1.

EXPERIMENTAL

Azlactones obtained from hippuric acid and vanillin substitution products. To check the method (1) an equimolecular mixture of vanillin, hippuric acid, anhydrous sodium acetate, and 2.5 molecular proportions of acetic anhydride was heated over a steam-bath. The

TABLE I

AZLACTONES FROM HIPPURIC ACID AND VANILLIN SUBSTITUTION PRODUCTS

SUBSTITUENT IN 4-ACETYLVANILLAL	YIELD, %	CRYSTAL FORM [a]	M.P., °C.	FORMULA	ANALYSES			
					Halogen		Nitrogen	
					Calc'd	Found	Calc'd	Found
5-Chloro-	80	Yellow plates	190.5–191.5	$C_{19}H_{14}ClNO_5$	9.55	9.42	—	—
6-Chloro-	68	Yellow needles	205–206	$C_{19}H_{14}ClNO_5$	9.55	9.53	—	—
5,6-Dichloro-	62	Fibrous masses of needles	239–240	$C_{19}H_{13}Cl_2NO_5$	17.48	17.44		
5-Bromo-	70	Yellow needles	191–191.5	$C_{19}H_{14}BrNO_5$	19.23	19.34	3.36	3.42
6-Bromo-	71	Silky yellow needles	211	$C_{19}H_{14}BrNO_5$	19.23	19.23	3.36	3.34
5,6-Dibromo-	51[b]	[c]	264	$C_{19}H_{13}Br_2NO_5$	32.32	32.21	—	—
2,5,6-Tribromo-	72[d]	Granules	190.5–191	$C_{19}H_{12}Br_3NO_5$	41.81	41.72	—	—
4-Methyl-5-bromo-	62	Yellow powder	167.5–168.5	$C_{18}H_{14}BrNO_4$	20.61	20.51	—	—
5-Iodo-	71	Yellow plates	180–181	$C_{19}H_{14}INO_5$	27.42	27.72	—	—

[a] These products were crystallized from acetic acid.
[b] Purified by extraction of foreign materials with acetic acid.
[c] Due to low solubility in all solvents tried this was not obtained in crystalline form.
[d] This represents crude product; other figures are for purified materials.

yellow viscous liquid first formed solidified within half an hour but was heated for fifteen minutes longer. The cooled solid was ground with cold alcohol, the mixture was filtered by suction and the residue was washed with water. Crystallization from acetic acid gave small yellow needles that melted at 188–188.5°. The yield was 72%. Mauthner (10) reported 194–195° for a compound made from the same starting materials though he designated the product as a 3-acetoxy-4-methoxy derivative and reported no yield. Harington and McCartney (11) observed the melting point 189°, and obtained a yield of 75%. Data for related products are given in Table I.

2-Bromohippuric acid. Hildebrandt (12) claims to have isolated this compound from the urine of a dog that had been fed 2-bromotoluene, and reported the melting point 153°. Novello, Miriam, and Sherwin (13) obtained by the action of 2-bromobenzoyl chloride on glycocoll a product that melted at 192–193°, but reported no yield. In our work the acid

was prepared from the required acyl chloride by Baum's (14) general method. A 70% yield of nearly colorless short thick needles, m.p. 193–194°, was obtained.

Anal. Calc'd for $C_9H_8BrNO_3$: Br, 31.00; N, 5.42.
Found: Br, 30.93; N, 5.37.

Data for azlactones obtained from this acid are given in Table II.

Azlactones from aceturic acid. The mother substance of the derivatives reported here was obtained by Erlenmeyer and Frühstück (8) who heated a mixture of equimolecular proportions of glycine, benzaldehyde, and anhydrous sodium acetate with three proportions

TABLE II

AZLACTONES FROM 2-BROMOHIPPURIC ACID

SUBSTITUENTS IN 4-ACETYLVANILLAL	YIELD, %[a]	CRYSTAL FORM[b]	M.P., °C.	FORMULA	HALOGEN ANALYSES	
					Calc'd	Found
Unsubst.	61	Yellow powder	158.5–159.5	$C_{19}H_{14}BrNO_5$	19.23	19.26
5-Bromo-	65	Yellow powder	187–188	$C_{19}H_{13}Br_2NO_5$	32.32	32.01
6-Bromo-	62	Yellow needles	197–198	$C_{19}H_{13}Br_2NO_5$	32.32	32.15
5,6-Dibromo-	62	Yellow powder	225–226	$C_{19}H_{12}Br_2NO_5$	41.81	41.77
2,5,6-Tribromo-	28	Yellow powder	189–191	$C_{19}H_{11}Br_4NO_5$	49.00	48.96

[a] These figures refer to purified materials.
[b] All compounds were crystallized from acetic acid.

TABLE III

AZLACTONES OBTAINED FROM ACETURIC ACID

SUBSTITUENT IN VANILLAL RESIDUE	YIELD %[a]	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HALOGEN	
						Calc'd	Found
5-Chloro-	55	Ethanol	Yellow needles	203–204	$C_{14}H_{12}ClNO_5$	11.46	11.25
4-Methyl-5-chloro-	[b]	Dilute ethanol	Yellow needles	169–170	$C_{13}H_{12}ClNO_4$	12.61	12.56
5-Bromo-	72	Ligroin	Yellow plates	206–207	$C_{14}H_{12}BrNO_5$	22.59	22.40
4-Methyl-5-bromo-	70	Dioxane	Yellow plates	162–163	$C_{13}H_{12}BrNO_4$	24.54	24.40
6-Bromo-	[b]	Ethanol	Yellow leaflets	119–120	$C_{14}H_{12}BrNO_5$	22.59	22.79
5-Iodo-	27	Acetic acid	Yellow plates	196–197	$C_{14}H_{12}INO_5$	31.67	31.42

[a] Figures refer to purified materials.
[b] Resinous material made purification difficult and caused much loss. The yield could not be determined.

of acetic anhydride. Their product melted at 146–147°, and gave a good analysis. No yield was recorded. In the present work a 70% yield of that product, m.p. 149–150°, was obtained by the method specified, with the exception that the glycine was replaced by a purified sample of aceturic acid prepared by Radenhausen's (9) method. Compounds obtained by condensation of this with vanillin substitution products are shown in Table III.

α-Benzoylamidoferulic acid (15). A mixture of 3.36 g. of the azlactone obtained from vanillin and hippuric acid and 300 cc. of approximately 3% solution of potassium hydroxide was slowly heated just to the boiling point, dilute hydrochloric acid was added to the cooled solution, and the colorless solid that separated was collected. Crystallization from

60% ethanol gave colorless prisms that melted at 208.5–209.5°. Sugii (16) reported 205°. A mixture of two grams of this acid and 1.5 cc. of acetic anhydride was heated on a steam-bath for fifteen minutes, the remaining anhydride was distilled under reduced pressure, the residue was boiled for a few minutes with 50 cc. of water, and the solid was collected. Crystallization from acetic acid gave yellow needles, m.p. 188–189°, that did not depress the melting point of the starting azlactone. Data for other ferulic acids are given in Table IV.

Ethyl ester of α-benzoylamino-5-bromoferulic acid. To a mixture of 7.2 g. of the required azlactone and 12 g. of absolute ethanol 2.5 g. of concentrated sulfuric acid was added and the whole was heated under a reflux condenser on a steam-bath until all lactone had dissolved, which required about two hours. Unused ethanol was distilled off under reduced pressure at about 65° and water was added to the residue to precipitate the ester. Crystallization from ethanol gave small colorless needles that melted at 196–197°.

TABLE IV

SUBSTITUTED AMIDOFERULIC ACIDS

SUBSTITUENT IN VANILLAL	ACYL IN α-POSITION	YIELD, %[a]	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HAL.	
							Calc'd	Found
5-Chloro-	Acetyl	86 (crude)	Water	Colorless plates	212–213	$C_{12}H_{12}ClNO_5$	12.43	12.68
	Benzoyl	Nearly quant.	Dil. ethanol	Colorless needles	227–228	$C_{17}H_{14}ClNO_5$	10.21	10.33
5-Bromo-	Acetyl	[b]	Ethanol	Colorless plates	203–304	$C_{12}H_{12}BrNO_5$	24.24	23.85
	Benzoyl	70	Ethanol 60%	Colorless needles	229–230	$C_{17}H_{14}BrNO_5$	20.40	20.28
4-Methyl-5-Bromo-	Acetyl	70	Water	Colorless needles	198–199	$C_{13}H_{14}BrNO_5$	23.25	23.08
	Benzoyl	[b]	Dilute [c] ethanol	Colorless needles	201–202	$C_{18}H_{16}BrNO_5$	19.70	19.72
5-Iodo	Acetyl	63	Dilute ethanol	Colorless needles	217–218	$C_{12}H_{12}INO_5$	33.68	33.62
	Benzoyl	84	Ethanol	Colorless needles	227–228	$C_{17}H_{14}INO_5$	28.92	29.10

[a] Figures refer to purified materials, unless otherwise indicated.

[b] Removal of resin caused much loss.

[c] By cooling solution obtained by slow addition of alcohol to hot mixture of solid and water.

The composition of this product was checked by preparation in a different way. Ethyl hippurate, obtained in 82% yield by the interaction of silver hippurate and ethyl iodide, was mixed with an ether solution of 5-bromovanillin, a small portion of sodium ethylate was added, the mixture stood for four hours at room temperature, was acidified with acetic acid, and filtered. The solid was extracted with cold ethanol, that dissolved the ester and left unchanged 5-bromovanillin. A mixture of this product and the ester described above melted without depression. Heating the ester with acetic anhydride over a steam-bath for four hours gave no azlactone. Properties of this and related esters are shown in Table V.

3-Methoxy-4-hydroxy-5-bromophenylpyruvic acid. A mixture of 25 g. of the azlactone obtained from 5-bromovanillin and hippuric acid, and 100 cc. of 6 *N* sodium hydroxide solution was placed in a flask attached to a reflux condenser the upper end of which was closed with a stopper bearing a bent tube arranged to conduct volatile material into a measured volume of standard sulfuric acid. The reaction mixture was boiled for six hours,

and the ammonia expelled was determined in the usual way. The amount was nearly quantitative. The mixture remaining in the reaction flask was acidified with hydrochloric acid and distilled with steam. The benzoic acid isolated from the distillate represented 94% of that required by theory. The nonvolatile solid remaining in the flask was collected

TABLE V

ESTERS OF α-BENZOYLAMIDO-5-BROMOFERULIC ACID

ADDITIONAL SUBSTITUENT IN VANILLAL	ALKYL PRESENT	YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C.	COMPOSITION	HALOGEN ANALYSES	
							Calc'd	Found
	Ethyl-	60	Ethanol	Colorless needles	196–197	$C_{19}H_{18}BrNO_5$	19.04	19.14
	Methyl-	72	Ethanol	Colorless powder	205–206	$C_{18}H_{16}BrNO_5$	19.70	19.67
4-Methyl-	Methyl-	68	Ethanol	Colorless needle	119–121	$C_{19}H_{18}BrNO_5$	19.04	19.08

TABLE VI

DERIVATIVES OF 3-METHOXY-4-HYDROXYPHENYLPYRUVIC ACID

COMPOUND	YIELD %[a]	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HALOGEN	
						Calc'd	Found
5-Chloro acid	49	Ethanol	Microscopic crystals	228–228.5	$C_{10}H_9ClO_5$	14.51	14.63
Oxime	84	Water	Colorless plates	158–159	$C_{10}H_{10}ClNO_5$	13.67	13.61
5-Bromo acid	47	Ethanol	Colorless powder	237.5–239 (decomp.)	$C_{10}H_9BrO_5$	27.68	27.67
Oxime	83	Ethanol	Colorless plates	169 (decomp.)	$C_{10}H_{10}BrNO$	26.31	26.63
Semicarbazone	60	Water	Colorless granules	195–196	$C_{11}H_{12}BrN_3O_5$	23.12	22.96
Diacetate	65	Ethanol	Colorless needles	193–194	$C_{14}H_{13}BrO_7$	21.44	21.11
4-Methoxy-5-bromo acid	37	Ethanol	Colorless powder	175–177	$C_{11}H_{11}BrO_5$	26.50	26.18
Methyl ether	90	Dilute ethanol	Colorless needles	162–163	$C_{12}H_{13}BrO_5$	25.23	25.29
Oxime	78	Ethanol	Colorless needles	143	$C_{11}H_{12}BrNO_5$	25.15	24.94
5-Iodo acid	43	Dilute ethanol	Colorless powder	234–235	$C_{10}H_9IO_5$	37.79	37.63
Oxime	Nearly quant.	Dilute ethanol	Colorless needles	170–171	$C_{10}H_{10}INO_5$	36.18	35.99

[a] Figures refer to purified materials.

on a filter and washed with a small portion of cold ethanol to remove color and resinous material. Crystallization of the residue from ethanol gave the pyruvic acid, which was identified by the preparation of several derivatives. Data for these are recorded in Table VI.

SUMMARY

1. Vanillin and many of its substitution products have been condensed with hippuric and aceturic acids, respectively, to give the inner esters of the related α-acylamidocinnamic acids, or azlactones.

2. Treatment of the azlactones for a short period with warm caustic alkali solution opens the lactone ring to give the corresponding α-acylamido acid. Heating the latter with acetic anhydride will close the lactone ring once more.

3. Prolonged treatment of these azlactones with boiling alkali solution decomposes the α-acylamido acids first formed to give ammonia, the acid represented by the acyl radical and the pyruvic acid related to the aldehyde used in preparing the lactone. These pyruvic acids exhibit tautomerism.

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SOLUBILITIES OF SOME NORMAL ALIPHATIC AMIDES, ANILIDES, AND N,N-DIPHENYLAMIDES

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The relatively high melting points of the saturated aliphatic amides combined with the fact that, unlike other aliphatic compounds, the amides do not exhibit the gradation in physical properties in the solid state characteristic of most homologous series has long been attributed to some form of molecular association. This is further evidenced by the high dielectric constants of these compounds. X-ray examination (1) has indicated that the amides are probably associated in their crystalline state, since their crystals consist of bimolecular layers with the polar groups adjacent. Cryoscopic and ebullioscopic investigations (2–7) of amides in various non-polar solvents have indicated that these compounds form large polymers, while the anilides are moderately associated, probably as dimers, and N,N-disubstitution appears to inhibit association.

The actual structure of the amides and their derivatives is controversial. Early preparations of imido ethers (8) and preparation of amides from sodamides (9) suggested the existence of the enol tautomer. Tautomerism of the amides is further demonstrated by measurements of their dielectric constants and dipole moments (10, 11), infrared absorption spectra (12, 13), and ultraviolet absorption spectra (14). Calculations from thermochemical data (15) show that the amides consist of resonating molecules. These investigations and those on the solubilities of halogen substituted hydrocarbons in amides (16, 17) suggest that the association of the amides and anilides is effected through hydrogen bonding. Thus, it has been shown that acetamide forms polymers of indefinite molecular weight, and the solubility of chloroform in N-ethylacetamide could be accounted for by assuming that the pure liquid consists largely of dimers (12, 16).

Several structures have been postulated for the amidic polymers. Linear polymers are probably eliminated, for they do not usually lead to excessively high melting points; it has been shown (16) that the large linear polymers formed by hydrogen bonding of the alcohols have relatively low melting points. Furthermore, it has been proved (12) that enolization in the amides would of necessity involve a molecular rearrangement equivalent to ionization of a hydrogen atom. Such an occurrence would be improbable in a non-polar solvent. A cyclical structure has been suggested, for example, one resulting from a fusion of dimers by hydrogen bonding (16). The high dielectric constants of these compounds appear to offer an objection to a symmetrical cyclic structure, since such a structure should involve neutralization of the dipole moments. The high dielectric constants observed may be due to the presence of a high percentage of monomeric molecules (16). No investigation has yet suggested that the large amidic polymers may exist as asymmetrical cyclic structures.

All previous studies have been made upon amides containing less than six carbon atoms. This paper is a report of the preliminary investigation of the be-

havior of the higher amides and presents the solubilities of caprylamide, capramide, capranilide, N,N-diphenylcapramide, lauramide, lauranilide, N,N-diphenyllauramide, myristamide, palmitamide, palmitanilide, N,N-diphenylpalmitamide, stearamide, stearanilide, and N,N-diphenylstearamide in benzene, cyclohexane, tetrachloromethane, ethyl and butyl acetates, acetone, 2-butanone, methanol, 95% ethanol, isopropanol, *n*-butanol, nitroethane, and acetonitrile.

TABLE I

FREEZING POINTS OF PURIFIED AMIDES

AMIDE	NO. OF C ATOMS	F.P., °C.	REF. (M.P., °C)
Caprylamide	8	105.9	104 (19) 105.5 (20) 106 (21) 105 (22) 106 (23)
Capramide	10	98.5	98 (19, 24, 25) 101.1 (20) 99 (22) 98–99 (23)
Lauramide	12	102.4	98–99 (19) 100 (22) 102 (26)
Myristamide	14	105.1	103 (22) 103.0 (setting pt.) (27) 102 (28) 102–103 (29)
Palmitamide	16	107.0	106 (22) 106–107 (25) 103–104 (29) 105.3 (30) 104–105 (31)
Stearamide	18	109.7	105–106 (19) 109 (22) 108.5–109 (26) 108.4 (30)

EXPERIMENTAL

The amides and their derivatives used in this investigation were prepared from fatty acids[1] which had been highly purified by previously described methods (18). Ammonia was passed through the acids at 190–210° for 10–14 hours to obtain the amides. The crude product was poured into water while still hot to remove excess ammonia and any ammonium soap which was formed. The product was then dissolved in tetrachloromethane, washed free of fatty acid with alcoholic potassium hydroxide, and recrystallized from acetone until a constant freezing point was obtained. The freezing points of the amides are listed in Table I.

[1] The freezing points of these acids were 16.26° for caprylic, 30.62° for capric, 43.77° for lauric, 54.15° for myristic, 62.30° for palmitic, and 69.28° for stearic acid.

During the course of this investigation it was decided to prepare an amide by another method as a check on the compounds prepared by the above method. Highly purified caprinitrile (10 g.) was poured into concentrated sulfuric acid (200 ml.) and left for 24 hours. The addition product thus formed was then hydrolyzed by pouring the mixture over a large excess of ice, and the amide which precipitated was filtered and recrystallized from acetone. The freezing point of this capramide was identical with that prepared by the reaction of ammonia with caproic acid, and the solubilities of the two compounds were identical. A small quantity of myristamide was obtained by Mr. E. F. Binkerd as a secondary reaction product in the course of the preparation of myristonitrile. This amide, upon purification, was identical with the myristamide prepared previously.

TABLE II

FREEZING POINTS OF PURIFIED SUBSTITUTED AMIDES

COMPOUND	NO. OF C* ATOMS	F.P., °C.	REF. (M.P., °C.)
Capranilide	10 ϕ	69.5	67–8 (19) 70 (22)
Lauranilide	12 ϕ	77.2	75 (19, 32) 78 (22)
Palmitanilide	16 ϕ	90.2	89 (22) 90.6 (30) 87 (32) 88–90.5 (33) 87.5 (34) 88.5 (35) 90.5 (36)
Stearanilide	18 ϕ	94.9	94 (22, 33) 95.05 (30) 88 (35) 93.6 (37)
N,N-Diphenylcapramide	10 $\phi\phi$	47.5	—
N,N-Diphenyllauramide	12 $\phi\phi$	57.0	—
N,N-Diphenylpalmitamide	16 $\phi\phi$	69.5	—
N,N-Diphenylstearamide	18 $\phi\phi$	72.3	—

* The numbers shown refer only to the number of carbon atoms in the aliphatic chain; ϕ = C_6H_5 in all tables and figures.

Capranilide, lauranilide, and palmitanilide were obtained by heating the appropriate fatty acids with redistilled aniline (added dropwise) for 2–3 hours at 150–170°. After washing by the treatment used for the amides, the anilides were recrystallized alternately from petroleum ether, b.p. 60–71°, (Skellysolve B) and from acetone-water mixtures until constant freezing points were obtained.

For stearanilide and the N,N-diphenylamides the corresponding acid chlorides were first prepared by the action of phosphorus trichloride upon the acids. After removal of the solvent (tetrachloromethane) and excess PCl_3, stearanilide was prepared by adding aniline (dropwise) to stearoyl chloride, maintaining the temperature of the reaction mixture below about 50°. The stearanilide was washed as above and crystallized from acetone to a constant freezing point.

The diphenylamides were prepared by heating the appropriate acid chlorides with diphenylamine for 2–4 hours at 135–145°. After washing, the compounds were crystallized from petroleum ether (Skellysolve B) to constant freezing points. The freezing points of the substituted amides are listed in Table II.

Nitrogen analyses were obtained for all of the compounds to check their identities, and cooling curves were run to verify their purity. It can be seen from Tables I and II that a number of the compounds had higher freezing points than some of the melting points previously reported.

The solubilities of the amides and their derivatives were determined in sealed tubes by the method and with the apparatus previously described (38, 39). The solvents which were employed were those used in previous solubility studies (40). Temperatures were measured with an accurately calibrated thermometer which was graduated in 0.1° intervals. Solution temperatures of the amides and their derivatives were reproducible to ±0.1°, and are, in general, considered accurate to at least ±0.2°.

RESULTS AND DISCUSSION

The solubilities of the amides, anilides, and N,N-diphenylamides in the solvents investigated are listed in Tables III–XV.

TABLE III

SOLUBILITIES IN BENZENE

COMPOUND*	G. PER 100 G. BENZENE					
	10.0°	30.0°	50.0°	60.0°	70.0°	80.1°
8	0.5	0.6	4.1	13.8	52	153
10	0.6	0.8	3.2	11.4	57	195
12	0.6	1.0	6.7	26.6	83	238
14	0.3	0.4	1.5	5.2	27.4	95
16	0.3	0.4	2.0	7.6	41.2	145
18	0.3	0.4	1.6	5.2	25.0	89
10 ϕ	10.1(13.7)	67(110)	283	720	∞	∞
12 ϕ	1.5	14.7(56)	155	340	1000	∞
16 ϕ	1.0	2.2	30.5	97	222	640
18 ϕ	0.7	1.5	14.1	56	145	555
10 $\phi\phi$	100	329	∞	∞	∞	∞
12 $\phi\phi$	56	179	915	∞	∞	∞
16 $\phi\phi$	18.8	81	283	720	∞	∞
18 $\phi\phi$	11.0	65	230	520	3500	∞

* ϕ = C_6H_5.

The absence of a homologous influence in the amide series is striking, since there appears to be no orderly arrangement of the solubility curves of these compounds in the less polar solvents. For example, in benzene, ethyl acetate, 2-butanone, and others, lauramide is, in general, more soluble than capramide, and palmitamide more soluble than myristamide, while in cyclohexane, the latter is less soluble than stearamide, and caprylamide is the least soluble compound investigated. However, in the three highly polar solvents, nitroethane, methanol, and acetonitrile, the solubilities decrease with increased molecular weight, although the intervals between the curves are not regular. All of the N-substituted derivatives, on the other hand, appear in orderly sequence in all solvents. This behavior is illustrated by the solubility curves of these compounds in several representative solvents of various polarities: benzene, Fig. 1; cyclohexane, Fig. 2; butyl acetate, Fig. 3; *n*-butanol, Fig. 4; 2-butanone, Fig. 5; 95% ethanol, Fig. 6; nitroethane, Fig. 7; and acetonitrile, Fig. 8.

In the course of examination of the anilides it was observed that the lower members of the series, capranilide and lauranilide, form an unstable modification which has a relatively greater solubility in a number of solvents than the stable

TABLE IV

SOLUBILITIES IN CYCLOHEXANE

COMPOUND*	G. PER 100 G. CYCLOHEXANE					
	10.0°	30.0°	50.0°	60.0°	70.0°	81.4°
8	—	0.1	0.2	0.3	1.2	53
10	—	0.4	0.5	0.6	3.3	150
12	—	0.5	0.6	1.3	23.9	163
14	—	0.2	0.3	0.4	1.7	61
16	—	0.3	0.4	0.8	8.8	122
18	—	0.3	0.4	0.6	3.3	88
10 ϕ	3.3(3.6)	29.9(78)	273	680	∞	∞
12 ϕ	0.6	0.9(2.8)	105	265	785	∞
16 ϕ	0.4	0.6	2.4	61	173	535
18 ϕ	0.3	0.4	1.1	17.7	105	308
10 $\phi\phi$	64	255	∞	∞	∞	∞
12 $\phi\phi$	27.2	119	800	∞	∞	∞
16 $\phi\phi$	9.2	38.5	232	660	∞	∞
18 $\phi\phi$	6.0	25.0	172	460	2850	∞

* ϕ = C_6H_5.

TABLE V

SOLUBILITIES IN TETRACHLOROMETHANE

COMPOUND*	G. PER 100 G. TETRACHLOROMETHANE					
	10.0°	30.0°	50.0°	60.0°	70.0°	76.0°
8	—	0.4	0.7	3.7	18.2	42.5
10	—	0.2	0.5	2.6	23.6	59
12	—	0.4	1.5	9.9	40.8	72
14	—	<0.1	0.2	1.4	10.1	27.6
16	—	0.1	0.3	3.5	19.8	46.5
18	—	<0.1	0.3	1.6	10.5	28.4
10 ϕ	34.2	52(110)	275	880	∞	∞
12 ϕ	8.5	14.0(43)	134	375	1375	almost ∞
16 ϕ	1.0	1.2	20.2	86	235	408
18 ϕ	0.4	0.5	7.0	43.3	167	300
10 $\phi\phi$	72	310	∞	∞	∞	∞
12 $\phi\phi$	37.9	147	1065	∞	∞	∞
16 $\phi\phi$	16.0	44.7	240	820	∞	∞
18 $\phi\phi$	10.5	30.1	166	485	3800	∞

* ϕ = C_6H_5.

modification. This phenomenon was observed by rapidly chilling tubes containing solutions of the anilides and then placing the tubes in a water-bath at temperatures below those at which the stable form of the compounds was soluble. If the samples are held at the lower temperatures for a short time they transform

into the stable modification. This transformation occurs more rapidly as the concentration of anilide is increased. This behavior appears to occur only in solvents with relatively low dielectric constants, *viz.*, benzene, cyclohexane,

TABLE VI

SOLUBILITIES IN ETHYL ACETATE

COMPOUND*	G. PER 100 G. ETHYL ACETATE					
	10.0°	30.0°	50.0°	60.0°	70.0°	77.2°
8	2.2	5.7	18.9	35.4	69	115
10	0.5	2.2	10.2	23.9	59	123
12	0.5	2.5	12.9	29.4	68	133
14	0.3	1.0	3.3	7.8	22.1	55
16	0.2	0.6	2.9	8.5	27.7	65
18	0.1	0.3	2.0	5.4	16.6	41.1
10 ϕ	17.1	53(72)	248	750	∞	∞
12 ϕ	6.8	17.2(23)	107	286	1250	∞
16 ϕ	0.7	3.0	17.2	52	159	410
18 ϕ	0.4	1.8	8.8	22.7	93	266
10 $\phi\phi$	68	302	∞	∞	∞	∞
12 $\phi\phi$	25.5	125	1075	∞	∞	∞
16 $\phi\phi$	7.7	24.7	182	610	∞	∞
18 $\phi\phi$	3.9	13.6	124	378	3125	∞

* ϕ = C_6H_5.

TABLE VII

SOLUBILITIES IN BUTYL ACETATE

COMPOUND*	G. PER 100 G. BUTYL ACETATE					
	10.0°	30.0°	50.0°	70.0°	90.0°	100.0°
8	2.6	6.0	17.0	48.1	205	740
10	0.9	2.9	9.6	39.5	505	∞
12	0.4	3.0	12.4	52	330	2550
14	0.3	1.2	5.0	22.4	165	700
16	0.2	0.8	4.6	25.0	205	670
18	0.1	0.5	2.9	17.0	135	465
10 ϕ	18.3	42.6(62)	198	∞	∞	∞
12 ϕ	10.5	21.1(25)	86	730	∞	∞
16 ϕ	1.0	4.3	18.9	116	almost ∞	∞
18 ϕ	0.4	1.8	8.7	68	930	∞
10 $\phi\phi$	54	221	∞	∞	∞	∞
12 $\phi\phi$	24.4	92	750	∞	∞	∞
16 $\phi\phi$	8.2	24.8	158	∞	∞	∞
18 $\phi\phi$	5.6	16.8	110	2350	∞	∞

* ϕ = C_6H_5.

tetrachloromethane, ethyl and butyl acetates, and *n*-butanol; in addition, this behavior occurs in isopropanol in spite of the fact that the dielectric constant of this solvent is higher than those of acetone, 2-butanone, and 95% ethanol,

in which the metastable compound formation does not appear. In Figs. 1–4 the solubilities of the unstable form are shown by broken lines, and in Tables III–VII, XII and XIII these solubilities are listed in parentheses.

TABLE VIII

SOLUBILITIES IN ACETONE

COMPOUND*	G. PER 100 G. ACETONE			
	10.0°	30.0°	50.0°	56.5°
8	3.4	7.8	31.4	48.4
10	2.0	3.8	15.4	23.9
12	1.3	3.4	18.3	30.5
14	0.4	1.0	3.7	6.4
16	0.3	0.8	3.9	6.9
18	0.2	0.5	2.0	3.7
10 ϕ	39.1	93	490	870
12 ϕ	6.3	12.5	210	352
16 ϕ	1.1	3.3	22.1	52.9
18 ϕ	0.7	2.0	13.0	28.5
10 $\phi\phi$	96	735	∞	∞
12 $\phi\phi$	46.8	192	1350	almost ∞
16 $\phi\phi$	12.0	45.5	298	630
18 $\phi\phi$	5.0	10.6	185	390

* ϕ = C_6H_5.

TABLE IX

SOLUBILITIES IN 2-BUTANONE

COMPOUND*	G. PER 100 G. 2-BUTANONE					
	10.0°	30.0°	50.0°	60.0°	70.0°	79.6°
8	3.4	8.3	27.9	50.8	89	163
10	2.2	3.8	13.3	30.8	79	189
12	1.2	3.8	17.6	41.6	93	194
14	0.6	1.2	4.7	11.1	32.8	100
16	0.4	1.0	4.8	12.7	39.1	118
18	0.3	0.7	2.9	8.2	23.6	79
10 ϕ	25.5	81	289	800	∞	∞
12 ϕ	10.7	34.8	152	358	1350	∞
16 ϕ	2.7	6.6	35.5	89	208	600
18 ϕ	0.8	2.2	14.0	47.0	121	327
10 $\phi\phi$	78	337	∞	∞	∞	∞
12 $\phi\phi$	41.5	162	1250	∞	∞	∞
16 $\phi\phi$	13.1	52	268	800	∞	∞
18 $\phi\phi$	5.6	23.9	147	432	3450	∞

* ϕ = C_6H_5.

The solubility curves for the N,N-diphenylamides in benzene are characteristic of compounds which are not associated in solution, in that the concentration is practically a linear function of the temperature. The amides and anilides, on

the other hand, exhibit the marked deviation from linearity which is typical of the solubility curves of long-chain compounds which are associated in solution,

TABLE X

SOLUBILITIES IN METHANOL

COMPOUND*	G. PER 100 G. METHANOL				
	10.0°	30.0°	50.0°	60.0°	64.7°
8	22.1	53.0	130	206	263
10	6.8	15.2	67	125	170
12	4.2	12.4	77	164	206
14	1.0	2.7	14.3	36.8	56
16	0.7	1.2	10.0	32.0	51
18	0.4	0.7	3.5	12.7	23.3
10 ϕ	18.3	70.1	400	1050	2250
12 ϕ	2.9	11.1	187	430	645
16 ϕ	0.5	0.8	6.3	25.4	68
18 ϕ	0.1	0.2	1.0	6.7	16.1
10 $\phi\phi$	32.6	200	∞	∞	∞
12 $\phi\phi$	9.0	81	965	∞	∞
16 $\phi\phi$	1.7	5.6	102	525	1400
18 $\phi\phi$	1.1	3.9	37.2	300	600

* ϕ = C_6H_5.

TABLE XI

SOLUBILITIES IN 95.0% ETHANOL

COMPOUND*	G. PER 100 G. 95% ETHANOL					
	10.0°	30.0°	50.0°	60.0°	70.0°	78.5°
8	13.4	32.8	76	120	193	303
10	4.3	12.0	43.7	88	174	350
12	2.9	11.4	54	102	193	370
14	1.2	3.8	15.1	33.5	81	180
16	0.4	1.5	10.6	29.4	89	216
18	0.2	0.8	5.7	15.6	50	124
10 ϕ	33.6	81	365	1125	∞	∞
12 ϕ	10.7	22.3	128	365	1450	∞
16 ϕ	0.6	2.2	14.2	49.5	205	720
18 ϕ	0.3	1.2	7.7	21.6	77	124
10 $\phi\phi$	48.4	275	∞	∞	∞	∞
12 $\phi\phi$	14.7	53	900	∞	∞	∞
16 $\phi\phi$	1.1	5.0	100	565	∞	∞
18 $\phi\phi$	0.8	2.6	52	310	3350	∞

* ϕ = C_6H_5.

the fatty acids (41), ketones (40), and amine salts (39). It is to be noted that only in benzene are the solubilities of all of the N,N-diphenylamides linear with temperature; in all of the other solvents the curves of the higher members of the

series deviate from linearity, and in the most polar solvents even the lower members of the series give irregular solubility curves.

TABLE XII

SOLUBILITIES IN ISOPROPANOL

COMPOUND*	G. PER 100 G. ISOPROPANOL					
	10.0°	30.0°	50.0°	60.0°	70.0°	82.3°
8	15.7	26.3	66	102	157	288
10	6.0	10.9	37.2	72	140	380
12	3.7	11.4	47.5	86	154	357
14	1.2	3.2	15.5	34.2	76	208
16	0.4	1.8	12.1	29.9	79	229
18	0.2	1.0	6.9	20.0	56	172
10 ϕ	19.0	46.4(67)	220	665	∞	∞
12 ϕ	6.7	16.6(25)	102	254	930	∞
16 ϕ	0.6	2.4	14.2	39.5	147	1050
18 ϕ	0.3	1.3	8.4	25.8	91	570
10 $\phi\phi$	51	224	∞	∞	∞	∞
12 $\phi\phi$	21.5	77	990	∞	∞	∞
16 $\phi\phi$	6.6	13.4	90	452	∞	∞
18 $\phi\phi$	4.3	10.9	41.6	232	2525	∞

* ϕ = C_6H_5.

TABLE XIII

SOLUBILITIES IN *n*-BUTANOL

COMPOUND*	G. PER 100 G. *n*-BUTANOL					
	10.0°	30.0°	50.0°	70.0°	90.0°	100.0°
8	17.1	25.8	51	132	420	1300
10	3.5	9.1	30.9	118	690	∞
12	2.2	10.1	38.1	126	580	3550
14	0.8	3.8	13.7	58	276	1150
16	0.3	1.9	11.2	67	353	1050
18	0.1	1.1	7.3	44	204	590
10 ϕ	25.3	55(100)	221	∞	∞	∞
12 ϕ	13.2	26.1(37)	108	890	∞	∞
16 ϕ	1.8	5.5	21.6	152	almost ∞	∞
18 ϕ	0.6	3.2	11.2	85	1450	∞
10 $\phi\phi$	57	226	∞	∞	∞	∞
12 $\phi\phi$	25.8	84	760	∞	∞	∞
16 $\phi\phi$	7.5	19.0	108	∞	∞	∞
18 $\phi\phi$	4.9	13.7	68	2500	∞	∞

* ϕ = C_6H_5.

There appears to be no general correlation between the solubilities of the amides and the polarities of the solvents. In general, the solubilities of a given compound at a given temperature are relatively the same in non-polar solvents

as in the most polar solvents investigated, while the solubilities are relatively much greater in the solvents of intermediate polarity, being the greatest in the

TABLE XIV

SOLUBILITIES IN NITROETHANE

COMPOUND*	G. PER 100 G. NITROETHANE					
	10.0°	30.0°	50.0°	70.0°	90.0°	100.0°
8	1.0	2.1	7.5	37.5	307	1600
10	0.8	1.1	4.2	25.2	850	∞
12	0.8	1.1	3.9	24.2	495	5100
14	0.3	0.5	2.0	7.5	142	1500
16	0.2	0.3	0.9	7.5	208	1075
18	0.1	0.2	0.5	5.2	93	61
10 ϕ	14.0	21.8	133	∞	∞	∞
12 ϕ	6.0	8.5	22.3	720	∞	∞
16 ϕ	0.5	0.8	3.4	41.8	almost ∞	∞
18 ϕ	0.4	0.6	2.0	14.7	1060	∞
10 $\phi\phi$	57	310	∞	∞	∞	∞
12 $\phi\phi$	29.0	118	1100	∞	∞	∞
16 $\phi\phi$	16.1	29.0	179	∞	∞	∞
18 $\phi\phi$	10.9	17.8	92	3100	∞	∞

* ϕ = C_6H_5.

TABLE XV

SOLUBILITIES IN ACETONITRILE

COMPOUND*	G. PER 100 G. ACETONITRILE					
	10.0°	30.0°	50.0°	60.0°	70.0°	82.0°
8	1.1	5.4	16.4	31.6	73	200
10	0.5	1.4	6.0	13.4	44.5	178
12	0.3	0.9	5.1	12.1	39.8	175
14	0.2	0.6	1.1	2.9	7.8	43.3
16	0.2	0.3	0.7	1.6	5.9	34.8
18	0.1	0.2	0.4	0.9	2.6	16.8
10 ϕ	9.3	18.0	297	825	∞	∞
12 ϕ	0.8	3.0	24.1	308	1100	∞
16 ϕ	0.3	0.7	2.2	5.5	32.5	733
18 ϕ	0.2	0.5	1.4	3.3	13.8	480
10 $\phi\phi$	39.3	252	∞	∞	∞	∞
12 $\phi\phi$	12.6	75	1075	∞	∞	∞
16 $\phi\phi$	1.5	5.8	75	635	∞	∞
18 $\phi\phi$	0.6	2.4	23.3	359	3350	∞

* ϕ = C_6H_5.

alcohols. Even in solvents of the same polarity, such as benzene and cyclohexane, there is, at 70° for instance, as much as 25- to 50-fold difference in the solubilities of a given amide. In general, the substituted amides behave simi-

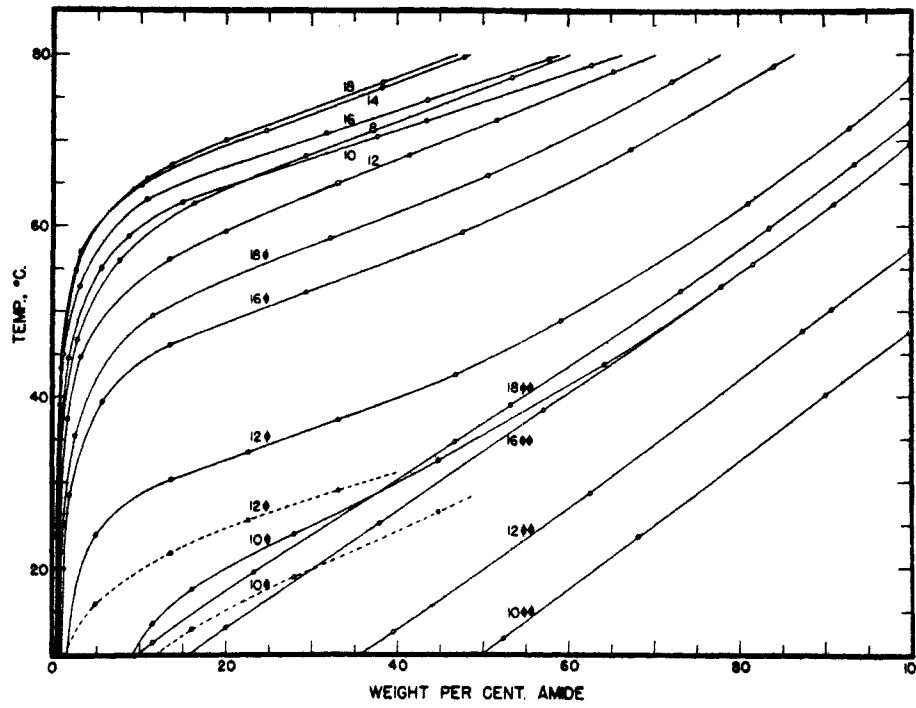

FIG. 1. SOLUBILITIES OF AMIDES AND SUBSTITUTED AMIDES IN BENZENE
The broken lines represent the solubilities of the metastable compounds

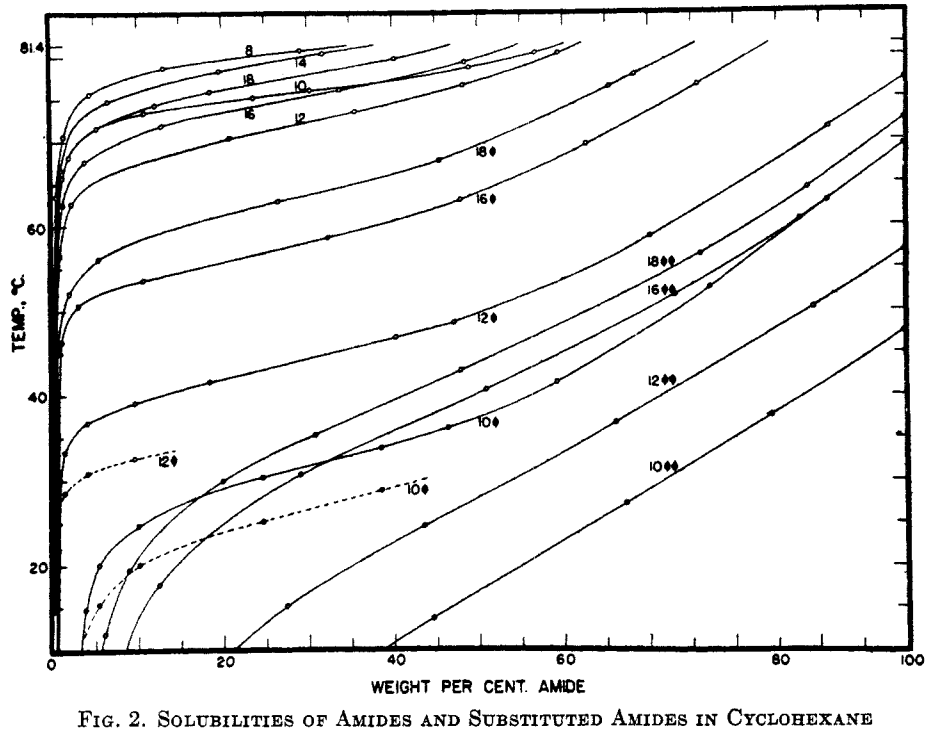

FIG. 2. SOLUBILITIES OF AMIDES AND SUBSTITUTED AMIDES IN CYCLOHEXANE

larly to the amides with respect to the polarities of the solvents, except that the solubilities of the N,N-diphenylamides decrease markedly with increased polarity of the solvent. In this respect, the behavior of the latter compounds is similar to that of the high molecular weight ketones (40).

The results of this investigation show that none of the structures yet proposed for the amides and their derivatives can adequately explain the anomalous

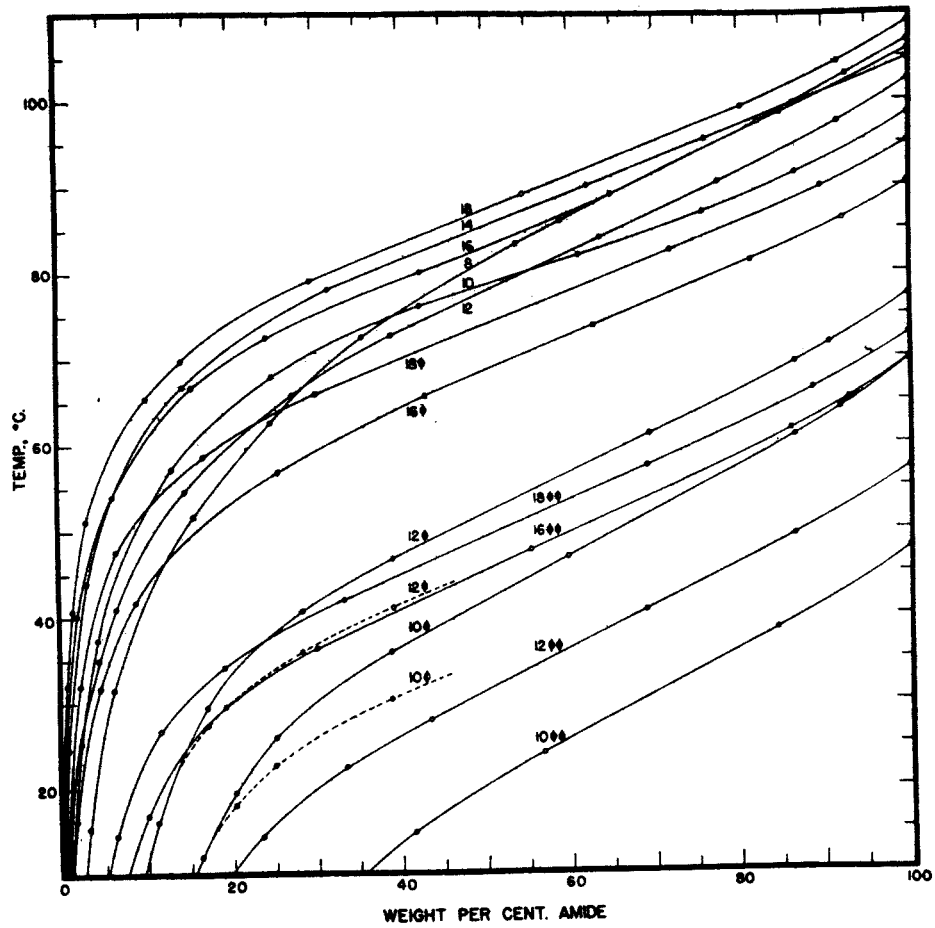

FIG. 3. SOLUBILITIES OF AMIDES AND SUBSTITUTED AMIDES IN BUTYL ACETATE

behavior of these compounds. All of the proposed theories imply a semblance of homology. The assumption of polymer formation does not *per se* explain, for instance, the anomalous solubilities of caprylamide and myristamide. The fact that the phenyl substituent of the anilides precludes the formation of polymers larger than dimers by hydrogen bonding does not explain why the slopes of the anilide solubility curves are less steep and break more sharply in dilute solutions than do those of the corresponding amides. There is no present ex-

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SCANDENIN—A CONSTITUENT OF THE ROOTS OF *DERRIS SCANDENS*

E. P. CLARK

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Recently our attention was directed to a specimen of *Derris scandens* cultivated in a nursery at St. Petersburg, Fla. Since the plant grows well and can be propagated easily, it was important to know whether or not it contained rotenone. To obtain this information, M. J. Soule, upon whose property the plant grows, placed at our disposal a small quantity of the roots.

The roots were air-dried, ground, and extracted with ether. The extractive did not contain rotenone, but a mixture of several crystalline substances was obtained which, although showing no similarity to rotenone or allied products, appeared to be closely related among themselves.

The crystalline mixture was separated into three fractions. The first, which predominated and was the most readily obtained in a pure condition, was a new compound, $C_{26}H_{26}O_6$, m.p. 231°. It has been designated as "scandenin." The second compound, which was present in appreciable quantities and gave little trouble in separation, was lonchocarpic acid, previously found in *Lonchocarpus* sp. by Jones (1).

Lonchocarpic acid was identified by comparison with an authentic sample supplied by Jones (1). In these experiments lonchocarpic acid partly sintered between 200–205°, and melted sharply at 223° (corr.). The authentic sample, the compound from *Derris scandens*, and mixtures of both all behaved in this manner.

The third substance, m.p. 190°, was found only in small quantities. On the basis of its solubility in alkali, its melting point (190°), and its behavior toward the Durham test, it is thought to be robustic acid (2), but the meager yield and the difficulty of separating it from coexisting materials precluded exhaustive purification.

Scandenin has the formula $C_{26}H_{26}O_6$, and hence is isomeric with lonchocarpic acid. It crystallizes in rhombic plates and prismatic forms, which are biaxial with strong birefringence. The minimum index of refraction, N_α, is 1.483 ± 0.002, N_β and N_γ are both greater than 1.733. Owing to the limited supply of material available, only a superficial chemical study of the substance could be made. Some of the experiments, while indicating certain structures, could not be carried to a satisfactory conclusion, but the definite results obtained are as follows: Scandenin has one methoxyl and two free hydroxyl groups; it probably contains a *p*-hydroxybenzoyl grouping, although no oxime or semicarbazone could be obtained; it shows considerable unsaturation; it is somewhat acidic, dissolving in dilute aqueous alkalies; it forms relatively insoluble sodium and potassium salts; and, finally, it fails to give a reaction for a 2,2-dimethyl-Δ^3-chromene system (3, 4). The last fact strongly indicates the lack of relationship to the rotenone group of fish poisons.

These conclusions are based upon the following experiments: The methoxyl group was shown by analysis. The hydroxyl groups were shown by acetylation and by methylation with diazomethane. Acetylation occurred readily and quantitatively to give a diacetate, but diazomethane did not react so well. A dimethoxyscandenin was obtained, but the yield was extremely poor. The diacetate was insoluble in dilute potassium hydroxide, showing that the acidity of the substance was due to a phenolic hydroxyl group. Hydrogenation, with platinum catalyst, occurred readily, and approximately 3 moles of hydrogen were consumed. The *p*-hydroxybenzoyl group was shown to be present by the formation of *p*-hydroxybenzoic acid upon oxidation with alkaline hydrogen peroxide. The phenolic group being para to the carbonyl group accounts for the failure of scandenin to give a ferric chloride test.

EXPERIMENTAL

Preparation of scandenin. One kilogram of ground air-dried roots was exhaustively percolated with ether. While the solvent was being removed from the extract, several crops of crystals separated. In all, 5 grams of material which melted at 231° was obtained. This was dissolved in acetone, and the solution was clarified and decolorized by filtration through a thin bed of Norit. The acetone was replaced by gradual addition of methanol to the boiling concentrated solution until crystallization began. The slightly greenish product consisted mostly of thick rhombic plates together with some prismatic forms. The material, which was obtained in good yield, melted at 231° and further recrystallization failed to raise the melting point.

The material gave brilliant polarization colors when viewed with parallel polarized light (crossed nicols). Many fragments extinguished sharply, but others remained bright when the microscope stage was rotated. Birefringence was extremely strong, and in convergent polarized light (crossed nicols) partial biaxial interference figures were observed. These usually represented sections inclined to the acute bisectrix, but only one optic axis and a portion of the brush was visible. Occasionally sections occurred perpendicular to the optic axis. Only the lowest index, N_α, was measurable and had the value of 1.483 ± 0.002. Some fragments matched methylene iodine, with an index of 1.733, but N_β and N_γ were both greater than this value.[1]

Anal. Calc'd for $C_{26}H_{26}O_6$: Mol. wt., 434.5; C, 71.87; H, 6.03; one OCH_3, 7.14.
Found: Mol. wt., 422; C, 71.62; H, 6.05; OCH_3, 7.18.

Scandenin acetate. A mixture of 100 mg. of scandenin, 25 mg. of anhydrous sodium acetate, and 1 cc. of acetic anhydride was boiled 5 minutes, and then 25 cc. of water was added. When the mixture was stirred, a white crystalline material, which melted at 150°, separated. It was recrystallized from hot 95% methanol with no change of melting point. It was insoluble in dilute aqueous potassium hydroxide.

Anal. Calc'd for $C_{30}H_{30}O_8$: Mol. wt., 518.5; C, 69.49; H, 5.83; one OCH_3, 5.99; 2 acetyl, 16.6
Found: Mol. wt., 518; C, 69.54; H, 5.88; OCH_3, 5.86; acetyl, 16.2.

Scandenin dimethyl ether. One gram of scandenin was suspended in 100 cc. of ether containing an excess of diazomethane. The mixture was occasionally stirred and allowed to stand overnight, after which time all the scandenin had dissolved. When the ether was removed, the residue would not crystallize, and much material soluble in aqueous alkali was found to be present. It was therefore redissolved in ether and extracted with aqueous

[1] The optical crystallographic data were determined by G. L. Keenan, Food and Drug Administration, Federal Security Agency, Washington, D. C.

potassium hydroxide. The portion remaining in the ether was obtained as a white crystalline product, which was recrystallized from methanol by the addition of water. The process was repeated until it had the constant melting point 129°. The quantity of material was only sufficient for a methoxyl determination.

Anal. Calc'd for $C_{29}H_{32}O_6$: 3 OCH_3, 19.54. Found: OCH_3, 19.96.

Action of alkaline hydrogen peroxide upon scandenin. One gram of scandenin was dissolved in 100 cc. of 0.2% warm aqueous potassium hydroxide, and oxidized with 15 cc. of 30% hydrogen peroxide added in 5-cc. portions. When the reaction subsided and frothing ceased, the solution was cooled, acidified with sulfuric acid, and distilled to collect any volatile fatty acids. The quantity obtained, calculated as acetic acid since its presence was indicated, was 83 mg., or a little more than 1 mole. Upon redistillation of the recovered acid according to the Dyer procedure (5), it was identified and shown to consist only of acetic acid.

The liquid residue from the first distillation was filtered and extracted with ether. The residue from the ethereal solution was dissolved in 1 cc. of water. This solution was frozen and then allowed to thaw slowly. A sticky product which remained adhering to the container was dried and sublimed. The sublimate, which melted at 213° and cleared at 215°, was identified as *p*-hydroxybenzoic acid by its failure to depress the melting point of a sublimed authentic sample of the acid.

Hydrogenation of scandenin. Two-tenths gram of scandenin in ethanol was reduced with hydrogen in the presence of reduced platinum oxide catalyst. Thirty-eight cubic centimeters, or approximately 3 moles, of hydrogen were consumed. Because of its poor crystallizing properties, the quantity available was insufficient to carry out a rigorous purification; hence no analysis of it is available. The experiment, however, does show the unsaturated nature of the compound.

Lonchocarpic and robustic acids. Further gradual concentration of the mother liquor from which scandenin was originally obtained gave several small quantities of crystals, melting unsharply between 193° and 195°, and a sticky mother liquor. The latter, when suspended in a small volume of ether, gave a small quantity of crystalline material which melted unsharply at 190°. All these crystalline fractions were united and digested in boiling benzene. The insoluble dried material melted at 220°. It was dissolved in acetone, the solution filtered through Norit, and the acetone replaced with methanol by boiling the liquid and adding the alcohol from time to time. Upon cooling, the solution crystallized, yielding prisms, rods, and plates which slightly sintered between 200–205°, then solidified, and melted sharply at 223° (1). Further recrystallization did not alter the melting point. A mixture with an authentic sample of lonchocarpic acid gave no depression of the melting point.

Upon cooling, the benzene mother liquor from the lonchocarpic acid gave a small crop of crystals, m.p. 185–210°. They were dissolved in methanol, and the solution was allowed to stand for several days. During this time some scandenin separated as large prisms. When these crystals were removed and water was added to the mother liquor, other crystals separated in the form of plates melting unsharply at 190°. After several recrystallizations the melting point became sharper. Because of its melting point, its solubility in alkali, and the evanescent, pale purple color given by the Durham test, it appeared to be robustic acid.

SUMMARY

The roots of *Derris scandens* have been examined for rotenone with negative results, but a new substance, scandenin, $C_{26}H_{26}O_6$, has been found. Lonchocarpic acid and possibly robustic acid have also been shown to be present.

Scandenin is isomeric with lonchocarpic acid. It contains one methoxyl,

two free hydroxyl groups, and probably a *p*-hydroxybenzoyl group. The acidic character of scandenin is probably due to a phenolic hydroxyl group.

BELTSVILLE, MD.

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[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, AGRICULTURAL RESEARCH ADMINISTRATION, UNITED STATES DEPARTMENT OF AGRICULTURE]

SOME DERIVATIVES OF LONCHOCARPIC ACID

HOWARD A. JONES AND H. L. HALLER

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Numerous species of *Derris* and *Lonchocarpus* have been examined for their insecticidal activity and especially for their rotenone content (1, 2). In the course of such studies Jones (3) isolated from an unknown species of *Lonchocarpus* from Venezuela a colorless crystalline compound, which he designated as lonchocarpic acid. More recently Harper (4) has obtained from *Derris robusta* a crystalline substance which in some of its reactions behaves similarly to lonchocarpic acid, and which he has called robustic acid. The latter has been assigned the tentative molecular formula $C_{27}H_{24}O_8$, and the former has been shown to correspond to $C_{26}H_{26}O_6$. The two compounds behave similarly, but in marked contrast to rotenone, in the Durham test (5), a reaction used for the detection of rotenone and some of its closely related compounds.

When lonchocarpic acid was first isolated, it appeared of interest to determine whether or not this compound was related to rotenone, but because it is insecticidally inert, it has been studied only intermittently over a period of several years. Since both of the authors are now engaged in work that will preclude further studies on lonchocarpic acid for some time, and in view of the publication by Harper (4) and one by Clark (6), our findings are recorded in this paper.

In the early experiments it was found difficult to obtain lonchocarpic acid in a pure state. Extraction of the crude crystalline product with hexane removed a small amount of waxy material and gave a product that could be satisfactorily crystallized from ethyl acetate, ethanol, or acetone. Ethyl acetate usually gave a product that melted at 204° (corr.) and did not resolidify, whereas the crystals from ethanol usually melted at 221° (corr.). Acetone, as previously recorded (3), gave sometimes one, sometimes the other form. The molecular weight (434) previously found by titration was confirmed by the Signer method (7). The compound did not reduce Fehling's solution, and the iodoform reaction was negative. Lonchocarpic acid is soluble in carbonate solution. On refluxing in alcoholic alkali, more than 90% of the product may be recovered. Partly on this basis the conclusion was drawn that the product is an acid, but in the light of subsequent experiments it now appears that a strongly acidic hydroxyl group is present instead.

Methylation of lonchocarpic acid with diazomethane in ether solution yielded a monomethyl derivative, but in methanol a dimethyl derivative was obtained. Both products are insoluble in alkali, and attempts to obtain an alkali-soluble product on saponification with alcoholic potash of either derivative were unsuccessful. Methylation with dimethyl sulfate yielded a product which from its methoxyl content appeared to be a mixture of the mono- and di-methyl derivatives.

Acetylation of lonchocarpic acid yielded a diacetyl derivative which was

insoluble in aqueous alkali. On saponification with alcoholic potash the diacetyl derivative yielded approximately 60% of lonchocarpic acid, about 25% of alkali-insoluble material, and a small quantity of alkali-soluble resin. The alkali-insoluble part gave a deep brown-violet color and the resin an intense green color with ferric chloride. Saponification of diacetyllonchocarpic acid with potassium acetate in absolute ethanol yielded a product that has not been satisfactorily purified. Treatment of diacetyllonchocarpic acid with diazomethane both in ether and in methanol produced no effect.

On catalytic hydrogenation of lonchocarpic acid a tetrahydro derivative was formed. Acetylation of this product gave a compound that was identical with the substance obtained on hydrogenation of the diacetyl derivative. With diazomethane the tetrahydro derivative reacted similarly to lonchocarpic acid.

Oxidation of lonchocarpic acid with iodine in alcohol in the presence of potassium acetate gave no recognizable product (*cf.* the formation of dehydrorotenone from rotenone) (8). When lonchocarpic acid was oxidized in alkaline solution with hydrogen peroxide, *p*-hydroxybenzoic acid was obtained in a yield of about 25%. Oxidation of the mono- and di-methyl derivatives have given inconclusive results.

Phosphorus pentachloride and thionyl chloride did not react with lonchocarpic acid.

The foregoing results indicate that, in spite of their closely related origin, no close relationship between lonchocarpic acid and rotenone exists. Furthermore, it is quite probable that the characteristic chromane-chromanone (9) system present in rotenone and the rotenoids is absent in lonchocarpic acid.

EXPERIMENTAL

Lonchocarpic acid. The compound used in these experiments was obtained from a second lot of the same species of *Lonchocarpus* that was used in the earlier experiments (3). The crude product obtained from the root as previously described was extracted with hexane and then recrystallized from either ethyl acetate or ethanol. The former solvent usually gave a compound that melted at 203–204° (corr.); the product from the latter solvent usually melted at 220–221° (corr.).

Anal. Calc'd for $C_{26}H_{26}O_6$: C, 71.86; H, 6.03; OCH_3, 7.14; Mol. wt., 434.
Found: C, 71.87, 71.87; H, 6.01, 5.98; OCH_3, 7.19, 7.25; Mol. wt. (Signer), 429.

Diacetyllonchocarpic acid. Five grams of lonchocarpic acid was refluxed for 2 hours in 50 cc. of acetic anhydride and 2.5 grams of anhydrous sodium acetate. The solution was cooled and poured into 250 cc. of methanol. Most of the solvent was removed on the steam-bath and water was added. The product that separated was washed with water and dried. The yield of crude product was 5.8 grams. After recrystallization from ethanol the product melted at 154°. The compound was insoluble in boiling 5% potassium hydroxide solution.

Anal. Calc'd for $C_{30}H_{30}O_8$: C, 69.45; H, 5.83; OCH_3, 5.98; CH_3CO, 16.6.
Found: C, 69.60, 69.20; H, 5.81, 5.82; OCH_3, 5.99; CH_3CO, 17.0.

Dimethyllonchocarpic acid. To 1 gram of lonchocarpic acid in 40 cc. of dry methanol was added 40 cc. of an ether solution of diazomethane (10 cc. = 0.118 g. CH_2N_2). A vigorous reaction took place. The slightly yellow solution was allowed to stand overnight, filtered, and then concentrated on the steam-bath. The crystalline product was recrystallized from methanol. It melted at 150–151°. The yield was 0.6 gram.

Anal. Calc'd for $C_{28}H_{30}O_6$: C, 72.70; H, 6.54; OCH_3, 20.12.
Found: C, 72.24, 72.16; H, 6.49, 6.45; OCH_3, 19.64, 19.9.

Monomethyllonchocarpic acid. When 2 grams of lonchocarpic acid was dissolved in dry ether and treated with diazomethane in a manner similar to that described above, a product was obtained that melted at 208–211°. After recrystallization from ethanol it melted at 210–212°. The yield was 1.7 grams.

Anal. Calc'd for $C_{27}H_{28}O_6$: C, 72.29; H, 6.30; OCH_3, 13.83.
Found: C, 71.97; H, 6.30; OCH_3, 14.22.

Tetrahydrolonchocarpic acid. Two and one-half grams of lonchocarpic acid in 100 cc. of ethanol was shaken with reduced platinum oxide in an atmosphere of hydrogen. Reduction took place rapidly and ceased when 300 cc. (uncorr.) of hydrogen had been absorbed (theory for 2 moles = 280 cc.). The solution was filtered, and concentrated, and the separated product was recrystallized from ethanol. It melted at 239–240°. The yield was 2.2 grams.

Anal. Calc'd for $C_{26}H_{30}O_6$: C, 71.20; H, 6.90; OCH_3, 7.07.
Found: C, 70.92, 71.36; H, 6.77, 6.89; OCH_3, 7.00.

Diacetyltetrahydrolonchocarpic acid. Acetylation of tetrahydrolonchocarpic acid with acetic anhydride and sodium acetate according to the procedure described above for lonchocarpic acid yielded the same product as that obtained on reduction of diacetyllonchocarpic acid by the hydrogenation procedure described for lonchocarpic acid. When recrystallized from ethanol it melted at 192–192.5°.

Anal. Calc'd for $C_{30}H_{34}O_8$: C, 68.94; H, 6.56; OCH_3, 5.93; CH_3CO, 16.46.
Found: C, 68.74; H, 6.50; OCH_3, 5.86; CH_3CO, 16.99.

Monomethyltetrahydrolonchocarpic acid. This compound was prepared by treatment of tetrahydrolonchocarpic acid in dry ether with diazomethane according to the procedure given for monomethyllonchocarpic acid. The product purified by recrystallization from ethanol melted at 211–212.5°.

Anal. Calc'd for $C_{27}H_{32}O_6$: C, 71.65; H, 7.13; OCH_3, 13.71.
Found: C, 71.49, 71.69; H, 7.21, 7.31; OCH_3, 13.88.

Dimethyltetrahydrolonchocarpic acid. This compound was obtained on methylation of tetrahydrolonchocarpic acid with diazomethane in methanol according to the procedure described for dimethyllonchocarpic acid. When recrystallized from ethanol it melted at 166–167°.

Anal. Calc'd for $C_{23}H_{34}O_6$: C, 72.07; H, 7.35; OCH_3, 19.95.
Found: C, 71.65, 71.53; H, 7.26, 7.23; OCH_3, 19.30.

Oxidation of lonchocarpic acid with hydrogen peroxide. Two grams of lonchocarpic acid was dissolved in 25 cc. of 5% potassium hydroxide, and to the solution 8 cc. of 30% hydrogen peroxide was added in small portions. The solution was heated on the steam-bath, boiled for a few minutes, and then cooled and saturated with carbon dioxide. The small amount of tarry material that had formed was extracted with ether. The aqueous solution was acidified to Congo red and then concentrated to a small volume under reduced pressure. On standing for several days the concentrated solution deposited brown nodules. These were removed by filtration and recrystallized from water with the aid of Norit. The recrystallized product melted at 209–210°. The yield was 0.2 gram. It was identified as *p*-hydroxybenzoic acid by titration, by mixture melting point determination with an authentic sample of this acid, and by a similar comparison of their acetates.

SUMMARY

Catalytic hydrogenation of lonchocarpic acid produces a tetrahydro derivative and acetylation yields a diacetyl derivative.

In ether solution lonchocarpic acid with diazomethane yields a monomethyl derivative, in methanol with the same reagent a dimethyl compound. On oxidation with hydrogen peroxide lonchocarpic acid yields *p*-hydroxybenzoic acid. Lonchocarpic acid is probably an acidic phenol.

BELTSVILLE, MD.

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[CONTRIBUTION FROM THE BUREAU OF ANIMAL INDUSTRY, AGRICULTURAL RESEARCH ADMINISTRATION, UNITED STATES DEPARTMENT OF AGRICULTURE]

THE SYNTHESIS OF CONDENSED RING COMPOUNDS. XII.[1] THE PREPARATION OF A 5,6,8-TRIKETO-9-METHYL-2-OCTALIN[2]

ELEANORE W. J. BUTZ AND LEWIS W. BUTZ

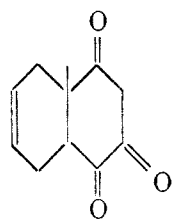
Received July 3, 1943

The preparation of a hydronaphthalene-1,2,4-trione with an angle methyl group from 5-acetoxy-1,4-toluquinone and hexatriene has been reported (1). This reaction has now been employed for the synthesis from butadiene of compound I, which will be designated 5-methyl-7-naphthitene-1,2,4-trione enol in conformity with a recent suggestion (2) for the systematic nomenclature of alicyclic compounds. Whether the crystalline trione isolated is a derivative of cis or trans-octalin is unknown. The possibility exists that conversion of the cis-adduct formed in the Diels-Alder reaction to the trans-isomer occurred, either under the conditions of adduct formation or during the subsequent manipulations which included solution in aqueous alkali.

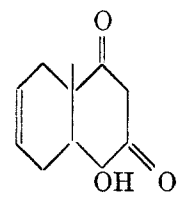
The trione enol, I, gives a color with ferric chloride and titrates as a monobasic acid with sodium hydroxide and phenolphthalein.

A dihydro and an octahydro derivative were prepared from the trione enol. The dihydro compound is probably the hydroxy diketone, II, because it gives a color with ferric chloride, is soluble in aqueous sodium carbonate, and exhibits maximal absorption in the ultraviolet at the same wave length (2560Å) as the trione enol. This maximum has been found to be characteristic for cyclohexane-1,2,4-triones and for cyclohexane-1,3-dione (3). The octahydro derivative is probably a 5-methylnaphthitane-1,2,4-triol (III). It has not yet been prepared in a quantity sufficient for its characterization.

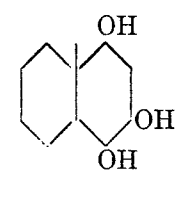
Some angle acetate was formed in the addition of 5-acetoxy-1,4-toluquinone to butadiene, since oxidation of an alkali-insoluble fraction gave 2-methyl-1,4-naphthoquinone. A quantitative study of the reaction products was not made because a more practical method for the preparation of the 5-methyl-7-naphthitene-1,2,4-trione enol was subsequently developed (4).



I



II



III

[1] For preceding paper in this series see *J. Am. Chem. Soc.*, in press.

[2] This work was supported by an allotment from the Special Research Fund (Bankhead-Jones Act of June 29, 1935).

EXPERIMENTAL[3]

5-Acetoxy-1,4-toluquinone was prepared from toluquinone by the method of Thiele and Winter (5). Toluquinone, converted in batches of 20 g., gave 60% of 2,4,5-triacetoxytoluene. Twelve grams of the triacetate gave 6 g. of triphenol, which was converted to 5-hydroxy-1,4-toluquinone in one-g. batches with 90% yield. Six grams of the hydroxyquinone gave 5 g. of acetoxytoluquinone, m.p. 75–76°.

5-Methyl-7-naphthitene-1,2,4-trione enol (*I*). 5-Acetoxy-1,4-toluquinone (10 g.) and 6 g. of butadiene (2 moles) were heated in 25 cc. of absolute ethanol in a sealed tube at 75° for 68 hours. Evaporation of the ethanol and excess butadiene at reduced pressure gave 12.5 g. of residue, which was shaken with 8 g. of potassium hydroxide in 110 cc. of water for one hour. After removal of the neutral and unsaponified products with ether, the aqueous portion was set in an ice-bath and normal hydrochloric acid was added, with stirring, until the mixture was just blue to Congo. Extraction with ether, finally with the addition of sodium sulfate, followed by drying and evaporation of the ether, gave 10 to 11 g. of residue. This was extracted exhaustively with hot water, avoiding actual boiling; the straw colored aqueous extract was cooled, extracted thoroughly with ether, salting out with sodium sulfate, the ether solution dried, and the ether evaporated to give 6.1 g. of crude enol. Recrystallization from carbon tetrachloride yielded 3.5 g. of trione enol, m.p. 173–175°. The compound can also be recrystallized from benzene, benzene-petroleum ether, ether-petroleum ether, and ether, but a really satisfactory solvent has not been found. More product, about 0.3 g., was isolated by drying the hot water-insoluble tar and subliming at 0.1 mm., bath, 140°. For analysis, a sample was sublimed at 0.1 mm. and 130–140° (bath) and the sublimate recrystallized from ether; m.p. 174–175°.

Anal. Calc'd for $C_{11}H_{12}O_3$: C, 68.7; H, 6.3.
Found: C, 68.5; H, 6.3.

The compound in ethanol gave a dark purple color with 0.15% ferric chloride in ethanol. In aqueous ethanol with phenolphthalein, 45.8 mg. required 1.85 cc. of 0.13 *N* sodium hydroxide.

Neutral products from the Diels-Alder reaction. Evaporation of a dried ether solution gave a straw colored crystalline residue which is changed quickly to a red-to-black material in air. Solution of this in ether gave a light colored product. The crystalline residue, 2 g., was dissolved in 15 cc. of ethanol and added to 20 g. of $FeCl_3 \cdot 6H_2O$ in 60 cc. of ethanol, the solution was warmed to 60° for five minutes, and then poured into 800 cc. of water. The precipitated yellow crystals, 0.8 g., m.p. 82–84°, became orange-red on standing. This product did not crystallize well from ether, methanol, or ethanol. Sublimation at reduced pressure gave no acetic acid, suggesting the absence of any angle acetate. The yellow compound may have been 5,8-dihydro-2-methyl-1,4-naphthoquinone; literature (6) m.p. 86–87°.

In another run, the residue obtained upon evaporation of the ether extract of the neutral products did not crystallize. This material was freed from a few drops of colorless oil by heating to 120° at 75 mm. Crystallization of the non-volatile part from ether and sublimation at reduced pressure yielded a small amount of yellow crystals, m.p. 74–78°, which were stable in air. These on recrystallization from petroleum ether gave 2-methyl-*p*-naphthoquinone, m.p. 100–102°; no depression with an authentic sample, m.p. 104–105°.

4-Hydroxy-10-methyl-7-naphthitene-1,3-dione (*II*). One and one-half grams of the trione enol was added slowly to 1.8 g. of zinc dust in 4 cc. of water and 3 cc. of acetic acid. Three cc. more of acetic acid was added after the enol. The vigorously stirred reaction mixture was kept at 65° for fifteen minutes. The hot mixture was filtered, poured onto ice, extracted with ether, and the ether solution dried. Ether and acetic acid were evaporated at reduced pressure. After several days over soda-lime and calcium chloride, the residue crystallized.

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[3] Analyses by Dr. Carl Tiedcke. All melting-points are corrected.

Recrystallization from ether-petroleum ether, and then from benzene, gave 0.5 g. of dihydro compound, faint pink color with ferric chloride, double m.p. 123–125° and 145–146°.

Anal. Calc'd for $C_{11}H_{14}O_3$: C, 68.0; H, 7.25.
Found: C, 68.2; H, 6.9.

A small portion was sublimed *in vacuo* and the sublimate crystallized from ether-petroleum ether and recrystallized from benzene. The product still showed a double m.p., 130° and 146–148°, and a faint pink color with ferric chloride.

An octahydro derivative by catalytic hydrogenation of the trione enol. Ninety-one milligrams of trione enol in 10 cc. of purified acetic acid was hydrogenated at 20° and atmospheric pressure in the presence of 25 mg. of Adams catalyst containing 4% palladium oxide. Three moles of hydrogen were absorbed in thirty minutes, and 0.2 mole more in the next hour. The catalyst was filtered and the solvent removed under reduced pressure. The residue was taken up in ether. About 10 mg. of insoluble material was discarded. The ether was evaporated, the remaining oil was extracted with warm hexane, and the hexane-insoluble part was crystallized by addition of ether. Recrystallization from ether and drying *in vacuo* at the temperature of boiling acetone gave 10 mg. of octahydro compound, m.p. 180–182°.

Anal. Calc'd for $C_{11}H_{20}O_3$: C, 65.8; H, 10.1.
Found: C, 65.7; H, 10.2.

SUMMARY

An angle methyl triketooctalin, 5-methyl-7-naphthitene-1,2,4-trione, has been prepared by the addition of 5-acetoxy-1,4-toluquinone to 1,3-butadiene, extraction of the products with aqueous alkali, and acidification of the water-soluble salts.

Reduction of this trione enol with zinc and acetic acid gave 4-hydroxy-10-methyl-7-naphthitene-1,3-dione and catalytic hydrogenation gave an octahydro compound which is probably one of the 5-methylnaphthitane-1,2,4-triols.

The triketooctalin resulted from the addition of butadiene to the methylethene link of the acetoxytoluquinone. Since 2-methyl-*p*-naphthoquinone was isolated after oxidation of the neutral products, some addition of the diene to the acetoxyethene link of the quinone also occurred.

BELTSVILLE, MD.

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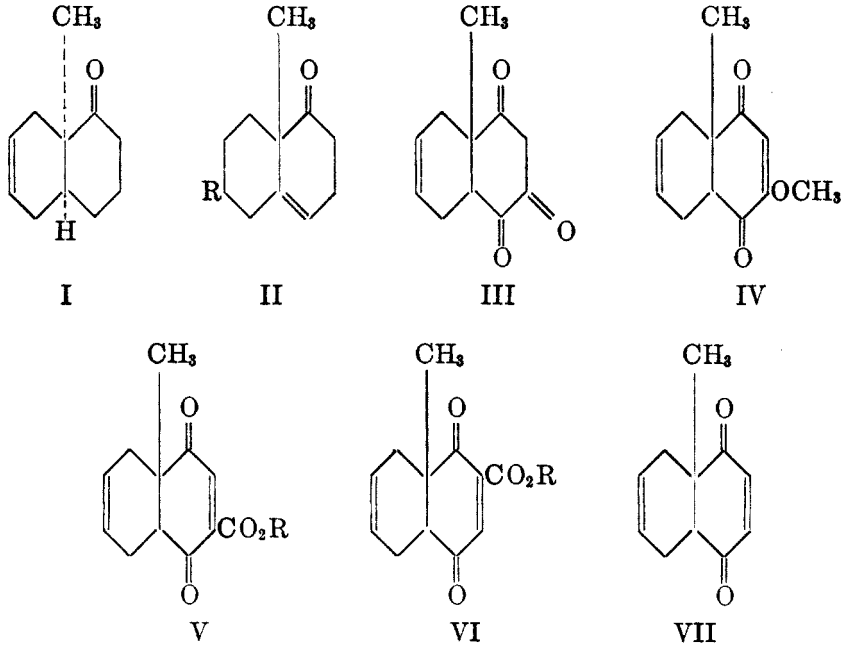
[CONTRIBUTION FROM THE BUREAU OF ANIMAL INDUSTRY, AGRICULTURAL RESEARCH ADMINISTRATION, UNITED STATES DEPARTMENT OF AGRICULTURE]

THE SYNTHESIS OF CONDENSED RING COMPOUNDS. XIII. THE PREPARATION OF 5- AND 6-CARBALKOXY-1,4-TOLUQUINONES. ADDITION OF 5-CARBOMETHOXY-1,4-TOLUQUINONE AND 6-CARBOMETHOXY-1,4-TOLUQUINONE TO BUTADIENE[1]

WALTER NUDENBERG, ADAM M. GADDIS, AND LEWIS W. BUTZ

Received July 3, 1943

cis-10-Methyl-7-naphthiten-1-one (I) is now available from butadiene and 1-methylcyclohexen-6-one (1), but the trans isomer and 7-substituted-10-methyl-4-naphthiten-1-ones (II) cannot be made so directly by a Diels-Alder synthesis. For these, the addition of 5- and 6-substituted-1,4-toluquinones to butadienes promises to be a fertile general procedure. The preparation of a methylnaphthitenetrione enol (III) and a methylmethoxynaphthitadienedione (IV) in practical yield may make available 10-methyl-1-ketones, of both the cis and the trans series, substituted in the ketonic ring (2). If compounds lacking the substituent at carbon-3 are desired, these two intermediates may not be immediately useful, since they belong to classes of compounds whose reactions are unfamiliar. The addition of carbalkoxytoluquinones to butadiene might yield V and VI, and these could perhaps without too much difficulty be converted to VII.



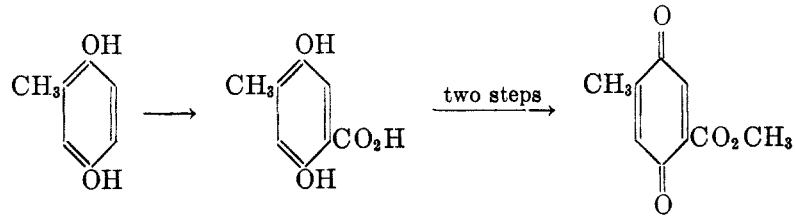
I II III IV

V VI VII

[1] This work was supported by an allotment from the Special Research Fund (Bankhead-Jones Act of June 29, 1935). Not subject to copyright.

Although carbalkoxy-*p*-benzoquinones are very sensitive compounds, Brunner (3) was able to prepare carbomethoxy-*p*-benzoquinone and carbethoxy-*p*-benzoquinone. By employing his procedure for oxidation of the corresponding quinols we have prepared 5-carbomethoxy-1,4-toluquinone and 6-carbomethoxy-1,4-toluquinone in crystalline form. The individual reactions utilized are shown in Charts 1 and 2.

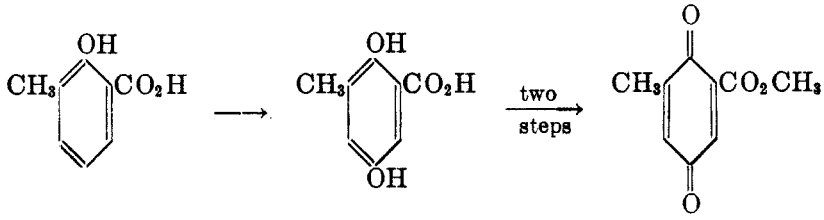
Butadiene combined with 5-carbomethoxy-1,4-toluquinone and with 6-carbomethoxy-1,4-toluquinone in dry benzene at 100°. The products, which were light yellow viscous liquids boiling at 137–139° (0.5 mm.) and 155–157° (1–2 mm.) respectively, had the expected composition, $C_{13}H_{14}O_4$. They were, however, not angle methyl compounds of the kind (V and VI) that we sought to prepare, for



VIII IX X

CHART 1

THE PREPARATION OF 5-CARBOMETHOXY-1,4-TOLUQUINONE FROM *p*-TOLUQUINOL



XI XII XIII

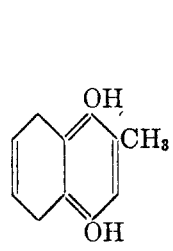
CHART 2

THE PREPARATION OF 6-CARBOMETHOXY-1,4-TOLUQUINONE FROM *o*-CRESOTIC ACID

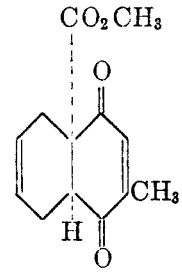
with aqueous methanolic potassium hydroxide they gave the known compound, 2-methyl-5,8-dihydronaphthalene-1,4-diol, XIV (4), with the methyl group at a peripheral position. The adducts must therefore consist, at least in part, of the angle carboxylates, XV and XVI. The liquid from 5-carbomethoxytoluquinone yielded 87% of the diphenol, XIV; and, since there is evidence that some of this angle carboxylate underwent scission of the enedione ring during the alkaline hydrolysis and decarboxylation, the amount of any angle methyl isomer in the adduct must have been very small. The liquid from 6-carbomethoxytoluquinone gave only 66% of XIV, but no evidence of the presence of angle methyl isomers was obtained. The yields of distilled analytically pure adducts from the two quinones were 77% and 78%. Hence butadiene added to the carbomethoxylated double bond to an extent of well over 80% of the quinone taken.

The fact that the adducts were liquids suggests that they may be mixtures of the two diastereoisomers. It is possible that partial conversion of XV to the trans isomer, XVII and of XVI to its trans isomer, XVIII occurred under the conditions of formation of XV and XVI.

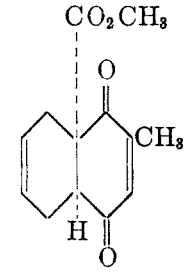
Catalytic hydrogenation of the methyl 1,4-diketo-2-methyl-2,7-naphthitadiene-10-carboxylate (XVI–XVIII) resulted in an uptake of three moles.



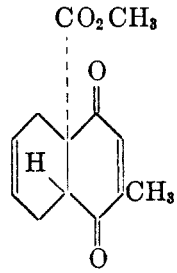
XIV



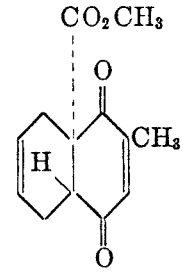
XV



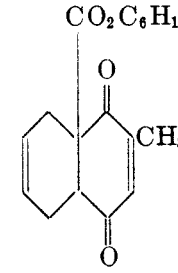
XVI



XVII



XVIII



XIX

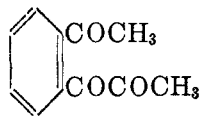
6-Carbomethoxy-1,4-toluquinone and butadiene were next heated together in methanol in order to determine whether the relative rate of addition of the methylated double bond of the quinone to the diene would be increased in a hydroxylic solvent. A yellow liquid boiling at 151–155° under one mm. was obtained in 68% yield. This contained a large proportion of XVI–XVIII as shown by the isolation of XIV in 62% yield after treatment with potassium hydroxide. The chief product of the reaction in methanol, as in benzene, is the angle carboxylate, XVI. 3-Methylgentisic acid, XII, was also found with the products of the alkaline decomposition of the adduct prepared in methanol. Methyl 3-methylgentisate may have been a contaminant of the distilled adduct.

Under the experimental conditions usually employed for the addition of toluquinones to dienes, then, 5-carbomethoxy-1,4-toluquinone reacts almost exclusively at its carbomethoxyethene link with butadiene, and 6-carbomethoxy-1,4-toluquinone reacts at least principally at this link. The selectivity in the formation of structural isomers exhibited by these reactants supports the generalization of Alder and Stein (5) and its extension to the prediction of the chief structural isomers, as recently proposed (6).

Still, it seemed possible that the size and shape of the substituent groups might

be important factors in determining the relative rates of addition at the two olefin links of such bifunctional dienophiles. It was thought that the rate of addition at the carbalkoxylated double bond might be reduced by increasing the size of the alkyl part of the ester group. Accordingly cyclohexyl 3-methylgentisate was prepared and oxidized to the quinone, which was used in benzene solution without isolation. Heating with butadiene at 100° gave 77% of a yellow viscous liquid boiling at 165–170° (0.6 mm.). This ester appeared to be more resistant to alkaline decomposition than the methyl esters. It did give the diphenol, XIV, as well as the corresponding quinone, and is therefore to be represented by XIX. Again no evidence was obtained that an angle methyl isomer had been formed, although a quantitative study of the product mixture was not undertaken.

From the acidic fraction of the products of alkaline decomposition of the adducts from 5-carbomethoxy-1,4-toluquinone and 6-carbocyclohexoxy-1,4-toluquinone there was isolated a few milligrams of a yellow solid, $C_{11}H_{10}O_3$, m.p. 171–173°. A very small quantity of material, m.p. 165–168°, was similarly obtained from the adduct from 6-carbomethoxy-1,4-toluquionone. This was the same compound, as indicated by a mixed melting point with the purer specimen. The substance in ethanol exhibited three maxima in the ultraviolet as follows:[2] Maxima: 2505 Å, ϵ 17000; 2770 Å, ϵ 18000; 3310 Å, ϵ 2600. Minima: 2610 Å, ϵ 11000; 3050 Å, ϵ 1350. Unfortunately not enough material was obtained to establish the structure of the compound. The few tests made (experimental part) were inconclusive. The compound probably was formed by hydrolytic splitting of the diketone ring (7) in the adducts, followed by decarboxylation and dehydrogenation. It is difficult to see how a compound with the properties observed could have been formed from the angle methyl compounds V and VI. If this guess is correct, the yellow compound may be *o*-pyruvylacetophenone, XX, or possibly the aldehyde, XXI. This hypothesis accords with the fact that all three adducts, regardless of the relative positions of the ester group and methyl group, gave the same product.



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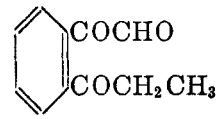

XXI

EXPERIMENTAL[3]

3-Methylgentisic acid (XII). The preparation of this hydroquinone carboxylic acid has already been described (8) but few details were given. The following procedure is a modification of that used by Neubauer and Flatow (9) for the preparation of gentisaldehyde from salicylaldehyde. *o*-Cresotic acid, XI, m.p. 165–166° (cresotinic acid, Dow Chemical Co.) (78.3 g., 0.5 mole) was dissolved in a solution of 55.5 g. (1.2 moles) of sodium hydroxide in 400 cc. of water. The light brown solution was cooled to 20° and treated, while stirring, with 20-cc. portions of 40% sodium hydroxide and 150-cc. portions of 10% potassium per-

[2] Our thanks are due to Mr. Harry Bastron for these observations.

[3] All melting points are corrected. Analyses by Dr. Carl Tiedcke.

sulfate solution, beginning with the hydroxide, at such a rate that a temperature of 30–35° was maintained and until ten portions of each had been added. In some runs additional amounts (150–500 cc.) of 10% potassium persulfate were added. This raised the yield 5–10%, but gave a product melting over a larger range. After the addition was completed, stirring was continued for one hour, the mixture was allowed to stand at room temperature for 16–20 hours, and concentrated hydrochloric acid was then added until blue to Congo. Unchanged cresotic acid separated at this point and was filtered. The filtrate was extracted with ether several times to recover the remainder of the cresotic acid. In all, 43–49 g. was recovered. The aqueous solution was now treated with 450–500 cc. of concentrated hydrochloric acid and then heated on a steam-bath to decompose the monosulfate of the 3-methylgentisic acid. The warm solution was allowed to cool to room temperature and the almost black crystalline solid which had come out was filtered, washed with water, and dried. This crude 3-methylgentisic acid (11–15 g.) by sublimation at one mm. and 140–160°, using a dry ice condenser on the sublimator, gave 7.3–11.3 g. of white 3-methylgentisic acid, m.p. 221–223°. By extraction of the aqueous filtrate from the precipitated acid with ether, there was obtained 13–25 g. more of crude brown product, which was leached with a small amount of water and then, on careful sublimation, gave 9–13 g. of acid, m.p. 219–222°. The total yield varied from 18 to 28 g., 58–70% based on the cresotic acid actually consumed. 3-Methylgentisic acid is reported to melt at 215° (8, 10).

Methyl 3-methylgentisate. Ten grams of sublimed 3-methylgentisic acid was dissolved in 125 cc. of absolute methanol, the solution was saturated with dry hydrogen chloride, refluxed for 7 hours, and cooled. The solution was again saturated with hydrogen chloride and refluxing was continued for 18 hours. The methanol, water, and hydrogen chloride were removed at reduced pressure. The practically white crystalline residue was washed with 150–175 cc. of ice-water and filtered. The acid-free crystals were then crystallized from 800–1000 cc. of water containing a few drops of methanol; 9.5 g. (89%), long white needles, m.p. 106.2–108.2°. A sample recrystallized first from water containing a drop of methanol, then from ether-petroleum ether, and finally from water-methanol, m.p. 106.6–108.2°, was taken for analysis.

Anal. Calc'd for $C_9H_{10}O_4$: C, 59.3; H, 5.5.
Found: C, 59.3; H, 5.6.

6-Carbomethoxy-1,4-toluquinone (XIII). Dry silver oxide was prepared by precipitating a solution of silver nitrate with sodium hydroxide, filtering, washing exhaustively with water, acetone, and ether, and drying in a vacuum over phosphorus pentoxide. Methyl 3-methylgentisate (2.5 g.) was completely dissolved in 126 cc. of dry benzene in an amber bottle by gently warming, 2.5 g. of anhydrous sodium carbonate and 7.5 g. of dry silver oxide were added, and the mixture was maintained at 40–50° with shaking for 20 minutes. After settling, the contents of five such bottles were poured through a sintered glass plate and the solids were washed with warm dry benzene. The yellow-orange benzene solution was allowed to stand over anhydrous sodium carbonate in the dark for 3 hours. The benzene was then removed in a vacuum (bath 40°), the last traces with an oil-pump. The residue crystallized on cooling to 0°. Recrystallization from carbon disulfide (dried over P_2O_5) under anhydrous conditions, with rejection of a small quantity of insoluble syrup, gave, after cooling in the dark in ice-salt mixture, long yellow crystals, m.p. 49.8–51°, 10.45 g. (84.2%). A portion was sublimed at 40–50° and one mm. for analysis; m.p. 50.2–51.4°. The compound was kept in nitrogen over phosphorus pentoxide in the dark.

Anal. Calc'd for $C_9H_8O_4$: C, 59.9; H, 4.5.
Found: C, 59.9; H, 4.7.

4-Methylgentisic acid (IX). *p*-Toluquinone (Eastman Kodak), without purification, was hydrogenated to *p*-toluquinol in ethanol with Adams catalyst in batches of 20 g.; yield, 91%. The *p*-toluquinol was carboxylated according to Brunner (11) with potassium bicarbonate and potassium sulfite in a sealed tube. The 4-methylgentisic acid, 40–60% based on the *p*-toluquinol consumed, melted at 203–204°.

Methyl 4-methylgentisate. 4-Methylgentisic acid, m.p. 201–208°, 7.7 g., was esterified

with 100 cc. of methanolic hydrogen chloride in exactly the same way as the 3-methylgentisic acid. The red oily residue which remained after removal of the methanol at reduced pressure crystallized on being scratched and cooled. Crystallization from 1200 cc. of water containing a few drops of methanol yielded crystals which appeared not to be homogeneous, since they melted from 79–109°. Fractional crystallization from water containing a little methanol finally gave 2.6 g. (34%) of material, m.p. 119–122°, which was taken to be methyl 4-methylgentisate. A small quantity of crystals which seemed to be homogeneous and melted at 79–81° was also obtained. These were not investigated. The ethyl ester was also prepared. Fractional crystallization gave, in poor yield, some material which corresponds to that reported by Brunner (11), m.p. 96–98°.

5-Carbomethoxy-1,4-toluquinone (*X*). The procedure used was the same as that used for the preparation of the 6-carbomethoxytoluquinone. The methyl 4-methylgentisate (2.4 g., m.p. 119–122°) was dissolved in 60 cc. of dry benzene and treated with 2.5 g. anhydrous sodium carbonate and 7.5 g. silver oxide. Yield, 1.5 g. (60%) of crude quinone, some of which was reddish and some yellow, melting at 35–39.4°, from dry carbon disulfide. A portion was sublimed in a vacuum for analysis; m.p. 38.4–39.4°.

Anal. Calc'd for $C_9H_8O_4$: C, 59.9; H, 4.5.
Found: C, 59.95; H, 4.4.

Methyl 1,4-diketo-2-methyl-2,7-naphthitadiene-5-carboxylate (*XV-XVII*). Methyl 4-methylgentisate, 2.5 g., was oxidized as just described, the benzene solution of the quinone was concentrated to 10 cc., and transferred to a Pyrex tube. Three grams of butadiene was added under anhydrous conditions. The tube was sealed and heated at 100° for 16 hours. Removal of the benzene at reduced pressure and distillation of the residue gave 2.48 g., 77%, of light yellow oil, b.p. (0.5 mm.) 137–139°.

Anal. Calc'd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.0.
Found: C, 65.8; H, 6.5.[4]

There was a higher-boiling residue of 0.25 g.

Reaction of XV-XVII with potassium hydroxide. A solution of 2 cc. of methanol and 20 cc. of 10% aqueous potassium hydroxide was added to 2.44 g. of XV-XVII in an atmosphere of nitrogen, and the mixture was shaken for 2 hours. The resulting purple solution was extracted five times with ether and the ether solution was washed with saturated sodium chloride and dried with sodium sulfate. Removal of the ether gave 1.6 g. of purple solid, 87% when calculated as 2-methyl-5,8-dihydronaphthalene-1,4-diol (XIV). Sublimation showed that this consisted entirely of XIV and its oxidation products. At one mm. and 130°, 100–150 mg. of it gave three fractions: A, 60 mg., yellow-brown, impure quinone, melting at 65–76° (2-methyl-5,8-dihydro-1,4-naphthoquinone, m. 86–87°)(4b); B, 20 mg., purple, m. 73–96°; and C, 50 mg., nearly white, m.p. 168–171°. Crystallization of C from benzene-petroleum ether and reduction of A in ether with sodium hydrosulfite, each gave XIV, m.p. 173–174°, identified by mixed m.p. with a specimen prepared according to the literature (4). Reduction of B gave an impure product, m.p. 163–165° alone, mixed with authentic XIV, m.p. 165–167°. The aqueous alkaline solution remaining after ether extraction of the products of decomposition of XV-XVII was acidified with hydrochloric acid, extracted with ether, the ether extract washed and dried, and the ether evaporated. This gave 260 mg. of greenish-yellow solid which darkened on standing, m. 110–135°. This was examined as described in the following section.

A product of ring cleavage of XV-XVII by hydrolysis, possibly o-pyruvylacetophenone (*XX*). The 260 mg. of material, m. 110–135°, just noted was dissolved in ether and treated with sodium hydrosulfite. The ether solution was dried and the ether evaporated to give a dark brown material containing yellow crystals. Repeated extraction of this with warm petroleum ether gave 25 mg., yellow, m.p. 167.8–170.6°; mixed melting point with XIV (m.p. 173–174°), 130–132.2°. This material from the acidic products of the alkaline de-

[4] Further purification was not attempted since the material gave a high yield of XIV with alkali.

composition of XV–XVII was therefore not XIV. Sublimation at 60–80° and 0.07–0.15 mm. gave 17 mg. of yellow sublimate, which softened at 169.8° and melted at 171.4–172°. This sublimate was analyzed. It did not decompose at the melting temperature, but formed fine yellow needles which upon reheating softened at 168.4° and melted at 171–171.4°.

Anal. Calc'd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30.
Found: C, 69.42; H, 5.05.

A mixed melting point of this compound with another specimen obtained by a similar series of operations from the cyclohexyl 1,4-diketo-2-methyl-2,7-naphthitadiene-10-carboxylate, XIX, was found to be 171.8–173°. XVI–XVIII (made in methanol) gave a very small quantity of what was very probably the same substance; m. 165–168°, mixed m.p. 167–170°.

Addition of one drop of 0.1 *N* sodium hydroxide to the yellow solution of the compound in aqueous methanol changed the color to cherry-red; hydrochloric acid restores the yellow color. Addition of hydrogen peroxide to the red alkaline solution of 6 mg. in methanol and warming gave a colorless solution from which no pure product could be isolated. The yellow compound gave a deep red color with ethanolic ferric chloride and metallic silver with Tollens' reagent. The absorption in the ultraviolet was measured with solutions in ethanol, 0.00003 to 0.003 *M* assuming the compound to be monomeric $C_{11}H_{10}O_3$.

Methyl 1,4-diketo-2-methyl-2,7-naphthitadiene-10-carboxylate (XVI–XVIII). Five grams of 6-carbomethoxy-1,4-toluquinone, XIII, m.p. 49.8–51° in 10 cc. of dry benzene was mixed with 3 g. (2 moles) of butadiene under anhydrous conditions. The mixture was heated in a sealed tube for 66 hours at 100°. After removal of the benzene at reduced pressure a light clear yellow oil remained which could not be crystallized. Distillation gave 5.1 g., 78%, slightly yellow oil, b. 155–157° at 1–2 mm., $n_D^{20.6}$ 1.5270. A small higher-boiling residue remained in the distilling flask. A portion of the adduct was redistilled and a middle cut, b. 184° at 4–5 mm. was taken for analysis.

Anal. Calc'd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.0.
Found: C, 66.4; H, 6.2.

When 139.3 mg. of the adduct ester (0.595 millimole) in ethanol was hydrogenated in the presence of 20 mg. of Adams catalyst, 43 ml. of hydrogen was absorbed in 25 minutes and 46.1 ml. in 3 hours. The calculated volume corresponding to 3 moles plus the volume required for the catalyst is 46.5 ml.

Reaction of XVI–XVIII with potassium hydroxide. Five and one-tenth grams of the adduct was shaken in an atmosphere of nitrogen with 35 cc. of 10% aqueous potassium hydroxide and 2 cc. of methanol. The shaking was done at 25° and continued for 3.75 hours. A light, fluffy precipitate came out. The alkaline mixture was extracted four times with ether. Some of the fluffy solid appeared to go into the ether. Washing the ether extract with saturated sodium chloride, drying with sodium sulfate, and concentration on a steam-bath precipitated a purple solid which was filtered; 2.51 g., 66% as XIV. When 70 mg. of this purple solid was heated at 3 mm. practically all of it (65 mg.) sublimed at 130°. Crystallization of the sublimate from benzene-petroleum ether gave fine white needles, m.p. 174–175.4° with darkening; mixed melting point with authentic XIV of m.p. 173–174°, 172.8–174°. Confirmation of the identity of this product with 2-methyl-5,8-dihydronaphthalene-1,4-diol was afforded by oxidizing it with silver oxide to 2-methyl-5,8-dihydro-1,4-naphthoquinone (4b), m.p. 86–87°, in quantitative yield. Also oxidation in glacial acetic acid with chromic acid gave 2-methyl-1,4-naphthoquinone.

The aqueous alkaline solution from the ether extraction was acidified with hydrochloric acid and extracted with ether; working up the extract gave 1.57 g. of oil. Distillation of a portion of this oil at very low pressure gave some solid, m.p. 148–151°, which did not readily crystallize from petroleum ether. This material was discarded before the yellow substance of m.p. 171–172°, provisionally assigned the structure of *o*-pyruvylacetophenone, had been isolated from similar fractions of the related reactions. It is probable that this same compound could have been isolated in this instance.

Reaction of 6-carbomethoxy-1,4-toluquinone (XIII) with butadiene in methanol. Six and one-tenth grams of quinone (0.034 mole) in 22 g. of absolute methanol was mixed under anhydrous conditions with 3 g. (0.055 mole) of butadiene, and the containing vessel was sealed off in a vacuum. The tube was heated at 75° for 88 hours. A small quantity (50–75 mg.) of solid was filtered out. This melted above 340° and was not further investigated. The methanol was removed and the residue which failed to crystallize was distilled. The fraction which distilled at 151–155° and one mm. was collected, 5.21 g. (68%). The higher-boiling residue was not investigated. Two and three-tenths grams of the distillate was shaken with 17.5 cc. of 10% potassium hydroxide and 4 cc. of methanol under the conditions described for the other preparations. The yield of purple solid from the neutral ether extract was 1.06 g. (62% as XIV). Sublimation gave two fractions which were shown to consist of XIV and the corresponding quinone.

The acidic ether extract gave an oily solid from which 210 mg. of solid, m. 204–210°, was obtained by treatment with warm benzene. This was shown to be 3-methylgentisic acid, XII, by conversion to the methyl ester, m.p. 106.8–108.2° (from water), by hydrogen chloride in methanol. Mixing with an authentic sample of methyl 3-methylgentisate did not depress the melting point.

Cyclohexyl 3-methylgentisate by ester interchange. To 75 cc. of cyclohexanol which had reacted with 200 mg. of potassium was added 18 g. of methyl 3-methylgentisate. The mixture was sealed off in a tube and heated 15 hours at 190°. The cyclohexanol was removed at 11 mm. and the residue was extracted with hot benzene. Concentration and cooling the benzene extract gave 4.2 g. of unchanged methyl ester. Distillation of the residue from the benzene mother liquors gave 4.2 g. more unchanged methyl ester, b. 140–150° (0.5 mm.) and then 4.4 g. (33.4% based on the methyl 3-methylgentisate converted) of cyclohexyl 3-methylgentisate, b. 179–182° (0.8 mm.). A portion of this was redistilled for analysis at 170–174° and 0.25 mm.

Anal. Calc'd for $C_{14}H_{18}O_4$: C, 67.2; H, 7.3.
Found: C, 66.9; H, 7.9.

Cyclohexyl 1,4-diketo-2-methyl-2,7-naphthitadiene-10-carboxylate (XIX). To 4.4 g. of cyclohexyl 3-methylgentisate in 175 cc. of dry benzene in an amber bottle were added 3.2 g. of anhydrous sodium carbonate and 9.6 g. of silver oxide. The mixture was warmed to 50°, shaken for 10 minutes, again warmed to 50°, and shaken for 10 minutes more. The solids were then removed by pouring through a sintered glass funnel and most of the benzene was distilled from the filtrate. The concentrated quinone solution so obtained was mixed with 2 g. of butadiene, sealed in a tube, and the mixture heated at 100° for 44 hours. The product was a yellow viscous material, b. 165–170° (0.6 mm.), 4.26 g., 77%. A cut, b. 160–161° (0.28 mm.), obtained on redistillation, was taken for analysis.

Anal. Calc'd for $C_{18}H_{22}O_4$: C, 71.5; H, 7.3.
Found: C, 71.4; H, 8.3 (?).

Reaction of XIX with potassium hydroxide. Two grams of XIX when treated with 13 cc. of 10% potassium hydroxide and 5 cc. of methanol under the conditions employed for the decomposition of the other adducts was not completely hydrolyzed. About 0.77 g. of oil remained unchanged. The aqueous methanolic alkaline solution was decanted from this oil, extracted with ether, the ethereal extract washed and dried, and the ether evaporated. Both XIV and the corresponding quinone were obtained from the residue by procedures already described. Extraction of the acidified aqueous layer with ether yielded 510 mg. of a red gum which was dissolved in ether and shaken with freshly prepared sodium hydrosulfite solution. Washing with saturated sodium chloride, drying, and evaporating gave 250 mg. of material which was sublimed at 60–80° and 0.07 mm. The semisolid yellow sublimate was crystallized from petroleum ether; 5 mg. of yellow needles, m.p. 170.8–173°, identical with the compound from methyl 1,4-diketo-2-methyl-2,7-naphthitadiene-5-carboxylate which may be *o*-pyruvylacetophenone.

SUMMARY

Under the experimental conditions employed, butadiene reacted only at the double bond with the ester group in 5-carbomethoxy-1,4-toluquinone and 6-carbomethoxy-1,4-toluquinone. The products, methyl 1,4-diketo-2-methyl-2,7-naphthitadiene-5-carboxylate and methyl 1,4-diketo-2-methyl-2,7-naphthitadiene-10-carboxylate, were obtained as high-boiling liquids which possibly are mixtures of the cis and trans isomerides.

These angle esters were converted by aqueous methanolic potassium hydroxide at room temperature into a mixture of products from which were isolated 2-methyl-5,8-dihydronaphthalene-1,4-diol, 2-methyl-5,8-dihydro-1,4-naphthoquinone, and a yellow crystalline compound which may be *o*-pyruvylacetophenone.

The same three products of alkaline decomposition were obtained from a reaction product of butadiene and 6-carbocyclohexoxy-1,4-toluquinone, but the conversion was much smaller. Hence the presence of some angle methyl adduct in the high-boiling liquid obtained is possible, although no positive evidence for it was found.

In addition to the foregoing, the following new compounds were prepared in the course of this work: Methyl 3-methylgentisate, cyclohexyl 3-methylgentisate, methyl 4-methylgentisate, 5-carbomethoxy-1,4-toluquinone, and 6-carbomethoxy-1,4-toluquinone.

BELTSVILLE, MD.

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[CONTRIBUTION FROM THE BUREAU OF ANIMAL INDUSTRY, AGRICULTURAL RESEARCH ADMINISTRATION, UNITED STATES DEPARTMENT OF AGRICULTURE]

THE SYNTHESIS OF CONDENSED RING COMPOUNDS. XIV. 2-METHOXY-5-METHYL-2,7-NAPHTHITADIENE-1,4-DIONE[1]

MILTON ORCHIN[2] AND LEWIS W. BUTZ

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The observation that Diels-Alder reactions are always cis-additions (2) does not, of course, render them useless for the synthesis of condensed ring compounds with trans configuration at the junction of rings. One can employ an open-chain dienophile, with proper substituents in the trans relation, and close one ring after the Diels-Alder addition (3) or one can provide the adduct with cis junction of rings with functional groups which will make possible conversion to the trans isomer. In the hydronaphthalene series this latter device might take the form of a cis-α-decalone $\rightarrow$ trans-α-decalone epimerization (4), a reaction which has not yet been established as possible for naphthitenones and naphthitadienones.

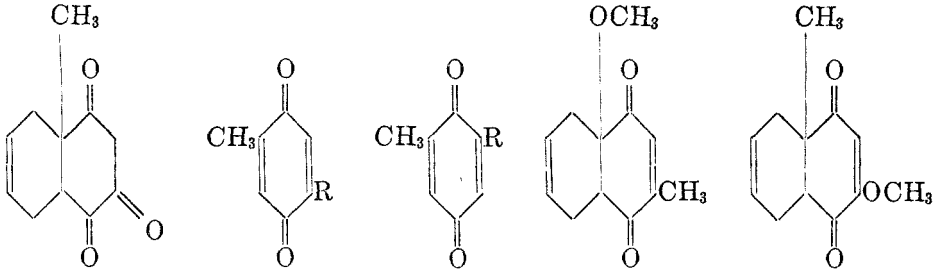
If conjugated dienes could be made to react with *p*-toluquinones at the methylated side, a great many hydronaphthalene derivatives with an angle methyl group would become easily available. *p*-Toluquinone itself (5), 5-carbomethoxy-1,4-toluquinone, and 6-carbomethoxy-1,4-toluquinone (6) react exclusively at the unmethylated side. 5-Acetoxy-1,4-toluquinone has been found to react with several dienes at both sides to give angle acetates and angle methyl compounds (7, 1). The composition of the product mixture from this quinone is complicated by hydrolysis of part of the acetate adduct to trione enol (7), although it appears practical to prepare the trione enols with angle methyl group by deliberate saponification of the mixture of products. In this way a crystalline 5-methyl-7-naphthitene-1,2,4-trione enol (cis or trans?) (I) was prepared (1).

As a guide in the choice of other 1,4-toluquinones, substituted at carbon 5 or 6 (II or III), which might yield chiefly angle methyl naphthitadienediones, there is the rule of Alder and Stein (2) applied to the prediction of position isomers which appeared (7) not to be contradicted by the observations on the additions of the 5-acetoxy quinone. As to toluquinones which do not have a substituent containing a doubly bonded atom, to which the rule of Alder and Stein would therefore not be applicable, there is the rule in its extended form of Alder and Windemuth (8) which undertakes to predict the influence of the location of groups containing atoms with unshared electrons pairs on the speed of addition. Besides these two generalizations of Alder, one might be guided by the principle that large groups retard reaction more than smaller ones and by the conception that reactivity of the dienophile double bonds may be determined to an important degree by their states of polarization which would depend on the character of the various other parts of the quinone molecule including the substituents at the dienophile double bonds.

[1] For nomenclature see a preceding paper (1). This work was supported by an allotment from the Special Research Fund (Bankhead-Jones Act of June 29, 1935).

[2] Present address, U. S. Bureau of Mines, Pittsburgh, Pa.

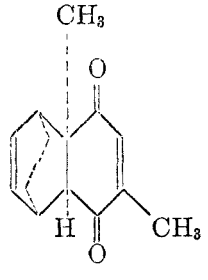
While attempting to recover some impure 5-acetoxy-1,4-toluquinone, it was found that refluxing it with methanol and sulfuric acid gave 5-methoxy-1,4-toluquinone [II, R is CH_3(9)] and a considerable quantity of this methyl ether was accumulated. Now the oxygen atom of the methoxyl group has an unshared electron pair and hence butadiene should react more rapidly at the methoxyethene link of 5-methoxy-1,4-toluquinone than at the methylethene link according to Alder and Windemuth (8); the chief product would therefore be IV. Likewise favoring the formation of IV would be the smaller volume of the methoxyl group compared with the methyl group. In spite of the seemingly poor chance of obtaining an angle methyl compound as the major product, the reaction of the methoxy quinone with butadiene was tried. Combination in ethanol at 100° gave white needles, melting at 94.5–95.5°, in 75% yield. Hot concentrated hydrochloric acid hydrolyzed the adduct to the triketone enol, I, previously known (1), and it must therefore have structure V.



I II III IV V

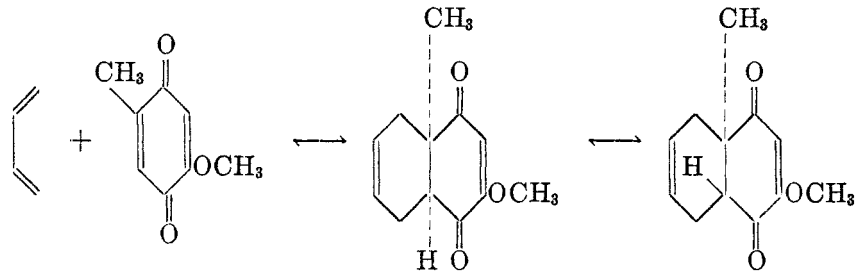
An interesting feature of the reaction is its slowness. After forty-eight hours the yield was only 27% and 20% of unchanged quinone was recovered. After sixty-five hours the yield was 75%; it was still possible to recover small quantities of unchanged quinone. It is suggested that cis-5-methyl-2,7-naphthitadiene-1,4-diones, such as VI, undergo two reactions to an important extent under the conditions of their formation; (a) decomposition into the toluquinone and diene,[3]

[3] Dr. E. W. J. Butz of this laboratory has prepared a colorless crystalline adduct, $C_{14}H_{16}O_2$, m.p. 65°, from 1,3-cyclohexadiene and 2,5-dimethyl-1,4-benzoquinone. This compound slowly decomposed at room temperature with the formation of 2,5-dimethyl-1,4-benzoquinone. Its structure is probably V-A and epimerization to the 5,10-trans isomer may be prevented by the 6,9-ethano bridge. *Anal.* Calc'd for $C_{14}H_{16}O_2$: C, 77.8; H, 7.4. Found: C, 77.9; H, 7.6.



V—A

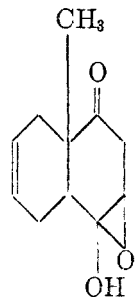
and (b) isomerization into the 5,10-trans isomer. More and more trans compound is gradually formed and, if it is not effectively removed from the system, the yield is determined by the proportion of it in the equilibrium mixture. If this conception is right, the new angle methyl compound is trans-2-methoxy-5-methyl-2,7-naphthitadiene-1,4-dione (VII).



VI VII

The methoxy diketone is not very soluble in water and is not readily hydrolyzed by water. A dilute solution obtained by heating in water at 90° for two minutes gave no enol test with ferric chloride. The compound also was not changed by heating in methanol-acetic acid solution at 60° for one hour. With zinc dust in methanol-acetic acid it gave a product which failed to crystallize when the solution was poured onto ice. Subsequent manipulations included the use of dilute hydrochloric acid. A pale greenish-yellow oil, $C_{11}H_{14}O_3$, distilling at 105–115° and 0.027 mm. was isolated. This contains one carbon atom less than the methoxy adduct and may have resulted from the hydrolysis or acetolysis of a 2,3-dihydro derivative. If the carbon and hydrogen content found is not fortuitous, the oil may represent a mixture of the substance VIII and its dimer. The composition of this oil is being investigated. The methoxy diketone adduct in methanol absorbed 3.1 moles of hydrogen at 20° in the presence of Adams catalyst.

EXPERIMENTAL[4]



VIII

5-Methoxy-2-methyl-1,4-benzoquinone from uncrystallized crude 5-acetoxy-2-methyl-1,4-benzoquinone. The methoxytoluquinone used in the following experiments was prepared in part according to a method in the literature (9) and in part from impure acetoxytolu-

[4] Microanalyses by Dr. Carl Tiedcke. All melting points are corrected.

quinone which may have been hydrolyzed to some extent to hydroxytoluquinone. This crude quinone (21.4 g.) was refluxed with 100 cc. of methanol and 1 cc. of sulfuric acid for 20 mins. Cooling, filtering the precipitated quinone, and washing with cold methanol gave about 80% of crude product. Recrystallization from a large volume of methanol gave 7.5 g. of 5-methoxy-2-methyl-1,4-benzoquinone, yellow plates, m.p. 176.2–178.4°, no depression in m.p. with a specimen prepared according to Ashley (9).

2-Methoxy-5-methyl-2,7-naphthitadiene-1,4-dione (V). A mixture of 6.3 g. of 5-methoxy-2-methyl-1,4-benzoquinone, 20 cc. of absolute ethanol, and about 12 cc. of butadiene was sealed in a tube and heated at 100° for 65 hours. The crude adduct sometimes separated as soon as the excess butadiene was removed by gentle warming, sometimes only after seeding or cooling in the refrigerator for a day. The white granular product was washed thoroughly with petroleum ether; 6.15 g., 73 %, m. 87–92°. Three recrystallizations from petroleum ether gave a product with m.p. 94.5–95.5°.

Anal. Calc'd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.8.
Found: C, 69.8; H, 7.15.

The original ethanol mother liquor was evaporated to dryness; 2 g. of partly crystalline residue. This was digested with 6 *N* hydrochloric acid at 60° for half an hour, extracted with ether, and the ether extract separated into a neutral and an acid part by sodium carbonate solution. The neutral fraction yielded 15 mg. of unchanged methoxytoluquinone. Evaporation of the ether from the acid fraction and crystallization from carbon tetrachloride gave 126 mg. of the trione enol, I, which corresponds to about 1.5% more of V. The yield of V was therefore about 75%.

In another run the time of reaction was 48 hours. One gram of methoxytoluquinone was taken. The precipitated product (880 mg.) was recrystallized from benzene-petroleum ether. Methoxytoluquinone, m.p. and mixed m.p. 174–175.5°, 195 mg. (19.5%) separated first; then 368 mg. (27.1%) of V.

5-Methyl-7-naphthitene-1,2,4-trione enol (I) from V. Some V, m.p. 93.5–94.5° (0.9 g.) and 3.5 cc. of concentrated hydrochloric acid were heated on a steam-bath for 15 minutes. The dark brown solution was extracted with ether, finally with the addition of solid sodium chloride. The ether extract was washed until neutral to Congo, filtered and dried. Evaporation of the ether and crystallization of the residue from carbon tetrachloride gave 0.487 g. (57%) of I, m.p. 172–173°, no depression with a specimen prepared from 5-acetoxy-2-methyl-1,4-benzoquinone (1). Some batches of the trione enol had a pink color which could be removed by warming with Norit in carbon tetrachloride.

The reaction of V with zinc in methanol-acetic acid. V (100 mg.) in 4 cc. of methanol and 16 cc. of acetic acid was heated at 60° for one hr. The solution was evaporated to dryness at reduced pressure (bath temperature below 50°) and the residue was crystallized from benzene-petroleum ether. Seventy milligrams of unchanged V, m.p. 93.6–94.4°, was recovered.

To 3 g. of V in 15 cc. of acetic acid and 10 cc. of methanol was added 6 g. of zinc dust. The mixture was kept at 50–55° for one hr., then filtered while warm, and poured onto cracked ice. As crystallization did not take place, the aqueous suspension was neutralized with sodium bicarbonate, made acid to Congo with dilute hydrochloric acid, extracted with ether, the ether extract washed with water, sodium bicarbonate solution, saturated sodium chloride solution, and then filtered through sodium sulfate. The ether was evaporated and the residue, which failed to crystallize, was distilled at 0.027 mm. A fraction, boiling at 105–115°, 1.9 g. was collected. This pale greenish-yellow oil gave no enol test with ferric chloride in ethanol solution. It has the composition, $C_{11}H_{14}O_3$.

Anal. Calc'd for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3.
" " $C_{12}H_{14}O_3$: C, 69.9; H, 6.8.
" " $C_{12}H_{16}O_3$: C, 69.2; H, 7.75.
Found: C, 67.8; H, 7.4.

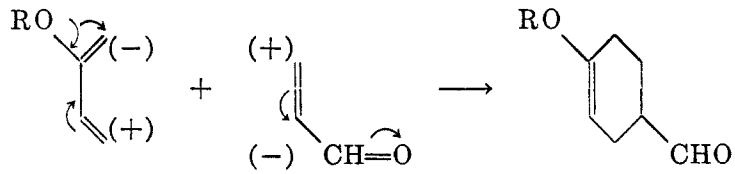
Catalytic hydrogenation of V. A half millimole of V (103 mg.) in 10 cc. of absolute methanol and in the presence of 20 mg. of Adams catalyst absorbed 43.2 cc. of hydrogen at 20°

and 660 mm.[5] in 35 mins. This is 3.1 millimoles. The catalyst was filtered and the filtrate taken to dryness. No crystalline material was obtained on the addition of ether.

THE ADDITION OF UNSYMMETRICALLY SUBSTITUTED *p*-BENZOQUINONES TO CONJUGATED DIENES

Enough experimental material may now be at hand to set up a working hypothesis as a guide in the choice of a substituted *p*-benzoquinone for combination with a diene in order to obtain a particular diketonaphthitadiene. The exclusive addition of butadiene to *p*-toluquinone at the unmethylated side is understandable if one simply assumes that reaction at the methylated side is slowed up on account of the relatively large size of the methyl group. The greater rate of addition of butadiene to the carbalkoxylated side of 5-carbalkoxy-1,4-toluquinones and 6-carbalkoxy-1,4-toluquinones (6) accords with the rule of Alder and Stein (2) relating to the tendency for the reactant molecules to orient so that maximal density of double bonds is attained. But the observation, reported in the present paper, that butadiene adds chiefly to the methylated side in 5-methoxy-1,4-toluquinone cannot be explained on either ground.

A number of workers have already used polarizations in the reactant molecules to explain observed selectivities in Diels-Alder additions. Petrov (10) and Fiesselmann (11) have both found that 2-alkoxybutadienes give only the 4-alkoxy-4-cyclohexen-1-aldehydes with acrolein, and Petrov explains this selectivity satisfactorily as follows:



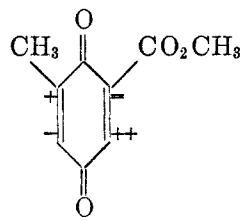
Evidently it is assumed that the more anionoid terminal carbon of the 1,3-diene system adds faster to the more cationoid carbon in the dienophile.

Now Price (12) has recently calculated the electrostatic polarizing force exerted by each of thirty-eight substituent groups upon the adjacent double bond in the benzene ring. The knowledge of the magnitudes of these forces may be useful for estimating the relative electronegativities of groups attached at the olefin links in substituted *p*-toluquinones. The values for methoxyl, methyl, hydrogen, and carbomethoxyl are respectively -1.21, -0.39, $+0.45$, and $+1.23 \times 10^{-4}$ dyne. The polarizing forces of the methoxyl and carbomethoxyl groups upon the adjacent double bond (in the benzene ring) are about equal, but of opposite sign. In its reaction with substituted toluquinones, under the experimental conditions, butadiene reacts faster at the carbomethoxyethene link than at the methylethene link and faster at the methylethene link than at the methoxyethene link. Might not substituents other than methoxyl of large negative polarizing capacity when placed at carbon 5 or 6 similarly retard reaction at the 5–6 bond so that the chief product will be that resulting from addition at the methylated side?

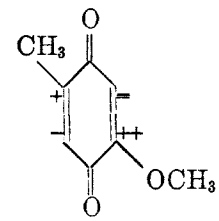
[5] The pressure due to hydrogen after correcting the observed atmospheric pressure for the vapor pressure of the solvent, methanol.

The working hypothesis then is this: *Butadiene reacts faster with carbon atoms attached to hydrogen than to others (steric effect) and of these, as an anionoid reagent, it reacts fastest with the most cationoid carbon in the quinone (electrostatic effect).* In some instances the rate of the favored reaction may so far exceed the rates of the other possible reactions that only one adduct is obtained.

The application of this rule to the reactions with 6-carbomethoxy-1,4-toluquinone and with 5-methoxy-1,4-toluquinone is shown in IX and X respectively. It is noteworthy that when butadiene, a symmetrical diene, is one reactant, it makes no difference whether the critical substituent is at position 5 or 6. In each quinone there are two annular carbons attached to hydrogen; of these the one marked with a double positive sign (++) reacts faster in IX and the one with a single negative sign (−) reacts faster in X. These signs denote the relative electrostatic charges on all four carbon atoms. If the steric factor were unimportant, addition would be fastest at the carbon attached to methoxyl (++) in X, which is contrary to the experimental observation, unless it be assumed that the rate of decomposition of cis-IV into diene and quinone is also critically faster than the rate of decomposition of cis-V.



IX



X

SUMMARY

5-Methyl-7-naphthitene-1,2,4-trione enol and its 2-methyl ether have been prepared in good yield from 5-methoxy-2-methyl-1,4-benzoquinone. The 2-methyl ether was obtained as the chief product (75% yield) in the addition of this quinone to butadiene. A working hypothesis has been presented which may be helpful in the synthesis of angle methyl compounds from other *p*-toluquinones.

BELTSVILLE, MD.

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[CONTRIBUTION FROM THE BUREAU OF ANIMAL INDUSTRY, AGRICULTURAL RESEARCH ADMINISTRATION, UNITED STATES DEPARTMENT OF AGRICULTURE]

ULTRAVIOLET ABSORPTION SPECTRA OF SOME ALICYCLIC DIKETONES AND TRIKETONES[1]

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In connection with the characterization of some intermediates in projected syntheses, we have collected ultraviolet absorption data for sixteen alicyclic ketones. The compounds examined fall into four groups: Derivatives of 2-cyclohexene-1,4-dione, cyclane-1,2,4-triones, cyclane-1,3-diones, and compounds of incompletely known structure. All were crystalline solids, which were dissolved in ethanol for spectrophotometric examination. With the exception of the 2-methylcyclohexane-1,3-dione, which was prepared by methylation of cyclohexane-1,3-dione,[2] all the ketones were prepared by methods described in the literature. References to these publications, the melting points of the specimens used, and the concentrations in ethanol are given in Tables I–IV along with the results of the spectrophotometric measurements. In addition to the locations and intensities of the maxima and minima recorded in the tables, complete wave length-intensity curves are reproduced for eleven of the compounds in Figs. 1–7.

A Bausch and Lomb large Littrow quartz spectrograph equipped with a sector photometer was employed. A condensed spark between high-speed steel electrodes served as light source.

DERIVATIVES OF 2-CYCLOHEXENE-1,4-DIONE

This group consisted of six hexahydronaphthalene diketones—II, III, IV, V, and VI in Table I, and VII in Table IV—obtained by the addition of *p*-benzoquinones to conjugated dienes. Wassermann had previously investigated the ultraviolet absorption of xxxx-6,9-methano-2,7-naphthitadiene-1,4-dione, I.[3] Since those of his data which were obtained with an ethanol solution are directly comparable with ours and since his are the only measurements previously reported for a 2,7-naphthitadiene-1,4-dione, we include this diketone in Table I.

cis-2-Methyl-2,7-naphthitadiene-1,4-dione, II, is structurally very like I, being a 5,10-cis compound. The atoms attached to carbons 5 and 10 in the two compounds may differ a little in configuration because of the greater mobility of the cyclohexene ring in II. The chief difference in the chromophore is the 2-methyl group in II. This substitution, if comparison be made directly with I, results in a displacement of the principal maximum of 150 Å toward longer wave lengths. This is exactly the displacement produced by alkyl substitution, shown

[1] This work was supported in part by an allotment from the Special Research Fund (Bankhead-Jones Act of June 29, 1935). Not copyrighted.

[2] By Mr. A. M. Gaddis of this laboratory. The specimen used was compared directly with a sample prepared by the method of Blaise (see Table III).

[3] Referred to by Wassermann as cyclopentadiene-*p*-benzoquinone. For the numbering and nomenclature employed here see the preceding three papers. For the configurational notation see Butz, Gaddis, Butz, and Davis, *J. Org. Chem.*, **5**, 383, footnote (1940).

by Woodward (1) and concurred in by Evans and Gillam (2), in α,β-unsaturated monoketones.

TABLE I

DERIVATIVES OF 2-CYCLOHEXENE-1,4-DIONE

CPD.	2,7-NAPHTHITADIENE-1,4-DIONE	M.P. (°C)	λ_{max}(Å)	ϵ	λ_{min}(Å)	ϵ	MOLARITY	REF.
I	xxxx-6,9-Methano-	75–76	2220	12800				12[a]
II	*cis*-2-Methyl	79.6–80.6	2370	12250	3210	43	0.00005–	13
			3540	62			.005	
III	5-Acetoxy-2,7,8-trimethyl	116–117	2360	20000	—	—	.0000105–	14
			—	—			.0021	
IV	xxxx-5-Acetoxy-6,9-ethano-2-methyl[b]	123.4	2300	8800	3290	56	.00024–	14
			3690	100			.0024	
V	xyyx-5-Acetoxy-6,9-ethano-2-methyl[b]	84.7	2350	8200	—	—	.00016–	14
			—	—			.0016	
VI	2-Methoxy-5-methyl	93.5–95	2690	8400	—	—	.000112–	6
			—	—			.00112	

[a] The m.p. and absorption data in the table are taken from this reference.

[b] The configurations were assigned entirely on the basis of the Alder-Stein rule. Which of the two isomers is xxxx and which xyyx is therefore uncertain.

TABLE II

CYCLANE-1,2,4-TRIONES

	COMPOUND	M.P.(°C)	λ_{max}(Å)	ϵ	λ_{min}(Å)	ϵ	MOLARITY	REF.
VIII	3-Methylcyclopentane-1,2,4-trione	118.2–119.6	2750	10500	—	—	0.00087	15
			2750	7300			.000087	
	3-Methylcyclopentane-1,2,4-trione monohydrate	78–80	2750	12500	—	—	.00096	15
			2750	9300			.000096	
IX	5-Methyl-7-naphthitene-1-2,4-trione	174–175	2560	14500	2810	2200	.000108	10
			3110	3900				

TABLE III

CYCLANE-1,3-DIONES

	COMPOUND	M.P.(°C)	λ_{max}(Å)	ϵ	λ_{min}(Å)	ϵ	MOLARITY	REF.
XI	Cyclohexane-1,3-dione	105–107	2550	16000	—	—	0.000158	16
			2800	20000			.0000158	
XII	2-Methylcyclohexane-1,3-dione	205–208	2610	17000	—	—	.000606	17
			2620	15000			.000121	
XIII	2-Methylcyclopentane-1,3-dione	212.2–214.6	2500	18000	—	—	.000203	4
XIV	4-Hydroxy-2-methylcyclopentane-1,3-dione	165–165.8	2490	16000	—	—	.00085	4
			2540	13000			.000085	

Moreover, the absolute value of the wave length of maximal absorption is the same, 2350 $\pm$ 50 Å, in these enediones as it is in disubstituted enones (3). The

maxima of all five of our 2-methyl diketones fall within this range. Therefore, bringing a second carbonyl group into conjugation with an α,β-enone system does not change the position of the short wave length maximum *when the entire chromophore system is within one six-carbon ring.* If the enedione system is spread over two rings, the second keto group displaces the maximum toward longer wave lengths. There are many examples in the literature to illustrate this point. Thus 6-oxoprogesterone as a disubstituted enone should have its maximum at about 2350 Å; the experimentally found value is 2550 Å (4). $\Delta^{9,10}$-Octalin-dione-1,5 (5-naphthitene-1,6-dione) as a trisubstituted enone might be expected to have its maximum at about 2500 Å; the experimental value (5) is 2630 Å.

It is interesting that a considerable difference was found, within the stated range, between the maxima for the two diastereoisomers, IV and V, while an analogous compound lacking the methano bridge (VII, Table IV) has the same

TABLE IV

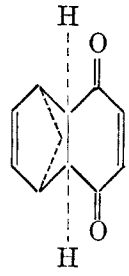
SUBSTANCES OF INCOMPLETELY KNOWN STRUCTURE

	COMPOUND[a]	M.P.(°C)	λ_{max}(Å)	ϵ	λ_{min}(Å)	ϵ	MOLARITY	REF.
VII	5-Acetoxy-2-methyl-6 (or 9)-vinyl-2,7-naph-thitadiene-1,4-dione[b]	109–110	2350 3450	8200 84	3160	60	0.00014– .0014	14[a]
X	5-Methyl-6(or 9)-vinyl-7-naphthitene-1,2,4-trione[b]	206–210	2560 3050	13000 3000	2830	2200	.00284– .0013	14[a]
XV	4-Hydroxy-10-methyl-7-naphithitene-1,3-dione[c]	123.5, then 145–146	2560	14000			.000146– .00146	10
XVI	Dimer of 1-methylcyclo-pentene-3,5-dione containing a dicyclopenta--*p*-dioxin nucleus	213.4–215.2	2520	19000			.00119	11

[a] Probable structures or the two possible alternative structures.
[b] Relative configurations at carbons 5, 6, 10 (or 5, 9, 10) unknown.
[c] Relative configurations at carbons 4, 5, 10 unknown.

maximum as V. The data for these three compounds, and those for III as well, show that the acetoxyl group at carbon 5, which is adjacent to the chromophore, has no influence on the absorption. The chromophore in VII is certainly the same as those in III, IV, and V; VII is placed here in Table IV because the position of the vinyl group has not been established.

The principal maximum in the spectrum of 2-methoxy-5-methyl-2,7-naphthitadiene-1,4-dione, VI, is quite different from those of the 2-methyl analogs. Possibly the large displacement to longer wave lengths of 340 Å is due to an additional olefin bond in conjugation. This could be furnished by enolization of the 1-carbonyl group. VI differs from the other diketones by its angle methyl group, but in view of the lack of effect of a similarly placed acetoxyl group upon the absorption, it seems unlikely that this methyl group makes an important contribution.



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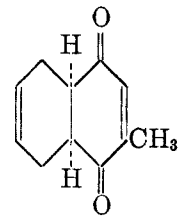

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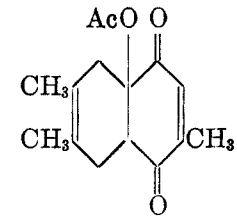

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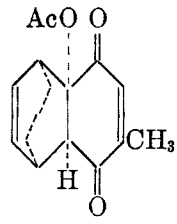

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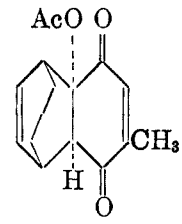

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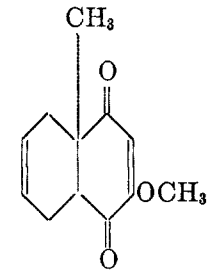

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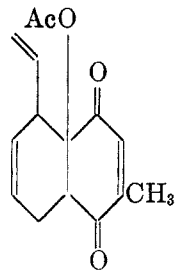
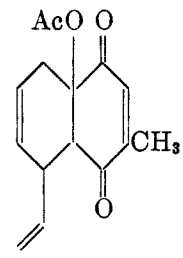


A



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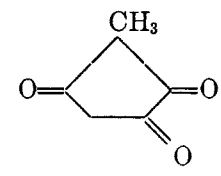

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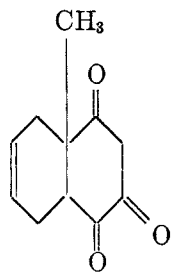

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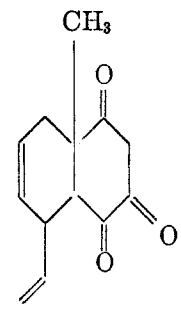

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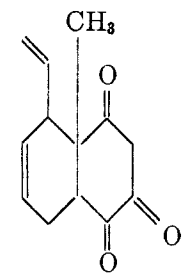

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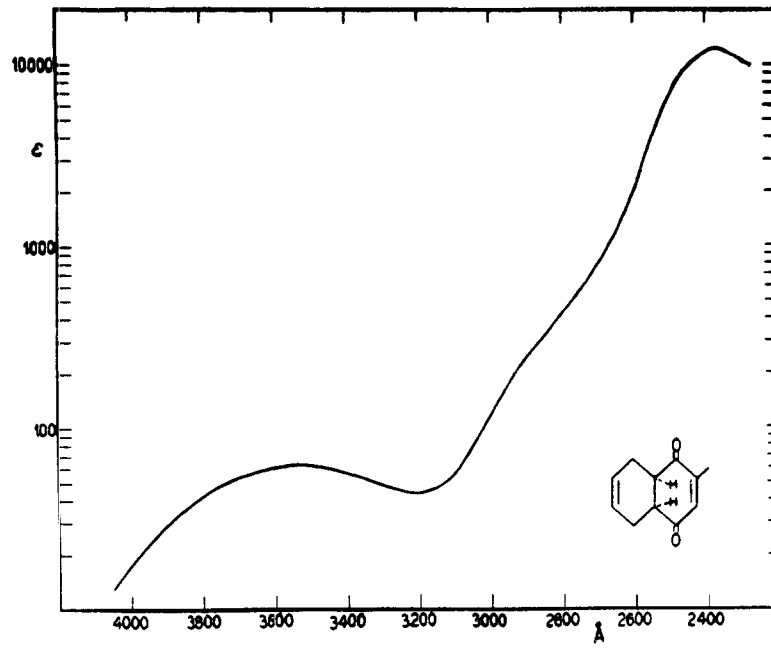


FIG. 1. ABSORPTION SPECTRUM OF *cis*-2-METHYL-2,7-NAPHTHITADIENE-1,4-DIONE IN ETHANOL, 0.00005 TO 0.005 MOLAR

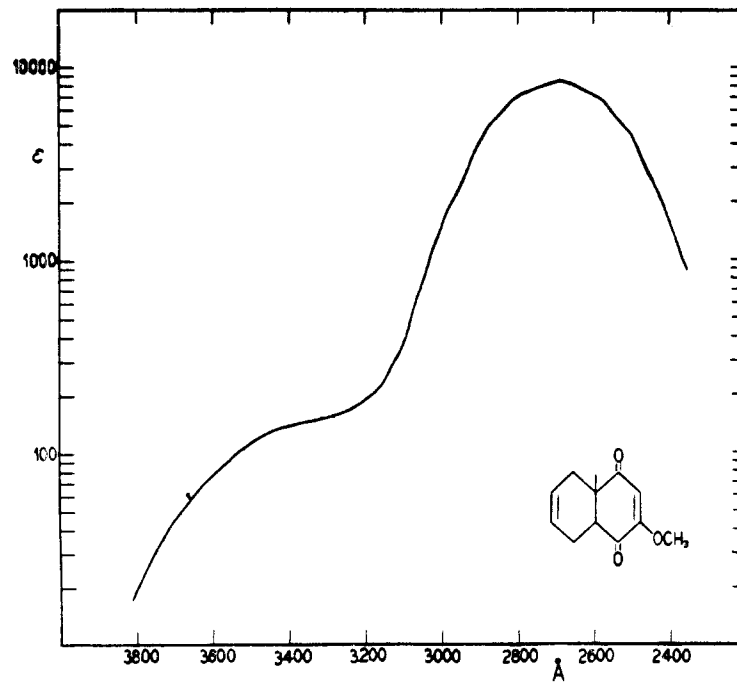


FIG. 2. ABSORPTION SPECTRUM OF 2-METHOXY-5-METHYL-2,7-NAPHTHITADIENE-1,4-DIONE IN ETHANOL, 0.000112 TO 0.00112 MOLAR

If III, VI, and VII exist in ethanol solution principally as a diketone rather than the monoenol, we cannot be certain whether the absorption is due to the 5,10-cis or 5,10-trans isomers for reasons set forth in a discussion in the preceding paper (6).

CYCLANE-1,2,4-TRIONES

Closely related to the methoxy diketone, VI, are the 1,2,4-trione enols, IX and X. X is placed in Table IV because the position of the vinyl group is undetermined. The chromophores in IX and X are very similar, as can be seen from the positions recorded for the two maxima and the minimum. It will be ob-

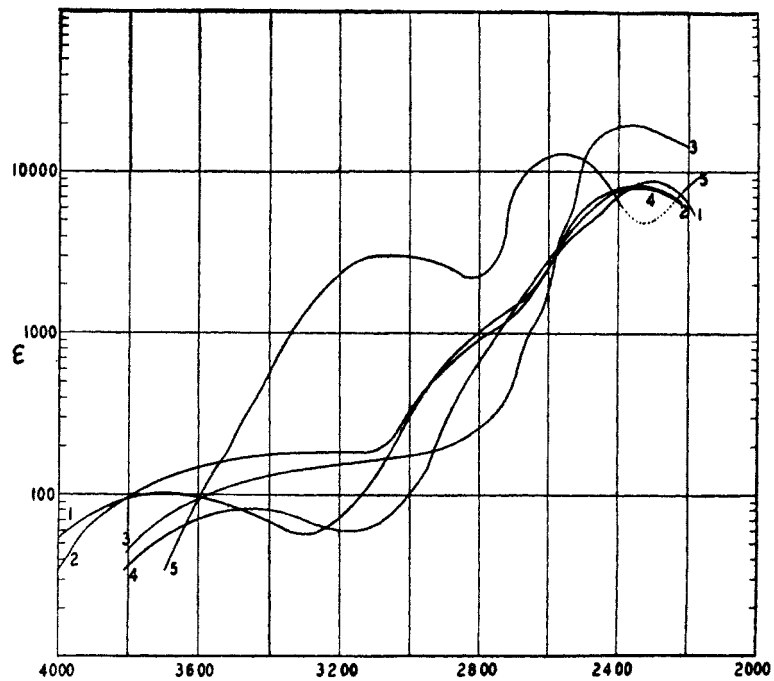


FIG. 3. ABSORPTION SPECTRA IN ETHANOL OF (1) IV, TABLE I, 0.00024 TO 0.0024 MOLAR; (2) V, TABLE I, 0.00016 TO 0.0016 MOLAR; (3) III, TABLE I, 0.00001 TO 0.005 MOLAR; (4) VII, TABLE IV, 0.00014 TO 0.0014 MOLAR; AND (5) X, TABLE IV, 0.0013–0.00284 MOLAR

served that the absorption due to the carbonyl group, maxima at 3110 Å and 3050 Å, is much more intense than in the 2-methylnaphthitadienediones. Indeed with some of the latter (III and V), and also the methoxy compound VI, carbonyl absorption was either absent or masked.

A comparison of the short wave length maxima of the two trione enols with the same maxima in the diketones shows that replacement of a 2-methyl group by a hydroxyl shifts the maximum about 200 Å to longer wave lengths while, as previously noted, replacement by a methoxyl group causes a still greater displacement of 340 Å. While this effect of a methoxyl group seems not to have been

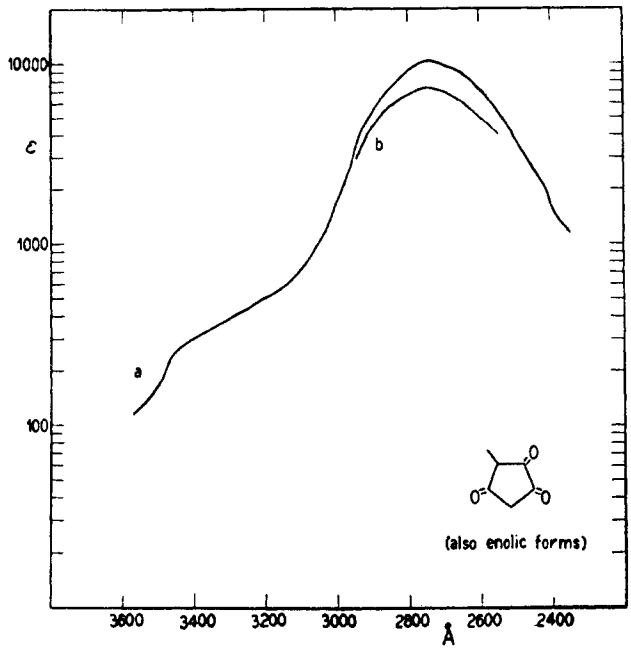


FIG. 4. ABSORPTION SPECTRUM OF 3-METHYLCYCLOPENTANE-1,2,4-TRIONE IN ETHANOL; (a) 0.00087 MOLAR, (b) 0.000087 MOLAR

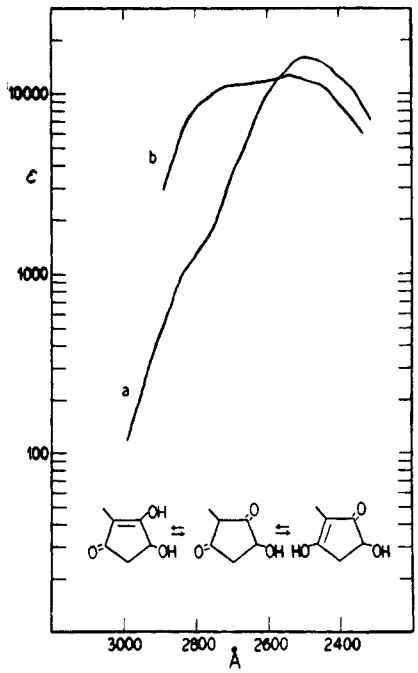


FIG. 5. ABSORPTION SPECTRUM OF 4-HYDROXY-2-METHYLCYCLOPENTANE-1,3-DIONE IN ETHANOL; (a) 0.00085 MOLAR, (b) 0.000085 MOLAR

observed before, the effect of the hydroxyl group has been observed and a number of examples have been brought together and discussed by Gillam *et al.* (7). Thus these investigators found that the monoketone, piperitone, shows the maximum 2355 Å, while α-hydroxypiperitone (diosphenol, an enolic 1,2-diketone) has its maximum at 2740 Å. It is perhaps significant that 3-methylcyclopentane-1,2,4-trione, VIII, and its hydrate (Table II) exhibit a maximum at 2750 Å.

CYCLANE-1,3-DIONES

Having in mind the lack of influence of the second carbonyl group in the naphthitadienediones upon the ultraviolet absorption, it occurred to us that the

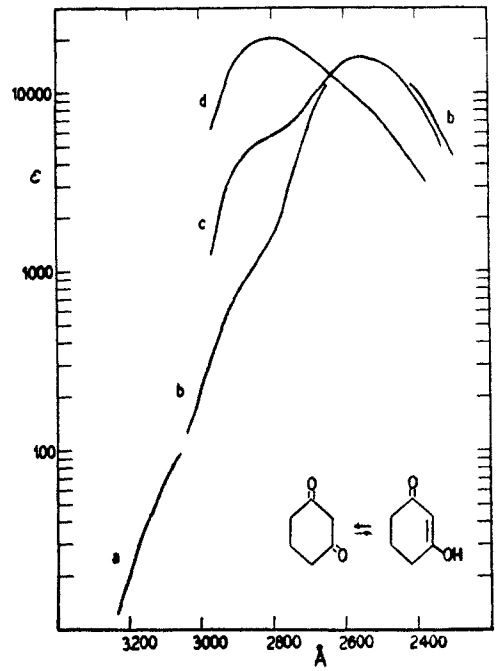


FIG. 6. ABSORPTION SPECTRUM OF CYCLOHEXANE-1,3-DIONE IN ETHANOL; (a) 0.0158 MOLAR, (b) 0.00158 MOLAR, (c) 0.000158 MOLAR, AND (d) 0.0000158 MOLAR

maxima exhibited by the naphthitenetrione enols might be largely due to the 1,3-dione (or β-hydroxyenone) part of their structures. Examination of some simple 1,3-diones has proved this idea to be correct, and has demonstrated some other interesting effects of alteration of structure upon absorption.

Cyclohexane-1,3-dione, XI, at the higher concentration in ethanol, exhibited a maximum at 2550 Å, which is almost identical with that found for the two naphthitenetriones. Woodward and Blout have recently (8) found a maximum at 2580 Å for 5,5-dimethylcyclohexane-1,3-dione. The usual effect of methyl substitution for hydrogen at an olefin carbon is seen in the maximum, at 2610 Å, shown by 2-methylcyclohexane-1,3-dione (XII). Next, passing from XII to its

analog in the cyclopentane series, XIII, we observe a shift in the maximum of 110 Å toward shorter wave lengths, a remarkable confirmation of the decrement of 110 Å found by Gillam and West (9) while studying monoketones of the cyclohexene and cyclopentene series.

The maximum found for 4-hydroxy-2-methylcyclopentane-1,3-dione, XIV, is very nearly the same as that of 2-methylcyclopentane-1,3-dione; at 2490 Å with the higher concentration in ethanol.

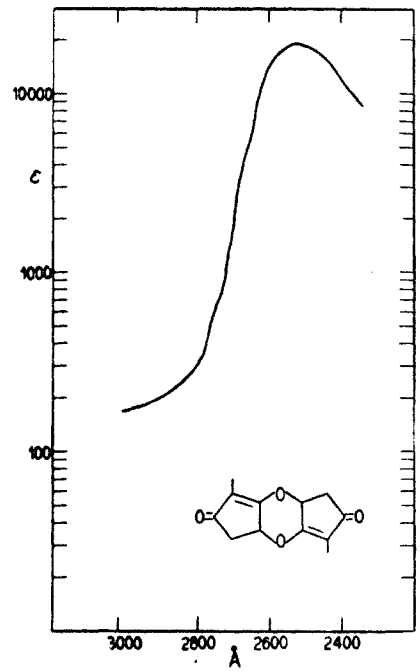


FIG. 7. ABSORPTION SPECTRUM OF XVI, TABLE IV, IN ETHANOL, 0.000119 TO 0.00119 MOLAR

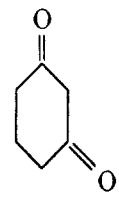
EFFECT OF CONCENTRATION UPON THE POSITION OF THE PRINCIPAL MAXIMUM IN ETHANOL SOLUTIONS OF CYCLANE-1,3-DIONES

It was with the hydroxy diketone, XIV, that we first observed a considerable shift in the position of the maximum on dilution. This is clearly seen from Fig. 5. Since this compound could exist in a great variety of tautomeric forms, three of which are shown in the figure, a change in the composition of the mixture of tautomers in solution was not surprising. We later found, however, that cyclohexane-1,3-dione behaves in the same way. Reference to Table III and Fig. 6 will show that ten-fold dilution results in a shift of the maximum from 2550 Å to 2800 Å, and the intensity of the latter is actually greater than that of the former. The more dilute solution perhaps contained a greater proportion of 1,3-cyclohexadiene-1,3-diol.

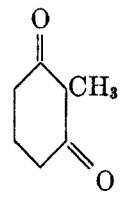
APPLICATION OF THE ULTRAVIOLET ABSORPTION DATA IN STRUCTURE ANALYSIS

From a group of possible intermediates in the synthesis of polycyclic compounds, we have selected four cases (Table IV) to illustrate the use of the new absorption data. The close relationship of diketone VII to diketones II, III, IV, and V, and of triketone X to triketone IX has already been indicated.

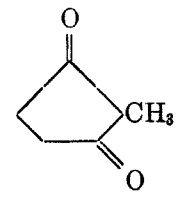
Reduction of the triketone IX gave a dihydro derivative (10) which might, from its method of preparation, be 2-hydroxy-5-methyl-7-naphthitene-1,4-dione (XVII). XVII is not an α, β-enone and no intense absorption in the ultraviolet



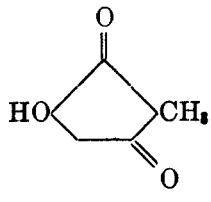
XI



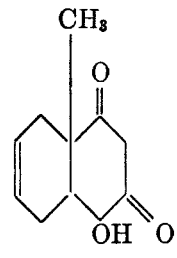
XII



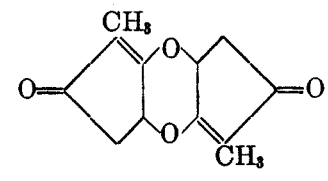
XIII



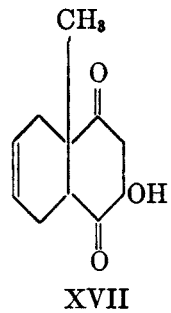
XIV



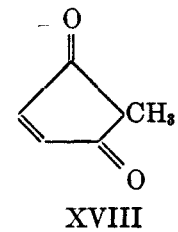
XV



XVI



XVII



XVIII

would be expected. The dihydro derivative obtained exhibited exactly the same maximum (XV, Table IV) as cyclohexane-1,3-dione and the triketones IX and X, and therefore cannot be XVII and is almost certainly a 1,3-diketooctalin. No derivatives of this compound have yet been made, but the absorption spectrum, taken with the observation that the compound is a strong acid, indicates it to be one of the diastereoisomeric 4-hydroxy-10-methyl-7-naphthitene-1,3-diones, XV.

Finally it was found that dehydration of 4-hydroxy-2-methylcyclopentane-1,3-dione, XIV, gave a beautiful crystalline compound which did not have the

chemical properties of the expected 4-methylcyclopentene-1,3-dione, XVIII. Cryoscopic examination showed the substance to be a dimer, which finding immediately posed the question of structure. Literature background suggested structure XVI, containing two chromophore systems very similar to cyclane-1,3-diones. The maximum found, at 2520 Å, is very similar to that exhibited by 2-methylcyclopentane-1,3-dione, and XVI appears more reasonable than two alternative structures (11) and is supported by the chemical evidence.

BELTSVILLE, MD.

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[CONTRIBUTION NO. 74 FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF UTAH]

ORGANOBORON-NITROGEN COMPOUNDS. III (1, 2). THE REACTIONS OF *p*-ANISIDINE, BENZYLAMINE, AND NITROBENZENE WITH BORON CHLORIDE

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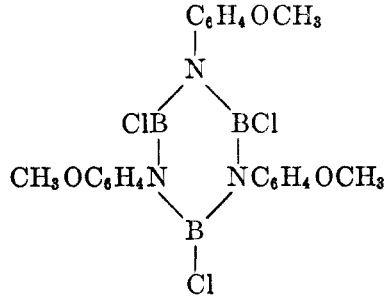
The study of organoboron-nitrogen compounds has been continued with *p*-anisidine and benzylamine. The former reacts with boron chloride as other aromatic amines have been found to react, but benzylamine shows certain differences in behavior. Surprisingly enough, nitrobenzene, although not an amine, reacts with boron chloride and the results of this work have been included.

The reaction of *p*-anisidine with boron chloride takes place readily, but the addition compound or salt formed easily loses hydrogen chloride, and difficulty was experienced in obtaining the pure compound by this method. The best procedure was to treat a cold suspension of *p*-anisidine hydrochloride in benzene with boron chloride. Under these conditions the boron chloride displaced the hydrogen chloride and the new salt was obtained pure (1).

$$CH_3OC_6H_4NH_2\cdot HCl + BCl_3 \rightarrow CH_3OC_6H_4NH_2\cdot BCl_3 + HCl$$

The salt loses two molecules of hydrogen chloride by heating in boiling benzene. The product is a trimer and was named tri-*p*-anisyltrichlorotriboron nitride. The cyclic structure below was assigned to the substance, following the practice established in the first paper (1).



The substance is hydrolyzed by cold water apparently to the corresponding hydroxyl derivative. With boiling water both compounds are completely hydrolyzed to anisidine and boric acid.

By heating boron chloride with an excess of *p*-anisidine, boric tri-*p*-anisidide is obtained.

$$BCl_3 + 6CH_3OC_6H_4NH_2 \rightarrow B(NHC_6H_4OCH_3)_3 + 3CH_3OC_6H_4NH_2\cdot HCl$$

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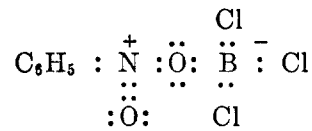
This substance is relatively air-stable, but is rapidly hydrolyzed by boiling water to boric acid and anisidine. The compound reacts with dry hydrogen chloride in cold benzene solution, forming a white precipitate. This appeared to be a mixture of anisidine boron chloride and anisidine hydrochloride formed by the following reaction.

$$B(NHC_6H_4OCH_3)_3 + 5HCl \rightarrow CH_3OC_6H_4NH_2 \cdot BCl_3 + 2CH_3OC_6H_4NH_2 \cdot HCl$$

Aliphatic amines react with boron chloride as well as aromatic amines, but difficulty has been experienced in isolating pure products. With benzylamine, however, more promising results were obtained. The reaction of this amine with boron chloride gave a good yield of the addition compound. The salt when heated lost two moles of hydrogen chloride in the usual way, but the expected trimeric product could not be isolated. Neither was it found possible to isolate boric tribenzylamide by the action of an excess of benzylamine on boron chloride. In view of these difficulties experienced with the aliphatic amines, it appears doubtful whether this method can be extended to include the preparation of the aliphatic boron-nitrogen compounds.

As a result of attempting to find a suitable solvent for certain organoboron-nitrogen compounds, it was observed that nitrobenzene forms an addition compound with boron chloride. Apparently aluminum chloride forms a similar compound with nitrobenzene (3), but such a derivative has not been reported with the boron halides, although a large variety of boron halide addition compounds are known. The new substance is well crystallized, but is low-melting. It decomposes into the original components slightly above the melting point. As might be expected it is extremely reactive and is rapidly decomposed by moisture in the air. Assuming that the boron chloride has formed a salt with an electron pair of the nitro group, the following structure is proposed.



EXPERIMENTAL

The salt of p-*anisidine and boron chloride,* $CH_3OC_6H_4NH_2 \cdot BCl_3$. Twelve grams (0.102 mole) of boron chloride was distilled into 100 g. of pure sodium-dried benzene contained in a 500-ml. two-necked flask equipped with a mercury-sealed stirrer and a dropping-funnel. The solution was stirred vigorously and cooled with an ice-bath while 9 g. (0.073 mole) of *p*-anisidine dissolved in 100 g. of benzene was dropped in during 1.5 hours. The contents of the dropping-funnel were protected by a calcium chloride tube. After the addition was complete, the cooling-bath was removed and the solution allowed to come to room temperature. A small quantity of solid had precipitated and the liquid had a pink color. About 10 minutes after filtering the solution crystallization set in, forming slightly pink plate-like crystals. These were filtered out, washed with dry benzene and with petroleum ether. After drying 15 minutes in a vacuum desiccator, the crystals were analyzed for boron and chlorine in the usual way by decomposition with water (1). This left a small white residue which resisted even boiling water. Consequently, the analyses were too low. The water-insoluble material appeared to be a mixture, possibly of the tri-*p*-anisyltrihydroxytriboron

nitride and boric tri-*p*-anisidide. It was not practicable to purify the substance by recrystallization because warming resulted in the loss of hydrogen chloride.

After considerable experimentation, the best method found for making the salt was by the displacement of hydrogen chloride from anisidine hydrochloride. Five grams (0.031 mole) of *p*-anisidine hydrochloride was suspended in 200 ml. of pure dry benzene. The mixture was cooled with an ice-bath and 16 g. (0.136 mole) of boron chloride distilled into the benzene during 30 minutes. The mixture was stirred cold for an hour then allowed to warm to room temperature. During this time the anisidine hydrochloride had been changed into small plate-like crystals. These were removed, washed with benzene and with petroleum ether, and dried in a vacuum desiccator. When treated with water no solid residue remained, as with the first preparation described, but a film of liquid was observed on the water. By heating the salt in a sulfuric acid-bath at 120° for 5 minutes a colorless liquid distilled out, which was condensed and was identified as benzene by nitration and identification of dinitrobenzene by mixed melting point. A sample of the salt weighing 0.4398 g. lost 0.0646 g. of benzene which showed that the salt contains 0.5 molecule of benzene of crystallization. Taking this information into consideration the following analytical data were obtained.

Anal. Calc'd for $C_7H_9BCl_2NO \cdot 0.5C_6H_6$: B, 3.87; Cl, 38.07.
Found: B, 3.86, 3.88, 3.91; Cl, 37.74, 37.35, 37.83.

The salt softened at 105° and melted at 108°, when heated slowly. Above 112°, gas was evolved. When heated rapidly the salt softened at 105° as before but suddenly melted with gas evolution at 110°. The substance could not be recrystallized from boiling benzene because of decomposition. The gas evolved was shown to be hydrogen chloride containing no boron chloride. On heating 0.1219 mole of the salt, 0.247 mole of HCl was obtained, which shows that two moles of hydrogen chloride were evolved per mole of salt.

Tri-p-*anisyltrichlorotriboron nitride*, $(CH_3OC_6H_4NBCl)_3$. A 3.4-g. (0.014 mole) sample of the salt of anisidine and boron chloride was heated in 100 g. of boiling benzene until no more hydrogen chloride was evolved. This required a total of 18 hours. The solution was concentrated to 50 ml. and allowed to cool. The product crystallized in small cubic crystals having a slight yellow color. At times, a jell formed from which crystals could not be obtained. The crystalline product was washed with benzene and petroleum ether, then dried in a vacuum desiccator. This compound, also, was found to crystallize with benzene of crystallization. An 0.8954-g. sample lost 0.1230 g. of benzene when heated. The molecular weight in freezing benzene was found to be 570, showing the trimeric nature of the substance. Using this information, the analytical data obtained compare with the theoretical as follows:

Anal. Calc'd for $(C_7H_7BClNO)_3 \cdot C_6H_6$: B, 5.60; Cl, 18.29; Mol. wt., 580.
Found: B, 5.67, 5.60; Cl, 18.36, 18.46; Mol. wt., 570.

The compound melted in a sealed capillary tube at 229–235° with the evolution of gas and formed a dark red liquid. A sample of the substance placed in cold water was changed in crystalline form, and chloride ion was detected in the water. The product melted at 95–115°. The only method found for purifying the substance was to dissolve it in the minimum of cold alcohol followed by dilution with water. This resulted in a large loss of material, but raised the melting point to 112–120°. When warmed with benzene or alcohol the compound dissolved, but no products were isolated, indicating further decomposition.

This instability was further demonstrated during the preparation of one sample which suddenly decomposed a short time after being filtered from the water. In this case the products were anisidine and boric acid, showing that complete hydrolysis had occurred. The crude compound was found to contain 6.6% boron as compared with the calculated value of 7.1% for the trihydroxide, $(CH_3OC_6H_4NBOH)_3$.

Boric tri-p-*anisidide*, $(CH_3OC_6H_4NH)_3B$. An ice-cold solution of 11 g. (0.094 mole) of boron chloride in 100 g. of dry benzene was placed in a 500-ml. two-necked flask and stirred while 60 g. (0.48 mole) of *p*-anisidine dissolved in 100 g. of dry benzene was slowly added over a period of two hours. At first a large amount of heat was liberated as the amine

entered the boron chloride solution, and a white precipitate formed which rapidly redissolved. Soon a permanent precipitate remained which increased in amount as the reaction progressed. After all of the amine had been added the ice-bath was replaced by an oil-bath heated to 120° and the mixture refluxed for 6 hours. The stirring was continued to minimize bumping. The mixture was filtered rapidly while hot and the solid residue extracted with two 75-ml. portions of boiling benzene. The benzene solution was concentrated to 100 ml. and allowed to cool to room temperature. Upon seeding the solution, crystallization proceeded smoothly. A 45% yield of pure cubic crystals was obtained, based upon the boron chloride used. The mother liquor yielded more of the product, but of less purity. The pure compound gave tests for boron and nitrogen, but not for chlorine.

Anal. Calc'd for $(CH_3OC_6H_4NH)_3B$: B, 2.86. Found: B, 2.83, 2.87, 2.87.

The melting point of boric tri-*p*-anisidide was found to be 124°. On cooling, the melt did not solidify, indicating decomposition. The compound when kept in a desiccator slowly decomposed, liberating crystals of anisidine which sublimed on to the container walls. It is not clear whether sufficient moisture was available in the air in the desiccator for hydrolysis, or whether the decomposition proceeded with the formation of a boric imide, but either reaction would account for the formation of anisidine.

$$(CH_3OC_6H_4NH)_3B + HOH \rightarrow (CH_3OC_6H_4NH)_2BOH + CH_3OC_6H_4NH_2$$

$$(CH_3OC_6H_4NH)_3B \rightarrow CH_3OC_6H_4NHB = NC_6H_4OCH_3 + CH_3OC_6H_4NH_2$$

Boric trianisidide in benzene solution reacted readily with dry hydrogen chloride, forming a white precipitate. The hydrogen chloride was absorbed quite completely at first, but more slowly as the reaction progressed. In one experiment the gas was passed into the solution for 10 hours. The product was washed with dry benzene and with dry petroleum ether. It gave qualitative tests for boron, nitrogen, and chlorine. When placed in water a part of the material reacted violently, behaving like the addition salt of anisidine and boron chloride. The remainder of the material dissolved more slowly and behaved like anisidine hydrochloride.

The salt of benzylamine and boron chloride, $C_6H_5CH_2NH_2 \cdot BCl_3$. Nine grams (0.084 mole) of benzylamine dissolved in 100 ml. of dry benzene was slowly added to 13.5 g. (0.115 mole) of boron chloride dissolved in 150 ml. of dry benzene contained in a 500-ml. two-necked flask cooled in ice. The mixture was stirred vigorously throughout the addition to minimize local excess of amine. A white precipitate began to form immediately and increased in quantity as the reaction progressed. The product was filtered rapidly in a current of dry air, washed with dry benzene and stored under dry benzene. The yield was 85% based on the amount of amine used.

Attempts to recrystallize the substance failed. When warmed with dry benzene, decomposition set in at 38° and only a small amount of product dissolved below that temperature. By using the dilute solutions indicated above, the product was sufficiently pure to give the analytical data following. Because of the basicity of benzylamine it was found necessary to distill out the amine with steam before titrating the boric acid. The chloride ion was determined gravimetrically as silver chloride.

Anal. Calc'd for $C_6H_5CH_2NH_2BCl_3$: B, 4.82; Cl, 47.44.
Found: B, 4.79, 4.55, 4.799; Cl, 47.60, 47.65, 48.30.

Benzylamine-boron chloride melted in a sealed tube at 166–167° to a colorless liquid which solidified at 158° and remelted again at 166–167°. This was repeated three times, indicating that the substance is unusually stable, considering its behavior in benzene solution. Above 185° gas was evolved and the material darkened. When heated with dry benzene, 0.00595 mole of the compound required 0.01157 equivalent of base to neutralize the hydrogen chloride evolved. This demonstrated that two moles of hydrogen chloride are evolved per mole of salt.

On concentrating the benzene solution, the expected trimer $(C_6H_5CH_2NBCl)_3$ was not obtained. A small quantity of needles crystallized out, which on standing soon changed to

small plates. These contained too little boron and too much chlorine to be any simple derivative that might be expected.

Anal. Found: B, 3.42, 3.45; Cl, 28.77, 29.86.

Because of the small yield of this product nothing further was done with it. Further concentration of the benzene mother liquor failed to yield any additional crystalline material.

Reaction of an excess of benzylamine on boron chloride. In an attempt to prepare boric tribenzylamide, 10 g. (0.085 mole) of boron chloride dissolved in 100 ml. of dry benzene was treated with 55 g. (0.0514 mole) of benzylamine dissolved in 100 ml. of dry benzene. The reaction flask was cooled with ice during the addition of the amine and stirred constantly. A precipitate formed which was probably the salt of the amine and boron chloride. After all of the amine had been added, the mixture was refluxed for as long as 18 hours, in an attempt to complete the reaction. The mixture was filtered hot, and the precipitate extracted with several small portions of boiling benzene. The residue gave qualitative tests for chlorine and nitrogen, but not for boron. The melting point was 255°, which is the melting point of pure benzylamine hydrochloride. These data indicate that the desired reaction was complete.

The benzene solutions were concentrated to 150 ml., and after several days one gram of crystals was filtered out. This material was recrystallized from benzene, and melted sharply at 145°. On cooling and remelting, the melting point was again 145°. The substance gave a qualitative test for nitrogen, but not for boron or chlorine. The compound was insoluble in water, dilute acid or base, but soluble in concentrated sulfuric acid. The molecular weight was 250. These data were insufficient to identify the substance and since it was not the compound desired, additional work on it was discontinued. Further concentration of the benzene solution left an oily residue from which no pure compound could be crystallized or extracted.

The reaction was also carried out in boiling xylene. In this experiment none of the substance melting at 145° was obtained. The product was a yellow-brown glass from which no pure substance could be obtained. Qualitative tests for boron, nitrogen, and chlorine were obtained on the material.

The salt of nitrobenzene and boron chloride, $C_6H_5NO_2 \cdot BCl_3$. A 47.5-g. (0.386 mole) sample of pure freshly distilled nitrobenzene was placed in a 125-ml. Erlenmeyer flask and cooled in an ice-bath. The flask was fitted with a stopper bearing a tube which reached nearly to the surface of the nitrobenzene. The tube was connected to a source of boron chloride and 11.5 g. (0.098 mole) was distilled into the nitrobenzene. At this point the flask was shaken slightly and the entire mass solidified. On warming to room temperature a portion of the material liquefied leaving a mat of fine yellow needles.

The product was extremely sensitive to the air, and was liquefied on two or three minutes exposure. Consequently, no attempt was made to determine the yield or to recrystallize it. The substance gave a positive test for boron, nitrogen, and chlorine. For analysis the crystals were filtered rapidly with suction and washed with dry petroleum ether. The crystals were dried *in vacuo* by inserting a stopper in the funnel and applying suction. The substance was then hurriedly weighed into dried weighing-bottles and decomposed with water.

Anal. Cal'd for $C_6H_5BCl_3NO_2$: B, 4.50; Cl, 44.26.
Found: B, 5.33, 7.10; Cl, 40.2, 39.2.

The salt melted at 45–47° in a sealed tube to a clear yellow liquid. On cooling and remelting, the melting point was again 45–47°. On heating to 50.5° bubbles appeared indicating dissociation of the salt. The compound was decomposed violently by water, producing nitrobenzene, boric acid, and hydrogen chloride. A similar reaction was also observed with ethanol.

SUMMARY

1. The salt of *p*-anisidine and boron chloride has been prepared. When heated it lost two molecules of hydrogen chloride and formed tri-*p*-anisyltrichlorotri-

boron nitride. This substance reacted with cold water to form the corresponding hydroxyl derivative.

2. Boric tri-*p*-anisidide has been prepared.

3. The salt of benzylamine and boron chloride has been obtained. This salt lost two moles of hydrogen chloride, but no other product could be isolated.

4. Boron chloride was found to combine with nitrobenzene forming a low-melting substance. This is believed to be a salt of boron chloride with an electron pair in the nitro group.

SALT LAKE CITY, UTAH

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[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THE REACTION OF ANISOLE WITH 1,1,1-TRICHLORO-2-METHYL-2-PROPENE

CHARLES C. PRICE AND HOWARD D. MARSHALL

Received July 22, 1943

The correlation of the effect of groups in orienting substitution in the benzene ring and addition to the olefinic double bond has been pointed out by Robinson (1). Those groups which orient *ortho-para* in benzene, direct addition according to Markownikoff's rule; those groups which orient *meta* in benzene, direct addition in opposition to Markownikoff's rule.

The report of Kharasch, Rossin, and Fields (2) that 1,1,1,2-tetrachloropropane (II) is formed by addition of hydrogen chloride to 1,1,1-trichloro-2-propene (I) appears to be one of the few exceptions to this generalization. In view of

$$\underset{\text{I}}{Cl_3CCH{=}CH_2} + HCl \longrightarrow \underset{\text{II}}{Cl_3CCHClCH_3}$$

the difficulty with which this olefin reacted with hydrogen halides, we have continued a similar investigation which was in progress at the time the work of Kharasch, Rossin, and Fields was published.

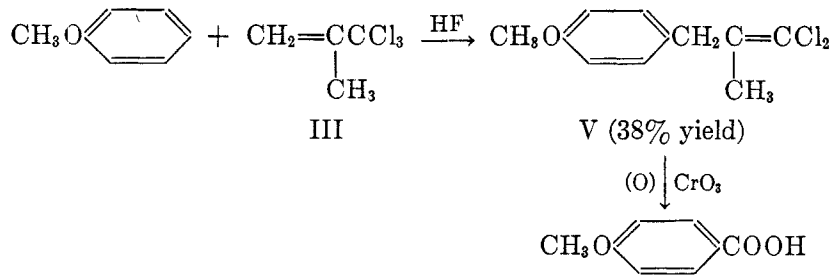
The homologous olefin, 1,1,1-trichloro-2-methyl-2-propene (III) (3), has shown the same remarkable resistance to any characteristic addition reaction at the double bond.

$$Cl_3C\overset{\overset{OH}{|}}{\underset{\underset{CH_3}{|}}{C}}CH_3 \xrightarrow[\text{quinoline}]{P_2O_5} \underset{\text{III}}{Cl_3CC{=}CH_2}\ (\underset{CH_3}{|})$$

The trichloroisobutylene (III) was resistant to attack by bromine and by potassium permanganate and did not dissolve in concentrated sulfuric acid. The addition of hydrogen chloride or bromide was not practicable because of the ease with which this olefin undergoes an allylic rearrangement (3).

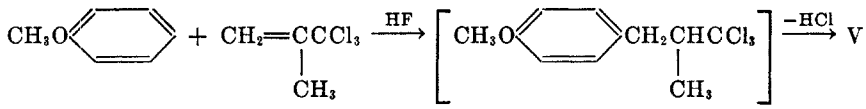
$$\underset{\text{III}}{Cl_3CC{=}CH_2}\ (\underset{CH_3}{|}) \xrightarrow{H^+} \underset{\text{IV}}{Cl_2C{=}CCH_2Cl}\ (\underset{CH_3}{|})$$

The reaction of anisole with the trichloroisobutylene (III), using hydrogen fluoride as a catalyst, proceeded smoothly. On the basis of analysis, oxidation to *p*-anisic acid, and chemical properties, the product has been assigned the structure of 1,1-dichloro-2-methyl-3-*p*-anisyl-1-propene (V).

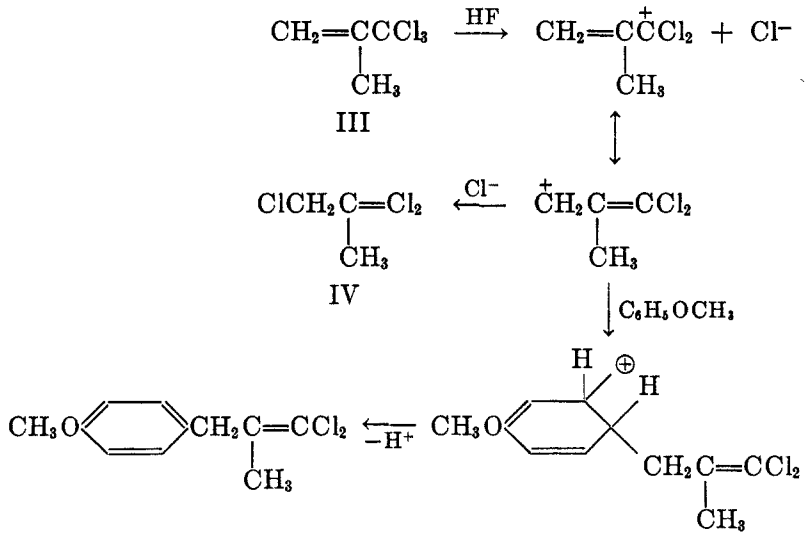


Compound V gave no precipitate when heated in alcoholic silver nitrate solution and was attacked by bromine in carbon tetrachloride and by permanganate only very slowly.

The allylic rearrangement product of III, isomer IV, formed from III in hydrogen fluoride, was found to give only very small yields (less than 5%) of V when treated with anisole and hydrogen fluoride under the same conditions. The formation of V from III may therefore be interpreted as a direct addition of anisole to the double bond of III in opposition to Markownikoff's rule. This addition product will yield V by loss of hydrogen chloride.



An alternative explanation which cannot be disregarded involves the possibility of the dissociation of III to give a resonating ion common to both the allylic rearrangement and the Friedel-Crafts reaction.



It has been pointed out by Hughes (4) that ionization of this sort is favored by accumulation of chlorine in the similarly-situated trichloromethyl group of benzotrichloride.

EXPERIMENTAL

Dehydration of chloretone hydrate. The chloretone used was obtained from Eastman Kodak Company, and was in the form of the monohydrate. The water of hydration was removed by dissolving the compound in a moderate excess of either benzene or ether, and drying with solid potassium carbonate. The benzene (or ether) was then distilled, and the anhydrous chloretone left was allowed to solidify, or was distilled. It usually melted at 95–96°. Distillation of the chloretone did not seem to offer any particular advantages.

Dehydration of chloretone. Twenty-one grams of anhydrous chloretone was dissolved in 29 cc. of quinoline (2 moles)[1] in a 500-cc. round-bottomed flask fitted with a delivery tube and a water-cooled condenser set downward for distillation. Fifty-two grams of phosphorus pentoxide[2] was added and mixed well with the quinoline solution. The flask was placed in an oil-bath at a temperature between 135° and 145°. The oil-bath was heated rapidly to 155°. The contents of the flask swelled, filled the flask completely, and sometimes even the delivery tube. The swelling helped to sweep over the distillate, which consisted of a mixture of trichloroisobutylene (III), the allylic rearrangement product (IV), α-chloroisobutyryl chloride,[3] and unreacted chloretone. The dehydration reaction required five to ten minutes. Under these conditions, 4 to 5 cc. of distillate, sometimes blue-colored, was obtained; this corresponds to 30 to 35% of the theoretical yield of trichloroisobutylene (III). The distillates of several runs were combined and washed with dilute, aqueous potassium carbonate until all the α-chloroisobutyryl chloride was hydrolyzed and neutralized. The product was then dried with solid potassium carbonate, and fractionated under diminished pressure. The main fraction distilled at 42–44° (29–30 mm.), and the second (small and sometimes negligible) distilled at 62–64° (29–30 mm.). Any residue is presumably unchanged chloretone.

Larger yields of distillate have been obtained by using somewhat larger quantities of starting materials. For example, 25 g. of chloretone, 60 g. of phosphorus pentoxide, and 34 cc. of quinoline gave a 43% yield. On being heated rapidly, however, these larger quantities may stop up the delivery tube, and cause a minor explosion. It is believed that larger yields of trichloroisobutylene could be obtained if the swelling of the reaction mixture could be reduced appreciably, or eliminated. Undoubtedly, a large portion of trichloroisobutylene simply remains in the flask, and is entrapped in the hard, insoluble residue.

Allylic rearrangement of trichloroisobutylene (III) (6). Approximately 10 cc. of trichloroisobutylene was added to 5 g. of phosphorus pentachloride in a 200-cc. round-bottomed flask fitted with a water-cooled condenser and a calcium chloride drying tube. After heating on a steam-bath for four hours, the reaction mixture was poured into cold, dilute potassium carbonate solution to hydrolyze and neutralize the phosphorus pentachloride. The organic material was separated, dissolved in ether, washed with water, and distilled under atmospheric pressure. About 8 cc. (80%) of material boiling at 153–156° was obtained. After redistillation, it boiled at 154–157°; n_D^{20} 1.4965; d_4^{20} 1.332. The constants reported by Jacob (3) were: b.p. 155°; n_D^{20} 1.497; d_4^{20} 1.335.

Reaction of anisole and trichloroisobutylene (III) in the presence of hydrogen fluoride. Trichloroisobutylene (5.5 g.) was mixed with 5.5 g. of anisole (1.5 equivalents), and approximately 40 cc. of hydrogen fluoride in a copper beaker cooled in an ice-bath. The mixture was mechanically stirred with a piece of bent copper wire, and was allowed to stand overnight. It was poured into about 60 cc. of water, made slightly alkaline with potassium

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[1] By using two moles of organic base, rather than one equivalent of dimethylaniline (3), much less allylic rearrangement occurred during the dehydration.

[2] Merck's phosphorus pentoxide was used, principally because it was much more dense than several other brands available. It was more easily handled and gave much more satisfactory results.

[3] Less than 5% of the distillate was α-chloroisobutyryl chloride. Its presence was established by treating unwashed distillate with aniline. The melting point of the α-chloroisobutyranilide (m.p. 69.5–70.5°) agreed with that reported by Kharasch and Brown (5).

carbonate, and extracted with two 40-cc. portions of ether, which yielded six grams of material after the ether was distilled. On distillation, 3.0 g. (38%) of 1,1-dichloro-2-methyl-3-*p*-anisyl-1-propene (V) was obtained as a somewhat yellow liquid which boiled at 124–126° (4 mm.); n_D^{20} 1.5518. It had a characteristic, pleasant odor. An analytical sample had the following properties: n_D^{20} 1.5504; d_4^{20} 1.210.

Anal. Calc'd for $C_{11}H_{12}Cl_2O$: C, 57.16; H, 5.23; M_D^{20}, 60.30.
Found: C, 57.50; H, 5.20; M_D^{20}, 60.90.

Chromic acid oxidation of V. The calculated amount of chromic acid (1.00 g.) dissolved in about 10 cc. of glacial acetic acid, was added to 1.73 g. of (III) dissolved in about 10 cc. of glacial acetic acid. The mixture was heated at about 70° for about twelve hours, at 95–100° for about thirty hours, and then boiled under reflux for four hours. During this time, about 5 cc. of acetic acid was added to replace that lost by evaporation. At the conclusion of the refluxing, the red color of chromic acid was only faintly visible by transmitted light. The mixture was poured into 100 cc. of water, and extracted with three 40-cc. portions of ether. The ether extract was washed with two 40-cc. portions of water, and then dilute potassium carbonate. The potassium carbonate solution yielded, on acidification, *p*-anisic acid (about 0.1 g.), m.p. 180–182°, corr.

Reaction of anisole and the allylic rearrangement isomer (IV) in the presence of hydrogen fluoride. Three separate runs were carried out with the allylic isomer (IV). The experimental procedure was the same as that with trichloroisobutylene (III), except that the samples were all slightly larger: 8.5 g., 6.5 g., and 6.0 g. The yields of V were, respectively, 0.5 g., 0.5 g., and 0.2 g., all less than 6% of the theoretical yield. The 6.0-g. sample was the most carefully purified. The other samples might have contained up to 10% of trichloroisobutylene (III).

Reaction of trichloroisobutylene (III) and hydrogen fluoride. Fifteen grams of trichloroisobutylene (III) was mixed with about 30 cc. of hydrogen fluoride in a copper beaker cooled in an ice-bath, and mechanically stirred with a piece of bent copper wire for about four hours. At first, the reaction mixture turned yellow, but the color disappeared after a short while. Usually the hydrogen fluoride fumes precluded observation of the reaction.

The reaction mixture was poured into ice-water and the hydrofluoric acid was neutralized with a slight excess of potassium carbonate. After standing overnight, the organic liquid was taken up in ether, and dried with solid potassium carbonate. The ether was distilled off and the residue fractionated. About 4.5 cc. of material was obtained in two fractions, with refractive indices of 1.4972 and 1.4986, and specific gravities of 1.333 and 1.336. This corresponds to a 40% yield of allylic rearrangement product. About 2 cc. of a third fraction, evidently a dimer or trimer, was obtained; b.p. 109–113° (3 mm.), n_D^{20} 1.5354.

SUMMARY

The double bond of 1,1,1-trichloro-2-methyl-2-propene is remarkably inert. This olefin is not attacked by bromine in carbon tetrachloride or by aqueous potassium permanganate and is insoluble in concentrated sulfuric acid.

It reacts readily with anisole in the presence of hydrogen fluoride to yield 1,1-dichloro-2-methyl-3-*p*-anisyl-1-propene.

URBANA, ILL.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, FACULTAD DE CIENCIAS EXACTAS, FÍSICAS Y NATURALES, UNIVERSITY OF BUENOS AIRES]

HYDRAZIDES OF DIPHENIC AND 4-NITRODIPHENIC ACIDS AND SOME OF THEIR REACTIONS

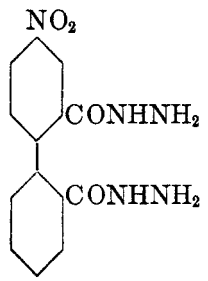
R. A. LABRIOLA AND A. FELITTE

Received July 24, 1943

The preparation and study of the diphenic acid hydrazides began comparatively recently. Kalb and Gross (1) obtained the dihydrazide; one of the present authors (2) obtained the monohydrazide and the secondary hydrazide.

Application of the Curtius degradation to the di- and mono-hydrazides was described in a recent work (3). The dihydrazide yielded 2,2′-diphenyleneurea and 2,2′-diaminobiphenyl. The monohydrazide, degraded in alcohol, produces phenanthridone; in alcoholic hydrogen chloride, N-carbethoxyphenanthridone. Similar reactions and preparations have now been carried out on 4-nitrodiphenic acid.

By the action of hydrogen peroxide on 2-nitrophenanthraquinone, an extension of the method of Chapman (4) for phenanthraquinone, 4-nitrodiphenic acid was obtained, which was converted to the dimethyl ester and anhydride. By the action of hydrazine on these derivatives, the dihydrazide (I) and the monohydrazide (II) were obtained. The amount of monohydrazide (II) which is obtained varies between 81–90% of the theoretical; the other isomer could not be isolated from the mother liquors.



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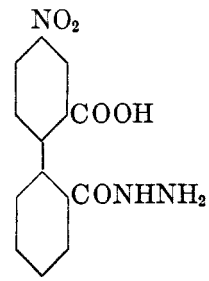
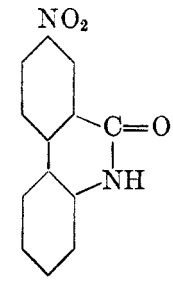
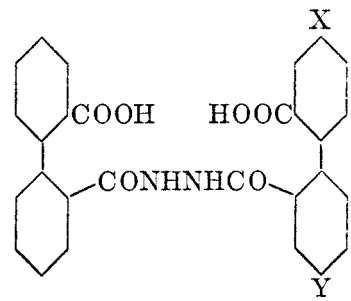


II



III



IV: X = H; Y = H
V: X = NO_2; Y = H
VI: X = H; Y = NO_2

By the action of ammonia, Moore and Huntress (5) obtained from 4-dinitrodiphenic anhydride the two amides, that corresponding to the hydrazide (II) in 23% yield, and the isomer in 32% yield.

The structure (I) of the hydrazide obtained by us was determined by degradation with nitrous acid. It produced the same phenanthridone (III) derivative that is formed by the Hofmann degradation of the structurally analogous amide obtained by Moore and Huntress. When heated *in vacuo*, this hydrazide is transformed into a high-melting isomer which may be N-amino-4-nitrodiphenimide.

When the diphenic acid monohydrazide is treated with diphenic anhydride, a symmetrically disubstituted hydrazine is formed which is also a dibasic acid (IV); this substance is also formed in small amount in the preparation of diphenic monohydrazide. The structure of this compound was confirmed by obtaining the dimethyl ester and by determination of the carboxyl and hydrazide groups. A similar substance is formed by the action of 4-nitrodiphenic anhydride, but in this case the two isomers (V) and (VI) are obtained in yields of 18–20%, respectively. The structure of isomer (V) turns out to be the same as that obtained by the action of diphenic anhydride on 4-nitrodiphenic hydrazide (II).

Acetic anhydride reacts readily with these disubstituted hydrazides (IV; V; VI) eliminating from them two molecules of water with the production of crystalline substances of very high melting point, which are insoluble in almost all solvents. If, instead of the free acid (IV), the methyl ester is treated with acetic anhydride, this reaction does not occur, and a monoacetyl derivative is obtained.

Stollé (6) found that treatment of the N,N′ disubstituted hydrazines with dehydrating agents led to formation of cyclic oxadiazoles, and we think that a similar reaction prevails here with the simultaneous formation of the anhydride of the dibasic acid. Most of the oxadiazoles prepared by Stollé were very resistant to the action of alkali. Our preparations hydrolyze relatively easily, yielding the original diphenic acids.

EXPERIMENTAL

4-Nitrodiphenic acid. A sample of 6 g. of 2-nitrophenanthraquinone, 50 cc. of acetic acid, and 50 cc. of hydrogen peroxide (20 volumes strength) was refluxed for 3 hours. The reaction mixture was made alkaline with sodium hydroxide, a small precipitate was filtered off, and the mixture was acidified to Congo red, precipitating 4-nitrodiphenic acid, which melted at 250°; yield 75–80%.

Dimethyl 4-nitrodiphenate. A sample of 2 g. of the acid was dissolved in cold methanol saturated with anhydrous hydrogen chloride. After standing 24 hours, the mixture was concentrated to half its volume, precipitating the diester. Following recrystallization from ethanol, the melting point was 96°; yield 90%.

Anal. Calc'd for $C_{16}H_{13}NO_6$: C, 60.95; H, 4.12.
Found: C, 60.81; H, 4.55.

4-Nitrodiphendihydrazide (I). A sample of 0.85 g. of the diester and 1 cc. of hydrazine monohydrate in 10 cc. of absolute ethanol was heated under reflux for 4 hours. The dihydrazide was precipitated by concentration of the reaction mixture. The melting point following recrystallization from ethanol was 209°; yield 45%. It is soluble in hydrochloric acid, and reduces silver nitrate.

Anal. Calc'd for $C_{14}H_{13}N_5O_4$: C, 53.33; H, 4.12; N, 22.22.
Found: C, 53.60; H, 4.36; N, 21.80.

Monohydrazide of 4-nitrodiphenic acid (II). A sample of 1 g. of 4-nitrodiphenic anhydride was treated with 1 cc. of 50% hydrazine hydrate, with chilling. Following the addition, the mixture was heated on the steam-bath for an hour. The solution was thrown into water and, with vigorous stirring, the monohydrazide was precipitated with diluted (1:2) hydrochloric acid. The precipitate was filtered off and recrystallized from ethanol, melting at 200°; yield 81–90%. It dissolves in alkalies, carbonates and bicarbonates, and likewise in acids when they are in slight excess.

Anal. Calc'd for $C_{14}H_{11}N_3O_5$: C, 55.81; H, 3.65; N, 13.95.
Found: C, 55.98; H, 3.94; N, 14.26.

Curtius degradation of 4-nitrodiphenmonohydrazide (II) to 7-nitrophenanthridone (III). A sample of 0.8 g. of the monohydrazide was dissolved in 10 cc. of 10% hydrochloric acid and the solution was covered with ether. The solution was chilled with ice and 5 cc. of 10% sodium nitrite solution was then introduced. The precipitate of azide readily passed into the ether layer on shaking. The aqueous layer was then separated and the ether thrown into dilute ethanol. The azide decomposed spontaneously and, on concentration, yellow needles of 7-nitrophenanthridone were obtained. After recrystallization from acetic acid or sublimation, it melted at 290° (Moore and Huntress: 284–285°).

Anal. Calc'd for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.53; N, 11.83.
Found: C, 65.01; H, 3.62; N, 11.87.

N-Amino-4-nitrodiphenimide. A sample of 1 g. of the nitrodiphenic acid monohydrazide was placed in a large test tube and heated *in vacuo* to 200°. A $CaCl_2$ tube absorbed the moisture given off. At the outset there was an active decomposition which ended in a short while. The mixture was cooled and the precipitate digested with alcohol. It was filtered and recrystallized from acetic acid, melting at 319°; yield 50%.

Anal. Calc'd for $C_{14}H_9N_3O_4$: C, 59.36; H, 3.18; N, 14.84.
Found: C, 59.47; H, 3.17; N, 14.87.

N,N'-bis-[o*(2-carboxyphenyl)benzoyl]hydrazine (IV).* A sample of 2 g. of diphenic acid monohydrazide and 1.76 g. of diphenic anhydride in 20 cc. of absolute ethanol was heated under reflux for two hours. On chilling, the di-acid precipitated. It was filtered and, by evaporation of the mother liquor, a new fraction was obtained. On recrystallization from alcohol it formed hexagonal prisms or plates which melted at 253° with decomposition; yield 75–80%. The same product was obtained as an insoluble residue in the preparation of the diphenic hydrazide by the method described by Labriola (2).

Anal. Calc'd for $C_{28}H_{20}N_2O_6$: C, 70.00; H, 4.16; N, 5.83.
Found: C, 70.20; H, 4.35; N, 5.90.

Anal. Calc'd for $C_{26}H_{18}N_2O_2(CO_2H)_2$: two equivalents 448.
Found: 438, 424.

Determination of nitrogen in N,N'-bis-[o*(2-carboxyphenyl)benzoyl]hydrazine (IV).* A sample of 158.6 mg. of di-acid was dissolved in 10 cc. of 40% KOH in a closed apparatus connected with an azotometer. Air was first eliminated from the apparatus with a strong current of CO_2, and then 6 cc. of saturated aqueous potassium ferricyanide was run in. The nitrogen evolved was collected and the reaction mixture was heated gently and acidified with sulfuric acid. The nitrogen was then displaced in a current of CO_2 until constant volume was reached. A volume of 8 cc. (27°/760 mm.) was obtained.

Anal. Calc'd for $C_{14}H_{10}O_3$-NH-NH-$C_{14}H_{10}O_3$: N, 5.83.
Found: N, 5.75, 6.24.

N,N'-bis-[o-*(2-carbomethoxyphenyl)benzoyl]hydrazine.* A sample of 5 g. of (IV) was dissolved in methanol and saturated with hydrogen chloride. After 24 hours a precipitate was obtained; purified from ethanol, m.p. 182°; yield 83%.

Anal. Calc'd for $C_{30}H_{24}N_2O_6$: C, 70.86; H, 4.72; N, 5.51.
Found: C, 70.99; H, 4.90; N, 5.50.

The saponification of the diester produces the original acid.

N-[o-*(2-carboxyphenyl)benzoyl]-N'-*[o-*(2-carboxy-4-nitrophenyl)benzoyl]hydrazine (V) and*

N-[o-(*2-carboxyphenyl*)*benzoyl*]-*N'*-[*2*-(*2'-carboxyphenyl*)-*5-nitrobenzoyl*]*hydrazine* (*VI*). A sample of 2 g. of 4-nitrodiphenic anhydride and 1.9 g. of the appropriate monohydrazide in 25 cc. of absolute ethanol was refluxed for 2 hours. On chilling, the isomer of m.p. 261° came out, and the m.p. was unchanged by subsequent recrystallizations; yield 0.7 g. (18%). On concentration of the alcoholic solution, the other isomer precipitated, and after successive recrystallizations reached the m.p. 252°; yield, 0.8 g. (20%).

A sample of 0.5 g. of 4-nitrodiphenic acid monohydrazide and 0.38 g. of the diphenic anhydride was heated with reflux for two hours. On concentrating and chilling, the crystals of the hydrazide came out, m.p. 261° after recrystallization from ethanol. On mixture with the isomer of the same m.p. previously obtained, no depression of the m.p. was observed.

Anal. Calc'd for $C_{28}H_{19}N_3O_8$: C, 64.00; H, 3.61; N, 8.00.
Found, isomer of m.p. 261°: C, 64.12; H, 3.81; N, 8.18.
Found, isomer of m.p. 252°: C, 64.40; H, 4.04; N, 8.01.

"Oxadiazole" derivatives of the N,N' disubstituted hydrazines. Oxadiazole(*A*). A sample of 10 g. of (IV) was boiled for 15–20 minutes with acetic anhydride. It dissolved, but soon formed a rather heavy precipitate. It was filtered off, washed repeatedly with hot alcohol and a portion was recrystallized from nitrobenzene, yielding prisms melting at 400°; yield 95%.

Anal. Calc'd for $C_{28}H_{16}N_2O_4$: C, 75.67; H, 3.60; N, 6.30.
Found: C, 75.67; H, 3.84; N, 6.16.

Oxadiazole (B). This compound was prepared similarly from V. Rectangular plates were formed which melted at 351°.

Anal. Calc'd for $C_{28}H_{15}N_3O_6$: C, 68.71; H, 3.06; N, 8.58.
Found: C, 68.67; H, 3.40; N, 8.75.

Oxadiazole (C). This compound was prepared from VI in the form of small plates which melted at 360°.

Anal. Calc'd for $C_{28}H_{15}N_3O_6$: C, 68.71; H, 3.06; N, 8.58.
Found: C, 68.77; H, 3.29; N, 8.71.

These oxadiazoles do not possess acetyl groups. All of the above described oxadiazoles heated with an excess of 10% alcoholic KOH for 30 minutes are converted into the original acids (mixed m.p.).

Acetylation of N,N'-bis-[o-(*2-carbomethoxyphenyl*)*benzoyl*]*hydrazine*. A sample of 2 g. of the di-ester was boiled for 4 hours with an excess of acetic anhydride. The excess was evaporated off and the residue crystallized from alcohol, m.p. 141–142°; yield 1.3 g.

Anal. Calc'd for $C_{32}H_{26}N_2O_7$: C, 69.81; H, 4.72; N, 5.09; CH_3CO, 7.81.
Found: C, 69.98; H, 4.74; N, 5.07; CH_3CO, 7.78.

SUMMARY

The hydrazides of 4-nitrodiphenic acid were prepared and the structure of the single monohydrazide obtained was determined.

N,N'-bis-[o-(2-carboxyphenyl)benzoyl]hydrazines were prepared from the substituted diphenic acids and it was shown that treatment with acetic anhydride removes water, forming products that may be oxadiazoles.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

THE REDUCTION OF NITROPARAFFINS IN LIQUID AMMONIA

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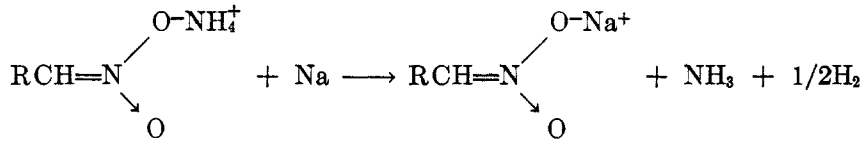
As a part of an extensive investigation of the reduction of organic nitro compounds in liquid ammonia (1), we have studied the behavior of nitroethane, 1-nitropropane, 2-nitropropane, 1-nitrobutane, and 2-nitrobutane toward (a) liquid ammonia, (b) hydrogen generated by the addition of sodium to liquid ammonia solutions of ammonium bromide, and (c) liquid ammonia solutions of sodium.

It has been found that these nitroparaffins dissolve in and react with anhydrous liquid ammonia at $-33.5°$ to form relatively unstable ammonium salts of the type $R—CH=N(\rightarrow O)O^-NH_4^+$. All of these salts are white crystalline solids which decompose slowly with liberation of ammonia. Qualitatively, the decreasing order of stability of the corresponding *ammonium salts* was found to be: 2-nitropropane > 2-nitrobutane > 1-nitropropane > 1-nitrobutane > nitroethane.

The formation of metal salts by the aci forms of the nitroparaffins is well known (2, 3, 4) and the existence of ammonium salts has been suggested (5). In 1905, Franklin and Kraus (6) reported the isolation of compounds which they represented by the formulas $CH_3NO_2 \cdot NH_3$, $CH_3NO_2 \cdot 2NH_3$, $CH(NO_2)_3 \cdot NH_3$, and $C(NO_2)_4 \cdot NH_3$. The composition of the first of these compounds was established by deammonation of the second, that of the second and third was determined from the weight of ammonia retained when a known weight of nitro compound was exposed to liquid ammonia, while the ammonia content of "trinitromethane ammonia" (6) was determined volumetrically.

When sodium is added to liquid ammonia solutions containing a nitroparaffin together with an excess of ammonium bromide, the quantity of hydrogen liberated is found to be almost exactly equivalent to the quantity of sodium added. Removal of the solvent and decomposition of the ammonium salts results in recovery of the nitroparaffins.

Addition of sodium to solutions of these nitroparaffins in liquid ammonia results in liberation of hydrogen, the formation of white precipitates (probably the sodium salts), and after addition of ammonium bromide, the isolation of the corresponding alkylhydroxylamines, solutions of which readily reduce ammoniacal silver nitrate at room temperature.



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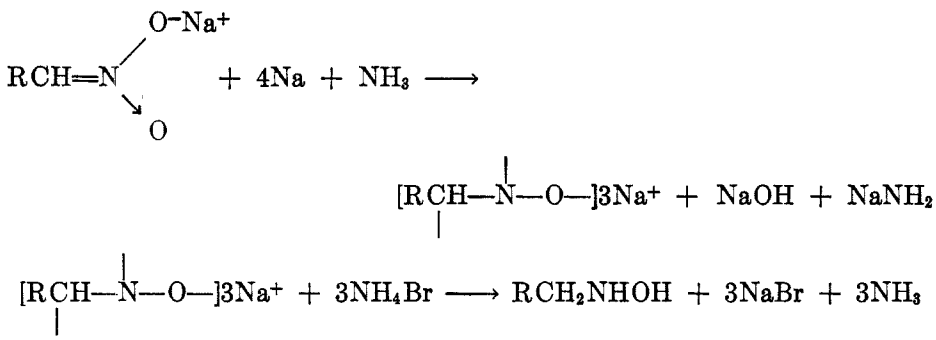

The yields of hydroxylamines are low due to slow and incomplete reduction and to difficulties encountered in the separation of small quantities of these products from relatively large quantities of inorganic salts. No success attended efforts to isolate reduction products other than the substituted hydroxylamines. The reaction ratios reported below provide an indication of the extent of reduction in each case.

In connection with the isolation of alkylhydroxylamines as their condensation products with *p*-nitrobenzaldehyde, it was found that these derivatives must be prepared *under anhydrous conditions*. In the presence of water, they are hydrolyzed to the oxime of *p*-nitrobenzaldehyde and the corresponding alcohols.

The reduction of nitroparaffins to the corresponding hydroxylamines has been accomplished previously by means of a rather wide variety of reducing agents. Since these reactions have been reviewed recently by Hass and Riley (7), it seems unnecessary to give further details here. On a comparative basis, however, it is significant that reduction by sodium in liquid ammonia at its boiling temperature provides the same degree of reduction as is realized through the use of other reducing systems at much higher temperatures.

EXPERIMENTAL

Materials. The nitropropanes and nitrobutanes were generously supplied by The Commercial Solvents Corporation. Nitroethane was obtained from the Eastman Kodak Company. All other materials were prepared as described by Knowles and Watt (8).

Methods. All reactions in liquid ammonia were conducted as described previously (8).

Formation of ammonium salts. A sample of each pure nitroparaffin was added to a large excess of pure anhydrous liquid ammonia at −33.5°, in which all of the ammonium salts were soluble. After complete removal of the solvent, the white crystalline ammonium salts were subjected to such analyses as were possible in view of the instability of the products. In each case, spontaneous or induced decomposition resulted in liberation of ammonia and regeneration of the nitroparaffin. The ammonium salts of nitroethane and 1-nitrobutane were so unstable that reproducible analytical data could not be obtained. Data relative to the other salts are given below.

1-Nitropropane: Anal. Calc'd for $C_3H_6NO_2^-NH_4^+$: NH_4^+, 16.97. Found: NH_4^+, 16.70.

2-Nitropropane: Anal. Calc'd for $C_3H_6NO_2^-NH_4^+$: NH_4^+, 16.97; N, 26.40. Found: NH_4^+, 16.85; N, 26.61.

2-Nitrobutane: Anal. Calc'd for $C_4H_8NO_2^-NH_4^+$: NH_4^+, 14.98. Found: NH_4^+, 14.78.

Reduction by hydrogen. Failure of any of these compounds to react with hydrogen is illustrated by the following example. Upon addition of 4.90 g. (0.2133 gram-atom) of sodium to a liquid ammonia solution containing 3.00 g. (0.0337 gram-mole) of 2-nitropropane

together with an excess of ammonium bromide, 0.2128 gram-atom of hydrogen was collected. After evaporation of the solvent and decomposition of the ammonium salt, the 2-nitropropane was recovered.

Reduction by sodium. Nitroethane. Small pieces of sodium (2.29 g. or 0.0995 gram-atom) were added slowly to a liquid ammonia solution of 3.06 g. (0.0408 gram-mole) of nitroethane. Hydrogen was evolved during the addition of sodium and a white solid separated from the solution. After the first appearance of the blue color characteristic of a liquid ammonia solution of sodium, a slight excess of sodium was added and the reaction mixture was stirred for one-half hour, during which there was no further visible evidence of reaction. The excess sodium was then destroyed by addition of an excess of ammonium bromide. From these data and the fact that a total of 0.0225 gram-atom of hydrogen was collected, the reaction ratio (8) was found to be 1.88. After removal of the solvent, the organic reaction product was extracted into anhydrous ether, treated with dry hydrogen chloride, and the resulting viscous insoluble product was separated, dissolved in absolute ethanol and treated with a solution of *p*-nitrobenzaldehyde in absolute ethanol in the presence of solid sodium hydrogen carbonate. After twelve hours, the reaction mixture was filtered, the filtrate was evaporated to dryness, and the residue was recrystallized from ethyl ether to provide pale yellow crystals of the condensation product (9) of ethylhydroxylamine and *p*-nitrobenzaldehyde, m.p. 122–123° cor.

Anal. Calc'd for $C_9H_{10}N_2O_3$: N, 14.43. Found: N, 14.35.

The ethylhydroxylamine hydrochloride from another reaction (in which the reaction ratio was 1.90) was dissolved in 95% ethanol and treated with an *aqueous* ethanolic solution containing *p*-nitrobenzaldehyde and sodium hydrogen carbonate. After twelve hours, dilution with water and cooling provided a white crystalline solid which was recrystallized from aqueous ethanol. The resulting product melted at 128–129° cor. and no depression in melting temperature was observed when this material was mixed with an authentic specimen of the oxime of *p*-nitrobenzaldehyde, m.p. 128–129° cor.

Anal. Calc'd for $C_7H_6N_2O_3$: N, 16.86. Found: N, 16.75.

A small sample of the condensation product of ethylhydroxylamine and *p*-nitrobenzaldehyde was prepared under anhydrous conditions and thereafter suspended in hot water for one hour. After filtration and cooling, the oxime of *p*-nitrobenzaldehyde crystallized and the solution gave a positive test for alcohol (formation of iodoform).

In this and in each of the cases described below, solutions of the substituted hydroxylamines (liberated from their hydrochlorides) readily reduced ammoniacal silver nitrate at room temperature.

1-Nitropropane. In the manner described above, 3.97 g. (0.0446 gram-mole) of 1-nitropropane was reduced by 2.80 g. (0.1217 gram-atom) of sodium. Hydrogen was evolved during the reduction reaction and a total of 0.0448 gram-atom of hydrogen was collected. Hence, the reaction ratio was 1.72. The product, *n*-propylhydroxylamine, was separated as described above and converted to the *p*-nitrobenzaldehyde condensation product, m.p. 77–78° cor.

Anal. Calc'd for $C_{10}H_{12}N_2O_3$: N, 13.45. Found: N, 13.55.

2-Nitropropane. In a similar manner, 4.73 g. (0.0532 gram-mole) of 2-nitropropane was reduced by 4.69 g. (0.2040 gram-atom) of sodium. Hydrogen was not evolved during the primary reduction reaction but 0.0743 gram-atom of hydrogen was collected when unreacted sodium was destroyed by addition of ammonium bromide. The reaction ratio was 2.44. The isopropylhydroxylamine was extracted into absolute ether, from which it was isolated as the hydrochloride (10).

Anal. Calc'd for $C_3H_9NO \cdot HCl$: HCl, 32.71. Found: HCl, 32.75.

1-Nitrobutane. Hydrogen was evolved and a white precipitate appeared during the reduction of 3.60 g. (0.0349 gram-mole) of 1-nitrobutane by means of 6.94 g. (0.3018 gram-atom) of sodium. Since 0.1770 gram-atom of hydrogen was collected, the reaction ratio was 3.56. By the methods already described, the substituted hydroxylamine was separated and converted to the hydrochloride (an oil) which was then dissolved in ethanol and treated

with chloroplatinic acid. The resulting yellow chloroplatinate was recrystallized from aqueous methanol.

Anal. Calc'd for $(C_4H_{11}NO)_2 \cdot H_2PtCl_6$: N, 4.76; Pt, 33.20.
Found: N, 4.77; Pt, 33.35.

2-Nitrobutane. Reduction of 3.87 g. (0.0375 gram-mole) of 2-nitrobutane by 3.38 g. (0.1470 gram-atom) of sodium occurred without liberation of hydrogen. However, 0.0201 gram-atom of hydrogen was collected when unreacted sodium was destroyed by addition of excess ammonium bromide. Hence, the reaction ratio was 3.48. The substituted hydroxylamine was separated and converted to its condensation product with *p*-nitrobenzaldehyde in the manner described for nitroethane. After recrystallization from petroleum ether, this product melted at 80–81° cor.

Anal. Calc'd for $C_{11}H_{14}N_2O_3$: N, 12.61. Found: N, 12.50.

Hydrolysis of this condensation product gave the oxime of *p*-nitrobenzaldehyde and a positive iodoform test.

SUMMARY

1. Five nitroparaffins have been shown to react with anhydrous liquid ammonia at −33.5° to form white crystalline and rather unstable ammonium salts of the type, $R—CH{=}N(\rightarrow O)O^-NH_4^+$. The decreasing order of stability of these salts is: 2-nitropropane > 2-nitrobutane > 1-nitropropane > 1-nitrobutane > nitroethane.

2. These nitroparaffins are not reduced by hydrogen generated by the addition of sodium to liquid ammonia solutions (at −33.5°) containing ammonium bromide.

3. Reduction of these nitroparaffins by liquid ammonia solutions of sodium at −33.5° has been found to be slow and incomplete and to yield the corresponding alkylhydroxylamines.

4. The condensation products of alkylhydroxylamines and *p*-nitrobenzaldehyde have been shown to undergo hydrolysis to the oxime of *p*-nitrobenzaldehyde and the corresponding alcohols.

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[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION,
TENNESSEE EASTMAN CORPORATION]

IMPROVED SYNTHESES OF QUINALDINES AND 3-ALKYL QUINOLINES

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Although quinaldine and other 2-methylquinolines have been prepared in a number of ways, the only methods in general use at present are modifications of the original Doebner-v. Miller method (1, 2). This method comprises heating aldol, ethylene glycol, paraldehyde, or lactic acid with a primary aromatic amine in the presence of a mineral acid (usually hydrochloric), and of an oxidizing agent, such as nitrobenzene, in some instances. The original method has been somewhat improved by a modification in which paraldehyde, a primary aromatic amine, conc'd hydrochloric acid, and anhydrous zinc chloride are refluxed together (3, 4). All of these methods give relatively large amounts of undesirable by-products (unchanged and N-alkylated amines, tetrahydroquinaldines, etc.) whose removal is tedious and often wasteful.

Of the various quinolines substituted with one alkyl group in the pyridine ring, those with such a group in the 3-position have been studied the least, and only a comparatively few 3-alkyl quinolines have been prepared and described. The classical Friedlaender synthesis, recently reviewed in detail (5), is generally applicable, but depends upon difficultly obtainable aromatic *o*-amino carbonyl compounds, such as *o*-aminobenzaldehyde, as starting materials. 3-Methylquinoline has been obtained in small yield as a by-product in the synthesis of 2-ethyl-3-methylquinoline from a mixture of aniline, propionaldehyde, formaldehyde, and hydrochloric acid (6). Some α-methylacrolein was probably formed as an intermediate in the reaction (7). In more recent times several 3-alkyl quinolines have been prepared by a Skraup type synthesis using α,γ-diethyl ethers of β-alkyl glycerols as the source of the hetero ring carbon chain (8). 3,8-Dimethylquinoline has been prepared in poor yield by application of the Doebner-v.Miller method to a mixture of *o*-toluidine, propionaldehyde, and the dimethyl acetal of formaldehyde (9).

It has been found in this laboratory that crotonaldehyde, α-methylacrolein and α-ethylacrolein, and their diesters may be reacted with equimolar quantities of primary aromatic amines, using a modified Skraup synthesis, to give fairly good yields of the corresponding quinaldines, and 3-methyl- and 3-ethyl-quinolines. Skraup originally employed crotonaldehyde in a quinaldine synthesis but thought that the product obtained was lepidine (10); a similar synthesis employing crotonaldehyde has been disclosed in the patent literature (11). Since the completion of the work in this laboratory, in 1941, some similar reactions employing α-methylacrolein and its dimethyl acetal have been disclosed (4).

Virtually all of the earlier methods reviewed above, especially those relating to 3-alkyl quinolines, have been impractical because of poor yields or relative inaccessibility of the necessary intermediates, or have been tedious due to the

necessity of purifying the product from several chemically similar by-products present in significant amounts.

In the present procedure, the crotonaldehyde or α-alkyl acrolein, or a diester of one of these, was slowly run into a stirred mixture of sulfuric acid, oxidizing agent, and primary aromatic amine at such a temperature and rate that the reaction did not become too violent. Water (and organic acid if a diester had been used) was distilled out through a short stillhead equipped with a variable reflux device. Mixtures containing the aldehyde diesters required higher temperatures and longer times of heating than did mixtures containing the free aldehydes. The reaction mixture was partially cooled, poured onto ice, and made alkaline; the crude alkyl quinoline was then worked up in a customary way, usually by steam distillation and fractionation of the organic layer of the distillate.

In practice it was found that the use of α-methylacrolein diesters was preferable to the use of α-methylacrolein itself, due to apparent polymerization of a part of the latter compound under the conditions of the reaction. This resulted in a lower yield of the 3-methylquinoline. However, crotonaldehyde and α-ethylacrolein gave approximately equal yields of quinolines from given primary aromatic amines as did their diesters. In these cases, the use of the free aldehydes was preferable because of lower cost, shorter reaction time, and lower reaction temperature, compared to reactions utilizing the aldehyde diesters. The α-alkyl acroleins employed were prepared in this laboratory by the vapor-phase reaction of formaldehyde with higher aliphatic aldehydes (12).

Good yields in these syntheses, as in other modifications of the Skraup reaction, depend on the use of a suitable oxidizing agent. An especially useful one is nitrobenzenesulfonic acid prepared in sulfuric acid solution. Arsenic acid was an alternative oxidizing agent used in syntheses with nitroanilines. The procedure employing nitrobenzenesulfonic acid possessed several advantages in comparison with previous methods of 2- or 3-alkyl quinoline syntheses. The quinaldine or 3-alkyl quinoline was much less contaminated by by-products than are the products from the usual Skraup or Doebner-v.Miller syntheses, and could be isolated in a satisfactory degree of purity by fractionation alone. Only one steam distillation was necessary. The amounts of unchanged and N-alkylated anilines and of alkyl tetrahydroquinolines which were present were so small that the usual diazotization procedure could be omitted. In addition, yields from this improved method were somewhat better than earlier yields, particularly with substituted anilines.

One run with α-ethylacrolein and aniline was made, using the zinc chloride modification of the Doebner-v.Miller method (3). The yield of 3-ethylquinoline was quite poor, compared with that obtained from the modified Skraup reaction described below.

The various alkyl quinolines prepared are listed according to method of preparation, reactants, and yields in Table I. A number of the 3-alkyl quinolines were characterized by physical properties, picrates, and ethiodides (Table II). Analyses of the ethiodides served to confirm the formulas of the parent quinoline

TABLE I

ALKYL QUINOLINES AND YIELDS

-QUINOLINE	METHOD	AMINE REACTANT	ACROLEIN REACTANT	YIELD, %
2-Methyl	B	Aniline	Crotonaldehyde	43
2-Methyl	A	Aniline	Crotonaldehyde diacetate	49.5
2,7-Dimethyl[a]	A	*m*-Toluidine	Crotonaldehyde diacetate	47
2,7-Dimethyl	B	*m*-Toluidine	Crotonaldehyde	62.5
2-Methyl-7-chloro[a]	B	*m*-Chloroaniline	Crotonaldehyde	60
2-Methyl-6-chloro	A	*p*-Chloroaniline	Crotonaldehyde diacetate	55
2,6-Dimethyl	A	*p*-Toluidine	Crotonaldehyde dipropionate	49
2-Methyl-6-nitro	D	*p*-Nitroaniline	Crotonaldehyde diacetate	30
3-Methyl	A	Aniline	α-Methylacrolein diacetate	49
3-Methyl	A	Aniline	α-Methylacrolein dipropionate	46
3-Methyl	B	Aniline	α-Methylacrolein	30
3-Ethyl	A	Aniline	α-Ethylacrolein diacetate	54
3-Ethyl	B	Aniline	α-Ethylacrolein	42
3-Ethyl	C	Aniline	α-Ethylacrolein	2.5
3,6-Dimethyl	A	*p*-Toluidine	α-Methylacrolein diacetate	54
3,7-Dimethyl[a]	A	*m*-Toluidine	α-Methylacrolein diacetate	65
3,7-Dimethyl	B	*m*-Toluidine	α-Methylacrolein	25
3,8-Dimethyl	A	*o*-Toluidine	α-Methylacrolein diacetate	45
3-Methyl-6-nitro	D	*p*-Nitroaniline	α-Methylacrolein dipropionate	35
3-Methyl-7-chloro[a]	A	*m*-Chloroaniline	α-Methylacrolein diacetate	52
3-Ethyl-6-methyl	A	*p*-Toluidine	α-Ethylacrolein diacetate	32
3-Ethyl-7-methyl[a]	A	*m*-Toluidine	α-Ethylacrolein diacetate	34
3-Ethyl-7-methyl[a]	B	*m*-Toluidine	α-Ethylacrolein	35

[a] Yields given for these products include the small quantities of 3,5-isomers present.

TABLE II

PROPERTIES OF 3-ALKYL QUINOLINES[a,b]

-QUINOLINE	B.P., °C	M.P., °C	n_D^{20}	d_{20}^{20}	PICRATE M.P., °C	ETHIODIDE M.P., °C	IODINE ANALYSES OF ETHIODIDES	
							Calc'd	Fd.
3-Methyl	252–253	—	1.6160	1.0688	187.5	226.5	42.4	41.9
3-Ethyl	265–266	—	1.5988	1.0526	199	215	40.5	40.2
3,6-Dimethyl	270–271.5	56.5	—	—	251	181	40.5	40.3
3,7-Dimethyl	270–271.5	78.5	—	—	240.5	250	40.5	40.2
3,8-Dimethyl	260–262	—	1.6063	1.0524	208.5	192	40.5	40.1
3-Methyl-7-chloro	142–144 at 10 mm.	84.5	—	—	187.5	270	38.1	37.8
3-Methyl-6-nitro[c]	—	151	—	—	200	—	—	—
3-Ethyl-6-methyl	284–285.5	—	1.5955	1.0298	247	204	38.8	38.3
3-Ethyl-7-methyl	282–283	—	1.5947	1.0304	224.5	180	38.8	38.4

[a] Values given for b.p. are not corrected; m.p. values are corrected.

[b] A dash marked in a space indicates the value was not determined (for example, m.p.'s of substances which were liquids at room temperature).

[c] This quinoline was not converted to the ethiodide. Calc'd for $C_{10}H_8N_2O_2$: N, 14.9. Found: N, 14.9.

bases. Physical properties of the various quinaldines prepared were in good agreement with literature values.

In these syntheses of the Skraup type, 2,7- and 3,7-dimethylquinolines were the chief products from the reactions of crotonaldehyde and of *alpha*-methylacrolein, respectively, with *m*-toluidine. This same result, and the proof of structure of the 5- and 7-methylquinolines arising from such syntheses have already been demonstrated in an earlier publication (4). By analogy, it is probable that the reactions of *alpha*-ethylacrolein with *m*-toluidine, and of crotonaldehyde and *alpha*-methylacrolein with *m*-chloroaniline also led chiefly to 7-substituted quinolines, and the products have been so designated in the tables.

Acknowledgment is due to Mr. D. C. Sievers for performing the analytical work recorded in Table II, and to Mr. W. E. King, Jr., for technical assistance.

EXPERIMENTAL

Preparation of oxidizing agent. Nitrobenzene (1970 g., 16.0 moles) was sulfonated by running it into 20% oleum (8800 g.) at 20–30°, and then heating the mixture, with stirring, to 60–70° over a period of approximately three hours. The mixture was maintained at this temperature for an additional six to eight hours until a sample was completely soluble in water. This mixture of nitrobenzenesulfonic acid and sulfuric acid is termed the "sulfo mix" in the following descriptions of experiments.

Method A. Aniline and α-ethylacrolein diacetate. Sulfo mix (202 g., containing 0.3 mole of nitrobenzenesulfonic acid) was poured into water (50 ml.) in a one-liter three-neck flask, equipped with a short stillhead and variable length finger condenser, dropping-funnel, thermometer, and stainless steel sweep stirrer. This diluted the sulfuric acid to a concentration of 75%. With stirring, aniline (47 g., 0.5 mole) was added; the aniline sulfate soon dissolved in the acid mixture.

The whole was heated to 125° in an oil-bath, and α-ethylacrolein diacetate (93 g., 0.5 mole) was added dropwise with stirring; the addition was momentarily stopped if the reaction became too violent. Both during and after the addition of the acrolein diester, the mixture was heated and stirred (stirring was momentarily stopped if excessive foaming occurred); meanwhile, the finger condenser was gradually moved up, so that a slow, steady distillation of water and acetic acid took place. In about three hours' time the oil-bath temperature had been allowed to rise to 175°; about 50 ml. of distillate had come over, and distillation had almost ceased. The reaction mixture was partially cooled, poured onto about 500 g. of ice, and neutralized with conc'd sodium hydroxide solution. The crude product was removed by steam distillation, preferably with super-heated steam. The 3-ethylquinoline was separated from the distillate, with the aid of carbon tetrachloride extraction. Fractionation of the solvent-quinoline mixture gave pure 3-ethylquinoline (42.5 g., 54%).

Method B. Aniline and α-ethylacrolein. Sulfo mix (202 g.), water (50 ml.), and aniline (47 g.) were mixed as in method A above. The mixture was heated with stirring to about 100°. α-Ethylacrolein (40 g., 0.475 mole) was run in dropwise, the addition being regulated to prevent too violent a reaction, and the temperature being held at 105–110°. After all of the α-ethylacrolein was added, the whole was stirred and heated for 30–40 minutes, during which time water distilled off. The maximum temperature reached was 135°. The mixture was worked up as before to give pure 3-ethylquinoline (31 g., 42%).

Method C. Aniline and α-ethylacrolein, Doebner-v. Miller method. To a well stirred mixture of aniline (186 g.) and conc'd hydrochloric acid (600 ml.), set in an ice-salt bath, α-ethylacrolein (170 g.) was added dropwise. Anhydrous zinc chloride (150 g.) was added, and the mixture was refluxed in an oil-bath (130°) for five hours. It was then neutralized

with conc'd sodium hydroxide solution and steam distilled. Most of the organic material present was a heavy tar which was not volatile with steam. The organic layer in the distillate was separated and taken through a diazotization procedure to remove the primary and secondary amines present. Steam distillation of the suspension resulting from treatment of the diazotized mixture with excess alkali gave only a small amount of organic layer. This upon separation and distillation gave 3-ethylquinoline (8 g., 2.5%).

Method D. p-*Nitroaniline and α-methylacrolein dipropionate.* α-Methylacrolein dipropionate (200 g., 1.15 mole) was added slowly, using the same apparatus as described in method A, to a hot stirred mixture of arsenic pentoxide (138 g., 0.6 mole), water (50 ml.), *p*-nitroaniline (138 g., 1.0 mole), and conc'd sulfuric acid (280 g.). The reaction was carried out as in previous examples. Neutralization of the reaction mixture gave a dark granular precipitate. The latter was dissolved in dilute hydrochloric acid, warmed with charcoal, filtered and chilled, and taken through a diazotization procedure to remove unreacted *p*-nitroaniline. The filtrate from this treatment, upon neutralization with ammonium hydroxide solution, gave crude 3-methyl-6-nitroquinoline (132 g., 70%) as a dull brown colored solid. Recrystallization from methanol and then from ethanol with aid of charcoal gave the product as light cream colored needles in about half the yield of crude material (35% over-all).

Other alkyl quinoline syntheses. Using methods A, B, and D, some other 3-alkyl quinolines and a number of quinaldines were prepared from primary aromatic amines and α-alkyl acroleins, crotonaldehyde, or their diesters. In all cases, the same relative amounts of reactants were employed as given in the above methods. These reactions are summarized in Table I. Physical properties and analyses of the 3-alkyl quinolines are listed in Table II.

These alkyl quinolines were colorless when freshly distilled, but on standing, especially if exposed to light, quickly became yellow or brown in color, and absorbed moisture from the air. The picrates were bright yellow crystalline solids when recrystallized from alcohol. The ethiodides were dull yellow to bright yellow crystalline solids.

SUMMARY

1. Various 2-methyl-, 3-methyl-, and 3-ethyl-quinolines have been prepared by the reaction of crotonaldehyde, α-methylacrolein, and α-ethylacrolein, respectively, with primary aromatic amines in the presence of sulfuric acid and nitrobenzene sulfonic acid. The diesters of the unsaturated aldehydes may be employed in place of the free aldehydes.

2. These reactions appear suitable for practical syntheses because of their simplicity, improved yields, and ease of isolation of product, compared with most of the preparations of corresponding quinolines described in the previous literature.

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[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY, BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY, AGRICULTURAL RESEARCH ADMINISTRATION, UNITED STATES DEPARTMENT OF AGRICULTURE]

GLYCIDYL ESTERS OF ALIPHATIC ACIDS

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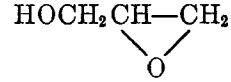
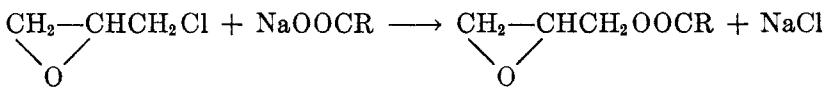
In the course of recent investigations of substitutes for phthalic esters and cresyl phosphates as plasticizers for vinyl resins and cellulose esters,[1] several series of aliphatic esters were prepared and characterized, among which is a group of compounds derived from the α,β-inner ether of glycerol commonly known as glycidol:



Although chemical literature contains many studies of glycerides, only a few simple esters of glycidol have been described. Zetsche and Aeschlimann (2) have reported the esterification of glycidol with acid chlorides by means of caustic soda to yield the benzoate and the stearate. Rider (3) heated glycidol several hours with acetyl chloride and obtained monochlorohydrin diacetate. As reported by Whitby (4), epichlorohydrin and acid chlorides react to form the β-esters of α,α'-glycerol dichlorohydrin. Glycidyl nitrate has been prepared by abstraction of hydrogen chloride from glyceryl monochlorohydrin mononitrate (5, 6, 7). Several esters have been made by the reaction of epichlorohydrin with alkali salts or soaps: the acetate (8, 9), the behenolate and stearolate (10), and glycidyl methyl phosphate (11). The last mentioned method was employed to synthesize various new aliphatic esters of glycidol in the investigation here described. Epichlorohydrin is now a commerically available product manufactured from propylene. It reacts readily with anhydrous soaps at reflux temperature according to the equation:



Levene and Walti (9) have stated that the reaction of epichlorohydrin and potassium acetate produces compounds other than glycidyl acetate, and they have identified diacetin, diacetylglyceryl-glycidol ether, and triacetyldiglyceryl-glycidol ether, among other high-molecular-weight compounds in the reaction product. Although these investigators specifically state that dry reagents were used, it is doubtful that all traces of moisture were eliminated, because 8 g. of diacetin, which contains a free hydroxyl group, was actually isolated, indicating the presence of about 0.8 g. or about 0.2% of water in the reactants. In the preparation of glycidyl esters of fatty acids, it has been our experience that carefully dried neutral soaps and epichlorohydrin result in high yields of the

[1] A report on the testing of new compounds at this Laboratory has been made by Elam, Preusser, and Page (1).

simple esters, whereas with imperfectly dried reagents the yields of these products are greatly lowered and those of the high-boiling by-products proportionately increased. Little if any simple ester of glycidol forms when soaps in aqueous solution are heated with epichlorohydrin.

Glycidol and glycidyl esters are known to polymerize in the presence of acidic catalysts such as stannic chloride (12). Levene and Walti (13) have studied the polymerization of glycidyl acetate at 135–140°. Here again the presence of water is indicated, since monoacetin and incompletely acetylated glycerol were identified in the products. We found it possible to redistill glycidyl esters of fatty acids with the formation of negligible quantities of high-boiling residues.

Esters of glycidol are readily hydrated to monoglycerides by cold dilute mineral acids. Mixed diglycerides form when a compound such as glycidyl nitrate is heated with formic acid and ferric chloride (14).

The higher fatty esters of glycidol are plasticizers for vinyl polymers (1). They are colorless, high-boiling oils or low-melting solids, almost insoluble in water. The shorter-chain homologs can be made to combine with partially acetylated cellulose through the epoxide ring under the catalytic influence of stannic chloride in a neutral solvent such as ethyl acetate. This is, of course, only an example of an etherification reaction whereby α,α'-ether esters of glycerol are formed.

The glycidyl esters of lauric, myristic, palmitic, stearic, and oleic acids were prepared by reaction of the sodium soaps in an excess of epichlorohydrin, and in one instance by the reaction of acid chloride with glycidol. Most favorable results in the synthesis from soaps were obtained at atmospheric pressure under strictly anhydrous conditions. Yields of ester greater than 90% have been obtained when this precaution was observed. The use of the bomb at superatmospheric pressures shortened the time of reaction considerably, but the increased temperature favored the formation of quantities of high-boiling material. The same was true of reactions at atmospheric pressure when the reactants were imperfectly dried. High-boiling and polymeric material was formed in these cases to the extent of 50–60%.

Glycidyl butyrate in impure form was also prepared from epichlorohydrin and sodium butyrate, but in this case it was necessary to use a temperature of 198° and dioxane to increase the solubility of the salt.

An excess of epichlorohydrin to produce fluidity of the soap suspension has been found preferable to a solvent such as toluene or petroleum ether, in the interest of high yield of desired product. It is advisable to distill the epichlorohydrin over lime before use.

Unsatisfactory results were obtained when an attempt was made to condense sodium sebacate with epichlorohydrin. Ester-like products of low purity and undistillable for the most part were obtained; these tended to polymerize to a gel in the distilling flask. Better results were obtained by condensing sebacyl chloride with glycidol in toluene. Glycidyl sebacate prepared in this manner is a white crystalline solid melting at 44°.

In this and other reactions of glycidol with acid chlorides in toluene, it was

found convenient to use triethylamine in place of pyridine as an acceptor of hydrogen chloride. The amine hydrochloride precipitated almost quantitatively and could be filtered off, washed, dried, and used to regenerate the free base.

Soaps for the reaction with epichlorohydrin were prepared by dissolving fatty acids in acetone, and, during vigorous agitation, adding their equivalent of 5 *N* caustic soda. Precipitation took place soon after the first few drops of caustic were introduced, but to complete the neutralization, it was necessary to continue the agitation for about an hour after the last of the alkali had been added. Soaps prepared in this way are readily filterable. For laboratory purposes, this method was found superior to others tried, which for the most part yielded gels.

The soaps should be dry and finely powdered. In obtaining reactive anhydrous soaps, treatment in a vacuum oven at 100° in a slow stream of dry air followed by grinding and sieving are preliminary steps. It is advisable, however, to complete the desiccation in the reaction flask itself by immersion in an oil-bath maintained at 100° and exhausting through a cold trap with a vacuum pump. It was observed that sodium soaps apparently completely dry from the vacuum oven treatment still contained about 2% of water. Epichlorohydrin is conveniently dried with silica gel and thereafter admitted to the charge of powdered soaps without coming in contact with moist air. When the reactants are prepared in this way, no difficulty with gels is experienced as the mixture is heated. The reflux condenser is vented through a calcium chloride tube to avoid admission of moist air during reaction.

Two series of syntheses are described below. Specimens of the simple esters were prepared from pure intermediates to establish physical constants. A second group of glycidyl esters was made from the soaps of the mixed acids occurring as glycerides in natural oils such as soybean, castor, and babassu and of the mixed acids of rosin, and are included to show details of the preparations and the type of products that may be expected from such raw materials. To permit a study of their potentialities as plasticizers, the glycidyl esters of mixed acids and technical fatty acids were prepared in considerable bulk.

Polymerization was in evidence to a greater or less degree in most of the syntheses. The polymers remained as still-residues, had an equivalent weight almost that of the unpolymerized ester, and contained little chlorine.

EXPERIMENTAL

Epichlorohydrin. Technical epichlorohydrin (Shell) was fractionated through a 30-inch column, b.p. 115–117°, at 760 mm. This material was heated with stirring on a steam-bath with one-fourth its weight of quicklime, then decanted and refractionated, b.p. 115.5°.

Oleic acid. Virgin olive oil, 856 g., was treated with 1000 ml. of methanol containing 18 g. of hydrogen chloride and refluxed for 17.5 hours. The oily methyl oleate layer was water-washed and dried over calcium chloride. It was distilled under a 24 x 1-inch column packed with 4-mm. sections of 4-mm. tubing. Sodium bicarbonate, 0.3 g., was added to the charge to ensure non-acid condition. A reflux ratio of 9:1 was maintained. When the refractive index n_D^{24} had reached 1.4508, 328 g. of product b.p. 137–140° at 1 mm. was collected without variation from this value. Fatty acids, obtained from the partially purified methyl oleate by saponification, were treated to remove saturated acids and linoleic acid according to the method of Brown (15) which specifies two crystallizations from acetone at −20° and

−60°, respectively. An additional crystallization from 1480 ml. of acetone at −50° yielded 100 g. of product, m.p. 12.9°, which was again recrystallized from 650 ml. of petroleum ether (30–60°). Weight of final product was 55 g.; m.p. 13.3°; I.V., 90.7 (calc'd for oleic acid, 89.9): neut. eq., 282.2 (calc'd for oleic acid, 282.45).

Fatty acid soaps. One mole of sodium hydroxide in 5 *N* aqueous solution was added dropwise to a solution of 1.2 moles of fatty acid in 10 volumes of dry acetone, with vigorous mechanical stirring. (With the higher fatty acids, particularly stearic acid, it was necessary to warm the acetone to effect complete solution before the caustic was added.) Stirring was continued for one hour or until an aliquot of the acetone filtrate showed no further reduction in acidity. The soaps were filtered, triturated with one to two volumes of acetone, and vacuum-dried to constant weight. The yield was quantitative on the basis of the caustic used.

Rosin soaps. Pale rosin, (200 g.; 0.58 eq. of acid) was dissolved in 500 ml. of absolute alcohol, filtered through charcoal and neutralized with 52.5 g. of 44% sodium hydroxide. The solid soaps were recovered by evaporation on the steam-bath. To remove unsaponifiable matter, the dried soaps were finely ground and triturated three times with 600-ml. portions of acetone. The air-dried product weighed 154 g. This soap dissolved to a clear yellow solution in water. The acids liberated from a sample showed a titration equivalent weight of 322 (calc'd for abietic acid, 302.43).

Glycidol (16). Redistilled glycerol-α-monochlorohydrin (75 g.; 0.68 mole) and 400 ml. of anhydrous ether were mixed in a 1-liter, 3-neck flask equipped with stirrer, baffle, and reflux condenser. The reaction vessel was cooled in an ice-water bath to 10–12°. Sodium shavings, (11 g.; 0.48 mole) were added and the mixture vigorously stirred for 7 hours. At the end of this time the sodium was consumed. The product was filtered from sodium chloride and distilled, b.p. 51–85° at 2.5 mm.; yield 33 g. (93% on basis of sodium).

Acid chlorides. The two acid chlorides used in the preparations, sebacyl chloride and palmitoyl chloride, were prepared from the acids and thionyl chloride by well-established procedures.

Glycidyl laurate (from sodium laurate and epichlorohydrin). The reaction of sodium laurate with epichlorohydrin is described in detail as illustrative of the general procedure used for the various esters prepared from similar reactants. Tables I and II summarize experimental data for the syntheses reported in this paper and include moles of reactants, reaction time allowed, per cent conversion of soaps, method of purification, and analytical figures.

Sodium laurate (47.8 g.; 0.215 mole) prepared from Eastman lauric acid, was ground to pass a 0.25-mm. sieve and charged with 48 g. of freshly activated silica gel into a 3-necked flask equipped with stirring device, thermometer well, dropping-funnel, and reflux condenser vented through a calcium chloride tube. The flask was heated for 16 hours under 2–4 mm. pressure by an oil-bath maintained at 150–160° with occasional stirring of the solid materials. The temperature was then lowered to 110° and freshly distilled epichlorohydrin (199 g.; 2.15 moles) was added through the dropping-funnel. Agitation was resumed and the bath temperature controlled to maintain a steady reflux for 8 hours. During this period, the temperature of the reactants rose from 117° to 121°. The flask was cooled and filtered with the aid of 10 g. of "Filter-Cel." The crude product, free of epichlorohydrin, weighed 32.8 g. (59.3% conversion of soap). It was fractionated under a 4-inch column, b.p. 126° at 1 mm.; weight of product, 24.3 g. The material was a clear water-white oil having a saponification equivalent weight of 256.3 (calc'd, 256.37).

Anal. Calc'd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01.
Found: C, 69.9; H, 10.9.

Glycidyl palmitate (from glycidol and palmitoyl chloride). Freshly prepared glycidol, (18.5 g.; 0.25 mole), triethylamine, (27.5 g.; 0.27 mole), and toluene (150 ml.) were mixed and cooled in an ice-water bath. Palmitoyl chloride (63 g.; 0.23 mole) was added dropwise with vigorous mechanical stirring over 25 minutes and the stirring continued for an additional 35 minutes. The mixture was allowed to come to room temperature and the tri-

TABLE I

REACTION OF PURE SOAPS WITH EPICHLOROHYDRIN BY REFLUXING AT NORMAL PRESSURES

ESTER	REACTANTS		REACTION TIME, HRS.	OTHER MATERIALS	CONVERSION OF SOAP, %	B.P. OF FRACTION, °C.	SOLVENT FOR CRYSTALLIZATION	EQUIVALENT WEIGHT		ANALYSIS			
	Soap, Moles	Epichlorohydrin, Moles						Calc'd	Found	Calc'd		Found	
										C	H	C	H
Glycidyl laurate	0.215	2.15	8	48 g. silica gel	59.3	126	—	256.37	256.3	70.27	11.01	69.9	10.9
Glycidyl myristate	0.228	2.0	11	20 g. aluminum oxide	59.5	141–145	Acetone	284.43	284.4	71.78	11.34	71.4	11.3
β-Methylglycidyl myristate	0.188	1.88*	7.25	10 g. K_2CO_3	90.3	129–133	—	298.45	298.2	72.43	11.48	72.3	11.4
Glycidyl palmitate	0.18	1.8	7	—	71.1	171–176	—	312.48	313.5	—	—	—	—
Glycidyl stearate	0.156	2.55	12	—	—	—	Acetone	340.53	339.3	74.06	11.84	73.8	11.8
Glycidyl oleate	0.082	0.82	5.5	—	88.5	168–169	—	338.51	340.0	74.51	11.31	74.2	11.3

* β-Methylepichlorohydrin (Eastman).

TABLE II

REACTION OF ACID CHLORIDES WITH GLYCIDOL

	ACID CHLORIDE, MOLES	GLYCIDOL, MOLES	REACTION TIME, HRS.	TRIETHYLAMINE, MOLES	TOLUENE, ML.	CONVERSION OF ACID CHLORIDE, %	SOLVENT FOR CRYSTALLIZATION	EQUIV. WT.		M.W.		ANALYSIS			
								Calc'd	Found	Calc'd	Found	Calc'd		Found	
												C	H	C	H
Glycidyl palmitate	0.23	0.25	1	0.27	150	88	Acetone	312.48	313	—	—	73.03	11.61	73.0	11.6
Glycidyl sebacate	0.1015	0.203	1.2	0.223	60	92	Ligroin 85–100°	157.18	155	314.37	315	61.13	8.33	61.1	8.3

ethylamine hydrochloride was filtered off. The filtrate when evaporated yielded a residue of 63 g. (88% calculated as glycidyl palmitate). This was crystallized twice from 200 ml. and 150 ml. of acetone, respectively, at 5°. It was redissolved in 150 ml. of acetone, cooled to 15° and filtered from the precipitate. The material contained in the liquors was crystal-

TABLE III

PHYSICAL PROPERTIES OF GLYCIDYL ESTERS

ESTER	B.P. °C.	B.P. mm.	M.P., °C.	d	°C.	n_D^{60}
Glycidyl laurate	126	1	21	0.9388	25	1.4310
	290 (dec.)	760		.9266	40	
				.9193	50	
				.9111	60	
Glycidyl myristate	146	1	33.5–34.5	.9092	50	1.4345
	310 (dec.)	760		.9012	60	
β-Methylglycidyl myristate	130	1	21.5	.9148	25	1.4309
				.8873	60	
Glycidyl palmitate	170	1	44.5–45.0	.8965	50	1.4363
				.8889	60	
Glycidyl stearate	193	1	50.5–51.3	.8867	60	1.4387
Glycidyl oleate	185	1	−1	.8987	60	1.4469
Glycidyl sebacate	—	—	44	1.0667	60	1.4490

TABLE IV

REACTION OF SOAPS OF NATURAL OILS AND ROSIN WITH EPICHLOROHYDRIN

SOAPS FROM MIXED ACIDS OF	REACTANTS: Soap, Moles	REACTANTS: Epicyloro-hydrin, Moles	OTHER MATERIALS	TEMP., °C.	REACTION TIME, HRS.	CONVERSION OF SOAP, %	B.P. OF MIXED ESTERS/ 1 MM. °C.	EQ. WT.
Babassu oil	2.33	13.5	1 g. NaOH	130–135	1.75	86.6	70–285	252
	2.26	12.76	50 g. "Drierite"	130	2.5	90.2	90–225	267.7
Castor oil	0.53	5.3	—	142–148	3	86	239–241	353.5
	0.532	5.32	0.5 g. NaOH	135–151	2.08	87	—	—
Walnut oil	0.614	6.22	—	135–150	1.5	86	148–255	327.1
Soybean oil	0.503	5.03	0.5 g. NaOH	160	1.5	89.3	125–220	329.5
Rosin	0.5	5.0	0.5 g. NaOH	175–180	1.5	90	180–225	—

lized from 175 ml. of ligroin (85–100°). The product was distilled at 1 mm. to yield 14.5 g. of pure glycidyl palmitate. Sap. eq. found, 313; calc'd, 312.48.

Anal. Calc'd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61.

Found: C, 73.0; H, 11.6.

The foregoing procedure was applied to the preparation of glycidyl sebacate except for minor differences as noted in Table II.

Table III lists the common physical properties of the pure glycidyl esters. Attention is called to the comparatively high density of glycidyl sebacate.

Glycidyl esters of mixed acids from natural products. Glycidyl esters of the mixed fatty acids of babassu, walnut, soybean and castor oils, and also of rosin acids, were prepared in a manner similar to that used for the simple esters except that the reaction of soaps with epichlorohydrin was carried out in a hydrogenation bomb (American Instrument Company) at slightly higher temperatures and for somewhat shorter time periods. The conditions used are summarized in Table IV. Bomb technique was also employed in the synthesis of glycidyl esters from technical grades of fatty acids but the results are not included because of the similarity of the products to the pure esters.

Acknowledgment. The analyses of the esters were performed by L. M. White of this Laboratory.

SUMMARY

The preparation and physical properties of glycidyl laurate, myristate, palmitate, stearate, oleate, and sebacate, and also of β-methylglycidyl myristate have been described. The syntheses involved reaction of soaps with epichlorohydrin and of acid chlorides with glycidol.

The synthesis of pure compounds has been extended to include the preparation of glycidyl esters of the mixed acids of babassu, soybean, walnut, and castor oils, and of rosin.

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[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

THE OXIDATION OF 2-AMINOBENZOTHIAZOLES[1]

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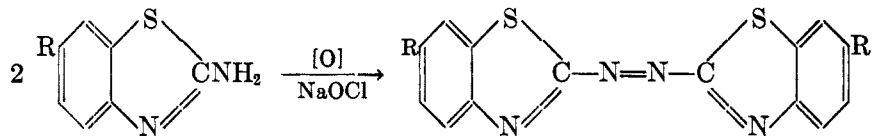
The so-called safety papers used in legal documents, checks, etc. are treated chemically during manufacture so as to prevent alteration by erasure and insertion. The 2-aminobenzothiazoles are an important group of substances which are used effectively in the protection of paper against forgery. Paper impregnated with a 2-aminobenzothiazole will develop a deep colored blot almost instantly when an ink eradicator (usually a hypochlorite solution) is applied. This action of a hypohalite (bleaching powder) on substituted 2-aminobenzothiazoles was first observed by Fischer and Besthorn (1) in 1882. However, neither they, nor subsequent investigators (2) determined the structure of the reaction products. Accordingly, the present study of the bright colored products of the sodium hypochlorite oxidation of various 2-aminobenzothiazoles was undertaken. Six different 2-aminobenzothiazoles were studied, particular attention being given to 2-amino-6-methylbenzothiazole and 2-amino-6-chlorobenzothiazole.

Oxidation was carried out by the addition of aqueous sodium hypochlorite to a solution of the 2-aminobenzothiazole in dioxane. Pure substances were isolated with difficulty from the crude reaction products by a procedure of extraction and sublimation in a high vacuum. The purified compounds were all bright red, insoluble, crystalline solids which melted with decomposition in the neighborhood of 300–350° and which exhibited red-yellow pleochroism. Elementary analyses indicated two atoms of hydrogen were removed from the 2-aminobenzothiazole in the oxidation. This suggested that the bright colored products were azo compounds formed by oxidation of the amino group as follows:



R = H, CH_3, Cl, Br, and OC_2H_5

That oxidation of the amino group had occurred was shown by attempting a hypochlorite oxidation of acyl derivatives of certain of the 2-aminobenzothiazoles. No reaction was observed when either 2-benzoylamino-6-methylbenzothiazole or 2-acetylamino-6-chlorobenzothiazole was treated with aqueous

[1] This paper is an abstract of a portion of the doctoral dissertation of William Kirk, Jr., submitted to the Graduate Faculty of Cornell University in February, 1943.

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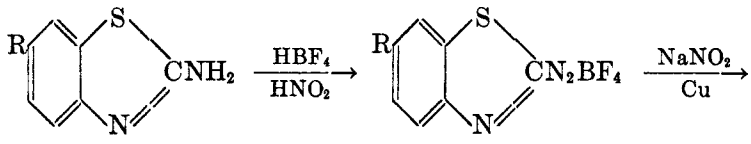
sodium hypochlorite. However, 2-acetylamino-6-methylbenzothiazole did give the characteristic red-brown precipitate when treated with the hypohalite. Presumably in this latter case the acetyl derivative was very readily hydrolyzed by the alkaline solution, liberating the free aminobenzothiazole.

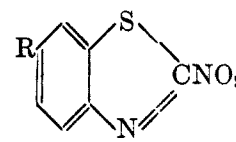
In view of the fact that Bogert (3) has assigned an azo structure to the chloramine yellow type of dyes which are prepared by the action of sodium hypochlorite on substituted 2-(*p*-anilino)benzothiazoles, the azo structure for the compounds formed in the oxidation of the 2-aminobenzothiazoles appeared reasonable.

Confirmation of this postulation was obtained by an independent synthesis of the substituted 2-azobenzothiazoles.

A series of substituted 2-nitrobenzothiazoles was prepared from the 2-aminobenzothiazoles through the diazonium fluoborates according to the following:

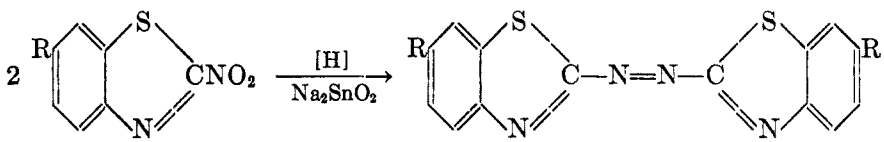


R = H, CH_3, Cl, Br, and OC_2H_5



The 2-nitrobenzothiazoles were identified by reduction to the corresponding 2-aminobenzothiazoles which in turn were converted to the acetyl derivatives. Mixed melting points of these derivatives with the acetyl derivatives of authentic specimens of 2-aminobenzothiazoles confirmed the identity. The 2-nitrobenzothiazoles which were prepared are listed in Table I.

The substituted 2-nitrobenzothiazoles were reduced readily by sodium stannite to the corresponding 2-azobenzothiazoles.



R = H, CH_3, Cl, Br, and OC_2H_5

The 2-azobenzothiazoles prepared in this manner (Table II) were identical with the products obtained by the hypochlorite oxidation of the corresponding 2-aminobenzothiazoles. There was exact agreement in melting point and mixed melting point. The identity of the compounds was also confirmed by microscopical examination.

Attempts to effect a reductive cleavage of the azo compound to 2-aminobenzothiazoles by chemical methods were unsuccessful. This was probably due to the extreme insolubility of the compounds in the usual solvents. Catalytic reduction

TABLE I

SUBSTITUTED 2-NITROBENZOTHIAZOLES

BENZOTHIAZOLE	AVERAGE YIELD, %[a]	M.P., °C (UNCORR.)	% NITROGEN	
			Calc'd	Found
2-Nitro-	33.3	157–158	15.56	15.82 15.79
2-Nitro-6-methyl-	8.5	131–132	14.43	14.28 14.39
2-Nitro-6-ethoxy-	2.6	151–152	12.50	12.56 12.56
2-Nitro-6-chloro-	11.2	160–161	13.05	13.19 13.07
2-Nitro-6-bromo-	4.4	179–180	10.81	10.86 10.75
2-Nitro-4-methyl-	16.9	152–153	14.43	14.23 14.48

[a] This is the average yield from three or more runs starting with 5 g. of the corresponding 2-aminobenzothiazole.

TABLE II

2-AZOBENZOTHIAZOLES FROM 2-NITROBENZOTHIAZOLES BY REDUCTION WITH SODIUM STANNITE[a]

2-AZOBENZOTHIAZOLE	COLOR	M.P., °C (UNCORR.)[b]	% YIELD[c]	ANALYSIS	
				Calc'd	Found
Unsubstituted	Dark red	295 decomp.	21	18.91 N	18.85 N 19.05 N
6,6′-Dimethyl-	Dark red	319 decomp.	24	17.26 N	17.22 N 17.22 N
6,6′-Dichloro-	Bright red	348 decomp.	20	19.42 Cl	19.30 Cl 19.20 Cl
6,6′-Dibromo-	Bright red	338 decomp.	16.5	12.33 N	12.18 N 12.19 N
6,6′-Diethoxy-	Dark purple	290 decomp.	25	14.58 N	14.53 N 14.60 N
4,4′-Dimethyl-	Bright red	301 decomp.	71.5	17.26 N	17.05 N 17.20 N

[a] Identical 2-azobenzothiazoles were obtained by the sodium hypochlorite oxidation of the corresponding 2-aminobenzothiazoles.

[b] All melting points taken on the Maquenne block.

[c] Starting with 0.2–0.3 g. of the 2-nitrobenzothiazole.

of 6,6′-dichloro-2-azobenzothiazole with a Raney nickel catalyst gave 2-amino-6-chlorobenzothiazole, identified as the acetyl derivative.

In order to demonstrate that the hypochlorite oxidation products of the 2-aminobenzothiazoles were azo compounds and not azoxy derivatives, reduction of the 2-nitrobenzothiazoles was carried out with dextrose. The resulting products were mainly the corresponding 2-azoxybenzothiazoles (Table III). However, dextrose reduction of the parent compound, 2-nitrobenzothiazole, produced only 2-azobenzothiazole. Like the azo compounds the 2-azoxybenzothiazoles were highly colored crystalline substances similar in properties to the correspond-

TABLE III

2-AZOXYBENZOTHIAZOLE FROM 2-NITROBENZOTHIAZOLES BY REDUCTION WITH DEXTROSE

2-AZOXYBENZOTHIAZOLE[a]	COLOR	M.P. °C[b] (UNCORR.)	% YIELD[c]	% NITROGEN	
				Calc'd	Found
6,6′-Dimethyl-	Bright red	314 decomp.	26	16.48	16.70[d] 16.80
6,6′-Dichloro-	Bright red	344 decomp.	20	14.70	15.19
6,6′-Dibromo-	Bright red	336 decomp.	12	11.92	11.80
6,6′-Diethoxy-	Dark purple	272 decomp.	38	14.00	13.99 14.07
4,4′-Dimethyl-	Bright red	293 decomp.	18.6	16.48	16.43 16.38

[a] Dextrose reduction of the unsubstituted 2-nitrobenzothiazole gave only the 2-azobenzothiazole described in Table II.

[b] All taken on the Maquenne block.

[c] Based on the amount obtained from 0.1–0.2 g. of the 2-nitrobenzothiazole.

[d] Also analyzed for carbon and hydrogen.

Anal. Calc'd for $C_{16}H_{12}N_4S_2O$: C, 56.43; H, 3.55
$C_{16}H_{12}N_4S_2$: C, 59.22; H, 3.72
Found: C, 57.90, 57.97

These calculations indicate that the product is probably a mixture of the azo and azoxy derivatives.

ing azo derivatives. Their melting points were slightly lower and in some cases twinning of the crystals was prominent.

The chemical evidence given above indicating an azo structure for the hypochlorite oxidation products of 2-aminobenzothiazoles is also supported by the high color of these products. An azo structure affords the maximum conjugation of double bonds possible in the benzothiazole nucleus. Although a 2-nitrosobenzothiazole would have about the same amount of conjugation, such compounds would be expected to melt much lower than 300-350° (the observed melting point range for the 2-azobenzothiazoles).

The 2-azobenzothiazoles in the oxidation of the 2-aminobenzothiazoles could be isolated in yields of 15 to 17% of the theoretical. The nature of the remainder of the oxidation product remains to be considered. The crude red-brown oxida-

tion products are reminiscent of the deeply colored mixture obtained when aniline is oxidized to bimolecular and polymolecular products. It is reasonable to suppose that the reaction products remaining after removal of the azobenzothiazoles consists of polymeric products of the aniline black type. The structure of these other products was not investigated.

EXPERIMENTAL

Preparation of the 2-aminobenzothiazoles. 2-Aminobenzothiazole was prepared by the method of Fischer and Besthorn (2), 2-amino-4-methyl- and 2-amino-6-methyl-benzothiazole were prepared according to the method of "Organic Syntheses" (4), and 2-amino-6-bromobenzothiazole according to the method of Kaufmann (5). 2-Amino-6-chlorobenzo thiazole and 2-amino-6-ethoxybenzothiazole were furnished through the courtesy of the E. I. du Pont de Nemours and Co. They were purified by recrystallization from a solvent consisting of equal parts (by volume) of dioxane, alcohol, and water. The 2-amino-6-chlorobenzothiazole then melted at 196–197° (uncorr.); the 2-amino-6-ethoxybenzothiazole melted at 163–164° (uncorr.).

Oxidation of the 2-aminobenzothiazoles. The sodium hypochlorite oxidation of the 2-aminobenzothiazoles was carried out in the same general way with all of the amino derivatives. The oxidation of 2-amino-6-methylbenzothiazole illustrates the general procedure.

A solution of 10 g. (0.061 mole) of 2-amino-6-methylbenzothiazole in 200 cc. of dioxane was added over a period of fifteen minutes to 200 g. of a well stirred solution of sodium hypochlorite ("Clorox") (0.134 mole) at room temperature. A red-brown, flocculent precipitate formed immediately upon addition. The temperature of the reaction mixture rose to 50° after one-half of the solution of the amine had been added, and no further increase in temperature occurred when the remainder of the reactant was added. Stirring was continued for ten minutes after addition was complete, 50 cc. of "Clorox" was added and stirring continued for half an hour. The precipitate was filtered and dried at 55°. The resulting amorphous powder was extracted with boiling 2-nitropropane and sublimed at 0.1 mm pressure and 250–260°.

Preparation of the 2-nitrobenzothiazoles. This series of compounds was prepared by a slight modification of the method of Starkey, which is now given in "Organic Syntheses" (6). Since all of the 2-nitrobenzothiazoles were prepared by the same method, only the procedure for 2-nitrobenzothiazole is described in detail.

In a 400-cc. beaker 5.0 g. (0.033 mole) of 2-aminobenzothiazole was dissolved in a solution of 100 g. of water and 20 g. of fluoboric acid solution (42%). This solution was cooled to 4° and maintained at this temperature with an ice-water bath during the addition of 2.3 g. (0.033 mole) of sodium nitrite dissolved in 10 cc. of water. The sodium nitrite solution was added under the amine solution, using moderate stirring. The diazotization required fifteen to twenty minutes. At the end of the diazotization, the reaction mixture contained some dissolved diazonium fluoborate as well as some of the precipitated salt. The mixture was added immediately to a boiling solution of 25 g. of sodium nitrite in 100 cc. of water containing 5 g. of copper powder (pure carbon copper which had been previously "wetted" with 10 cc. of alcohol to prevent foaming). This mixture was steam distilled at once and 1500 cc. of distillate was collected which contained the light yellow crystalline product. The 2-nitrobenzothiazole was purified by recrystallization from hot alcohol. The yield was 2.0 g. of the pure compound or 33%; m.p. 157–158° (uncorr.). The average yields, melting points, and analyses of the substituted 2-nitrobenzothiazoles are given in a preceding table (Table I).

The 2-nitrobenzothiazoles listed in the foregoing table were identified by reduction to the corresponding 2-aminobenzothiazoles with tin and hydrochloric acid. They were then acetylated and the melting points of the products were compared with authentic samples of substituted 2-acetylaminobenzothiazoles.

Reduction of the 2-nitrobenzothiazoles by sodium stannite. The substituted 2-azobenzothiazoles were all prepared in the same manner. The preparation of 4,4′-dimethyl-2-azobenzothiazole is described in detail.

In a 50-cc. flask were placed 0.20 g. (0.0010 mole) of 2-nitro-4-methylbenzothiazole and 20 cc. of ethyl alcohol. The solution was warmed to 50° on a water-bath and 0.464 g. (0.00206 mole) of stannous chloride dihydrate dissolved in 5 cc. of 10% sodium hydroxide was added all at once. The solution flashed bright red upon addition of the stannite solution and turned green in a few seconds. The flask was fitted with a reflux condenser and warmed over a water-bath at 80° for two hours. The warm solution was neutralized by dropwise addition of concentrated hydrochloric acid, which produced a bright red, flocculent precipitate. The mixture was filtered when cool and the precipitate was extracted with boiling 2-nitropropane and recrystallized from the same solvent. Long, dark red needles were obtained. The yield was 0.121 g. of pure 4,4′-dimethyl-2-azobenzothiazole, or 71.5%; m.p. 301° decomp. (uncorr.) on the Maquenne block. The melting points, etc., of the 2-azobenzothiazoles are given in Table II.

The melting points of the 2-azobenzothiazoles agreed exactly with the melting points of the oxidation products of the corresponding 2-aminobenzothiazoles. Mixed melting point determinations confirmed the identity of the compounds prepared by the two methods.

Reduction of the 2-nitrobenzothiazoles by dextrose. In a 50-cc. flask were placed 0.200 g. (0.00103 mole) of 2-nitro-4-methylbenzothiazole, 0.150 g. (0.00075 mole) of dextrose, and 20 cc. of water; 1 cc. of alcohol was added to "wet" the nitro compound. This mixture was warmed to 50° and 3 cc. of 10% sodium hydroxide was added. The flask was fitted with a reflux condenser and warmed to 60–70° for two hours. At the end of this time the red precipitate which formed was filtered off and dried at 55°. This crude reaction product was extracted with boiling 2-nitropropane and recrystallized from the same solvent. There was obtained 0.033 g. of bright red crystals of 4,4′-dimethyl-2-azoxybenzothiazole; m.p. 293° decomp. (uncorr.) on the Maquenne block.

The reduction of other 2-nitrobenzothiazoles by dextrose was carried out similarly. The results are given in Table III.

Catalytic reduction of 6,6′-dichloro-2-azobenzothiazole. In a thick-walled glass hydrogenation bottle were placed 0.30 g. of 6,6′-dichloro-2-azobenzothiazole (prepared by the sodium hypochlorite oxidation of 2-amino-6-chlorobenzothiazole), 50 cc. of dry ether, and 0.3–0.4 g. of Raney nickel. (Peroxide-free dioxane was also tried as a solvent; reduction apparently took place, but the difficulty of removing that solvent from a small amount of product made identification impossible.) The solution was shaken for two hours under a pressure of 43.5 pounds of hydrogen and at 26°. At the end of this time the Raney nickel was filtered off and the ether evaporated to dryness. About 0.1 g. of solid residue remained which was converted *in situ* to the acetyl derivative by adding 10 cc. of acetic anhydride and two drops of concentrated sulfuric acid to the flask and warming to 50–60° for ten minutes. Water was added dropwise with care until the sputtering subsided; 50 cc. of water was added and the unreacted anhydride allowed to hydrolyze. This gave a crystalline product which melted at 226–227° (uncorr.) when recrystallized from dilute alcohol. [Melting point of 2-acetylamino-6-chlorobenzothiazole is 227–228° (uncorr.)]. The mixed melting point was 227–228°.

SUMMARY

1. The action of sodium hypochlorite on a number of 2-aminobenzothiazoles has been studied. The highly colored products formed in the reaction have been isolated in a pure state and assigned an azo structure.

2. A new series of compounds, the 2-nitrobenzothiazoles, has been prepared. Reduction of the 2-nitrobenzothiazoles with sodium stannite produces 2-azo-

benzothiazoles, whereas reduction with dextrose yields mainly the 2-azoxybenzothiazoles.

ITHACA, N. Y.

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[CONTRIBUTION OF THE RESEARCH LABORATORIES, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

AMINO ALCOHOLS. XII. OPTICAL ISOMERS IN THE EPHEDRINE SERIES OF COMPOUNDS (1)

CHARLES JAROWSKI AND WALTER H. HARTUNG

Received September 9, 1943

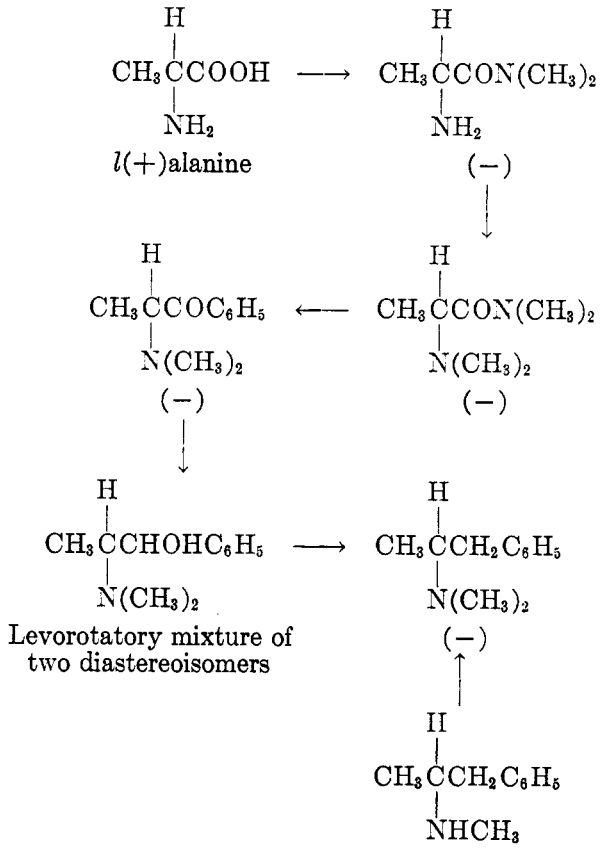
The position isomers and homologs of the ephedrine-epinephrine type of compounds have been extensively studied, and considerable correlation between chemical structure and physiological activity is possible. The chemical and pharmacodynamic properties of the optical isomers are not so well known. (−)Epinephrine possesses about 20 times the circulatory activity of the dextrorotatory isomer (2). (+)Benzedrine is 3 to 4 times more effective as a stimulant for the central nervous system than its (−)isomer (3). The four optical isomers of ephedrine, investigated qualitatively and quantitatively by Chen, Wu, and Henriksen (4), show appreciable variation in their mydriatic properties, effect on isolated tissues and pressor action; the pressor activity apparently decreases with increase in solubility of the (−) mandelate of the four diastereoisomers.

These differences do not appear unexpected if it is remembered that diastereoisomers are in fact different compounds, showing appreciable variations in both physical and chemical properties which are not suggested in the conventional projection formulas.[1] The protoplasmic reaction of the optical isomers with the tissue components undoubtedly increases the diastereoisomeric complexity and is a factor which contributes to their different qualitative and quantitative biological behavior.

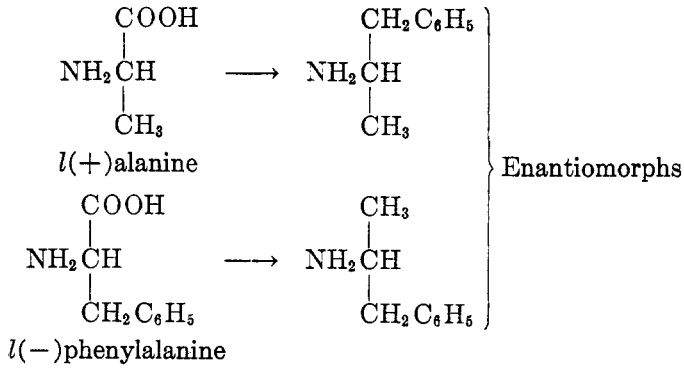
Efforts have been made to establish the relative configuration of the two asymmetric centers in ephedrine, $C_6H_5\underset{H}{\overset{OH}{C}}-\underset{NHCH_3}{\overset{H}{C}}CH_3$. The hydroxyl-bearing carbon atom, which is levorotatory, is placed in the *d*-series by virtue of the following sequence of reactions: *d*(−)mandelic acid → *d*(−)mandelamide $\xrightarrow{CH_3MgI}$ *d*(−)-phenylacetyl carbinol $\xrightarrow[H + CH_3NH_2]{}$ (−)ephedrine (6).

The status of the methylamino-bearing carbon atom, which is dextrorotatory, is not definite. By comparing nor-desoxyephedrine (benzedrine) with optically active α-phenethylamine of known relative configuration, Leithe (7) placed this carbon atom in the *d*-series. On the other hand by synthesizing N-methyldesoxyephedrine from *l*(+)alanine through the following series of products:

[1] For a more extended discussion of these phenomena see Jenkins and Hartung (5).



Freudenberg and Nikolai (8) assigned to this carbon atom the *l*-configuration. This confusion is not hard to understand, for it is primarily a question of whether desoxyephedrine is to be looked upon as related to *l*(+) alanine or to *l*(−)phen-



ylalanine, *e.g.*, it at once becomes apparent that if the −COOH of *l*(+) alanine is converted into $-CH_2C_6H_5$ the product is the mirror image of that obtained

when the $-COOH$ of $l(-)$phenylalanine is converted into $-CH_3$. Consequently the relative configuration of the amino-bearing carbon of ephedrine is still unsettled.

A study of the optical isomers of various members of the pressor compounds has been initiated in these laboratories. The resolution and the solubility of the salts of the isomers of propadrine, $C_6H_5CHOHCH(NH_2)CH_3$, benzedrine, $C_6H_5CH_2CH(NH_2)CH_3$, β-phenylpropylamine, $C_6H_5CH(CH_3)CH_2NH_2$, and phenylethanolamine, $C_6H_5CHOHCH_2NH_2$ are now reported.

TABLE I

THE PHYSICAL PROPERTIES OF THE MANDELATES STUDIED

NAME OF COMPOUND	M.P., °C	$(\alpha)_D$	T. °C.	Conc. (water)
1. (−) Ephedrine (−)mandelate	170	−70.6	26.5	2.4056
2. (−)Ephedrine (+)mandelate	78–91	21.3	25.5	2.8180
3. (−)Propadrine (−)mandelate	171.5–172	−70.6	29.0	2.3506
4. (+)Propadrine (−)mandelate	164.5–165	−42.8	29.0	1.2390
5. (+)Propadrine (+)mandelate	171.5–172	70.7	29.5	2.3460
6. *dl*-Propadrine *dl*-mandelate	161–162			
7. (+)ψ-Propadrine (−)mandelate	170	−45.3	32.4	1.1905
8. (−)ψ-Propadrine (−)mandelate	163.5	−41.3	32.4	0.7999
9. *dl*-ψ-Propadrine *dl*-mandelate	162.5–163			
10. (+)Benzedrine (−)mandelate	162–163	−50.0	25.0	2.2368
11. (−)Benzedrine (−)mandelate	166	−68.6	26.0	1.7054
12. (−)Benzedrine (+)mandelate	163	49.8	28.0	1.6045
13. *dl*-Benzedrine *dl*-mandelate	156.5			
14. (−)Isobenzedrine* (−)mand	127.127.5	−57.8	25.6	2.0735
15. (+)Isobenzedrine (+)mand	127–127.5	58.7	29.8	1.5818
16. (+)Isobenzedrine (−)mand	118.5–119	−47.5	29.8	1.2841
17. *dl*-Isobenzedrine *dl*-mand	119.5–120.5			
18. *dl*-Phenylethanolamine *dl*-mand	129.5–130			
19. (−)Phenylethanolamine (−)mand	144–145	−58.3	31.0	0.8916

* Synonym for β-phenylpropylamine.

EXPERIMENTAL

Mandelic acid was resolved according to the method of Roger (9). The reported and observed constants for the enantiomorphs are:

(−)mandelic acid: m.133.8°, $(\alpha)_D$ −178° (reported); observed, m.133–134°, $(\alpha)_D$ −178.4° (conc. 0.6948 in ethanol).

(+)mandelic acid: m.133°, $(\alpha)_D$ 159–173° (reported); observed, m.132–133°, $(\alpha)_D$ 173°, (conc. 0.6907, in ethanol).

Separation of the dl- *and* dl-ψ-*propadrine.* A mixture of the four bases prepared by the reduction of phenylnitropropanol, $C_6H_5CHOHCH(NO_2)CH_3$, was obtained through the courtesy of the Commercial Solvents Corporation. The two racemic mixtures were separated from any impurities in the crude product by precipitating them as the hydrochloride from benzene, treating with Norit, basification, extraction, and reprecipitation from benzene as before. The two racemic hydrochlorides were separated by repeated crystallizations from absolute ethanol. The less soluble salt was *dl*-propadrine hydrochloride, m.194. Racemic ψ-propadrine hydrochloride was procured from the mother liquors by the addition of excess ether, m.170.5–171.5°.

Resolution of the bases. *dl*-Propadrine, *dl*-ψ-propadrine, phenylethanolamine, benzedrine, and β-phenylpropylamine were resolved into their optically active components by substantially identical procedures. To a hot ethanol solution of the *dl*-base was added a

TABLE II

PHYSICAL PROPERTIES OF THE ISOMERS STUDIED

NAME OF COMPOUND	M.P., °C	ROTATION		
		$(\alpha)_D$	T., °C	Conc. Abs. EtOH
(−)Ephedrine	34–40	−3.47	27	4.3130
(−)Propadrine	102	−19.90	30	0.2641
(+)Propadrine	102	20.80	32	0.2400
(+)ψ-Propadrine hydrochloride	179	41	29	0.1583
(−)ψ-Propadrine hydrochloride	178	−38.7	32	0.2100
(+)Benzedrine		3.8	25	3.4168
(−)Benzedrine		−3.8	28	2.5633
(−)Isobenzedrine		−18.82	30	2.5492
(+)Isobenzedrine		18.8	30	2.4651
(−)Phenylethanolamine		−20.90	30	0.0956

TABLE III

SOLUBILITY OF THE DIASTEREOISOMERIC MANDELATES

	SOLUBILITY 37°			SOLUBILITY 25°		
	Distilled Water	Normal Saline	Difference	Distilled Water	Normal Saline	Difference
1	6.27	6.99	0.72	6.00	5.95	−0.05
2	80.61	92.34	11.73	77.48	88.68	11.20
3	7.39	7.36	−0.03	6.08	6.30	0.22
4	10.69	10.19	−0.50	7.70	7.26	−0.44
5	8.36	7.34	−1.02	5.58	5.95	0.37
6	8.08	8.14	0.06	5.35	6.00	0.65
7	8.43	9.56	1.13	6.22	6.23	0.01
8	18.74	19.01	0.27	11.95	15.02	3.07
9	11.41	11.06	−0.35	5.67	8.66	−0.01
10	4.63	4.77	0.14	3.93	4.16	0.25
11	7.25	7.56	0.31	5.98	6.24	0.26
12	4.80	4.65	0.05	3.94	4.21	0.27
13	6.98	7.42	0.44	5.73	6.19	0.46
14	25.30	28.08	2.78	14.59	15.59	1.00
15	27.23	31.95	4.72	14.39	15.54	1.15
16	63.46	61.15	−2.31	51.15	48.86	−2.27
17	20.13	18.36	−1.77	11.50	11.31	−0.19
18	18.56	19.79	1.23	11.63	11.76	0.15
19	—	—	—	—	—	—

hot alcoholic solution of an equivalent amount of the optically active mandelic acid. Upon cooling, the less soluble salt crystallized out. The solid product was recrystallized to constant rotation and maximum melting point. The more soluble mandelate was procured by concentration of the mother liquor from the initial crystallization, addition of excess dry ether to the hot ethanolic solution, and adequate cooling. Several recrystallizations from

ether-alcohol yielded the more soluble salt in pure form. Absolute ethanol was used as the solvent in all cases except in the resolution of phenylethanolamine and β-phenylpropylamine in which instances secondary butyl alcohol proved to be more expeditious. The melting points and rotations of the various salts are listed in Table I.

The purified salts, treated with alkali, liberated the optically pure free bases. The properties of the bases are given in Table II.

Solubility measurements. Saturated solutions of the various salts at 25° and 37° in normal saline and distilled water were prepared as follows: To 10 cc. of normal saline or distilled water in a 20-cc. test tube, immersed in a thermostat at the desired temperature, was added an excess of the mandelate. The tubes were stoppered and frequently agitated during the course of six hours. About 3 cc. of solution was pipetted off and weighed. The weight of the residue was then determined after removal of the water on a steam-cone and drying in an electrically heated oven to constant weight. The weight of the residue from the normal saline solutions was corrected in regard to the amount of sodium chloride present. The solubility data are listed in Table III. The numbers in column 1 correspond to the compounds in Table I.

The optically active salts have been studied by Dr. K. K. Chen, who will publish elsewhere a more elaborate report of his observations. However through the courtesy of Dr. Chen a summary of the pressure ratios is included here.

DISCUSSION OF RESULTS

From Table I it can be seen that the less soluble salts of (−)mandelic acid from each pair of enantiomorphous bases are: (−)propadrine, (+)ψ-propadrine, (−)phenylethanolamine, (−)β-phenylpropylamine, and (+)benzedrine. The spatial relationships of the asymmetric carbons in the compounds studied show a definite correlation to the solubility of their salts. Thus in those pressor amines possessing only one asymmetric center, the less soluble (−)mandelate is formed by that base whose phenyl-bearing carbon is levorotatory [Example: (−)phenylethanolamine and (−)β-phenylpropylamine] or whose carbinamine carbon is dextrorotatory [Example: (+)benzedrine].

Propadrine and ephedrine each possess two centers of asymmetry. It has been established by the work of Nagai (10), Leithe (11), Freudenberg (12) and others that in (−)ephedrine and (−)propadrine the hydroxyl-bearing carbon is levorotatory while the carbinamine carbon is dextrorotatory. In (+)ψ-propadrine and (+)ψ-ephedrine both centers of asymmetry are exerting their effect in the same direction. Thus of the four possible isomers of these two bases the least soluble is found to be that one answering the specifications mentioned before; namely that the carbinamine carbon be dextrorotatory while the hydroxyl-bearing carbon have a levorotation. In the event both centers of asymmetry are of similar sign it is the dextrorotatory isomer which forms the less soluble mandelate.

Pharmacodynamic information about the sympathomimetic amines studied shows that of the enantiomorphous pairs (−)propadrine, (−)ephedrine, (+)benzedrine, (−)ψ-propadrine, (+)ψ-ephedrine, and (−)β-phenylpropylamine are the more active. Neither quantitative nor qualitative comparisons in the physiological behavior of the optical isomers of phenylethanolamine are available. However from the analogies with the compounds described above the prediction is ventured that the levorotating isomer will prove to be the more active. In

epinephrine, where the hydroxyl-bearing carbon is asymmetric, the levorotatory isomer is more active physiologically. In phenylethanolamine the corresponding carbon atom is asymmetric.

TABLE IV

PHARMACOLOGICAL DATA

NAME OF COMPOUND	AMOUNT PRODUCING THE SAME INTENSITY OF PRESSOR ACTION (AVERAGE) AS 0.01 MG. OF EPINEPHRINE
(−)Benzedrine (−)mandelate	2.82 mg.
(−)Benzedrine (+)mandelate	4.17 "
(+)Benzedrine (−)mandelate	2.70 "
(−)Isobenzedrine (−)mandelate	4.68 "
(+)Isobenzedrine (−)mandelate	5.30 "
(+)Isobenzedrine (+)mandelate	6.73 "
(−)Propadrine (−)mandelate	3.17 "
(+)Propadrine (−)mandelate	4.73 "
(−)Pseudopropadrine (−)mandelate	17.00 "
(+)Pseudopropadrine (−)mandelate	19.00 "
(−)Phenylethanolamine (−)mandelate	5.48 "

TABLE V

COMPARISON OF THE PHYSICAL AND PHYSIOLOGICAL PROPERTIES OF β-PHENYLPROPYLAMINE AND PHENYLETHANOLAMINE

NAME OF COMPOUND	M.P., °C	$(\alpha)_D$	AMOUNT CAUSING THE SAME ACTION AS 0.01 MG. OF EPINEPHRINE
(−)Isobenzedrine (−)mandelate	127–127.5	−57.8	4.68 mg.
(−)Phenylethanolamine (−)mandelate	144–145	−58.7	5.48 "
dl-Isobenzedrine *dl*-mandelate	119.5–120.5		
dl-Phenylethanolamine *dl*-mandelate	129.5–130		
(−)Isobenzedrine		−18.82	
(−)Phenylethanolamine		−20.7	

SOLUBILITY

	37°		25°	
	Distilled Water	Saline	Distilled Water	Saline
dl-Isobenzedrine *dl*-mandelate	20.13	18.36	11.50	11.31
dl-Phenylethanolamine *dl*-mandelate	18.56	19.72	11.63	11.78

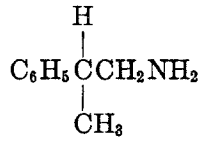
It is interesting to note that the levorotating base of the two ψ-propadrine isomers is the more active physiologically. This is unexpected in view of the fact that *d*-ψ-ephedrine is almost seven times more active as a pressor than is *l*-ψ-ephedrine (4). The explanation of this apparent discrepancy between the ψ-ephedrine bases and their nor-homologs must be left to the future.

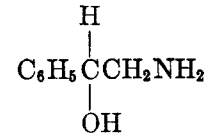
From these results one is led to believe that the optimum configuration for activity is found in those isomers in which the phenyl-bearing carbon atom, if asymmetric, is dextrorotatory (*d*-series if referred to phenylalanine, *l*-series if referred to alanine).

Other correlations between solubility and physiological effects do not appear in the data thus far procured. It is not unlikely, however, that as more information about the physical and physiological properties becomes available that further correlations may be found.

This study reveals a striking parallelism of properties between β-phenylpropylamine and phenylethanolamine as may be seen from Table V.

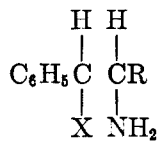
This suggests an unusual type of isosterism,





in which a hydroxyl group of a physiologically active compound may be replaced by a methyl and only relatively minor changes in physical properties are produced. This isosteric analogy apparently holds for physiological properties both quantitatively and qualitatively. When given parenterally both are effective pressors; on the other hand oral administration shows no activity. Furthermore both compounds exert only a slight stimulant action on the central nervous system (13).

These correlations suggest the desirability of comparing the physical and physiological properties of an active molecule of the type:



in which X represents the first elements in groups IV, V, VI, and VII of the periodic table joined by a single bond to the remainder of the molecule, the other valences being satisfied with hydrogen atoms, thus

—CH_3	—NH_2	—OH	—F
(m.w. 15)	(m.w. 16)	(m.w. 17)	(a.w. 19)

The molecular weights of the four isosters would be nearly the same and there should be little difference in electronic structure and molecular size.

SUMMARY

1. Mandelic acid was separated into *dextro* and *levo* components by the use of (−)ephedrine.

2. Phenylethanolamine, β-phenylpropylamine, benzedrine, propadrine, and ψ-propadrine were resolved by means of *d*- and *l*-mandelic acids, and a study of

the solubility of the mandelates at 25° and 37° in distilled water and normal saline was made.

3. From the data procured one is led to believe that the optimum configuration for activity is found in those isomers in which the phenyl-bearing carbon atom, if asymmetric, is levorotatory, and in which the carbinamine carbon, if asymmetric, is dextrorotatory. In all cases except that of the ψ-propadrines, the isomer forming the less soluble mandelate was the more active physiologically.

4. An interesting isosteric analogy between β-phenylpropylamine and phenylethanolamine is pointed out.

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AMORPHIN, A GLYCOSIDE IN *AMORPHA FRUTICOSA* L.

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In 1937 Moore (4) reported the presence of rotenone in the roots, stem bark, and seeds of the legume *Amorpha fruticosa* L. from Nebraska, because they gave a positive Durham test (3). This test has been accepted as a qualitative test for rotenone and some of the rotenoids (5) when applied to leguminous plants. In 1942 Featherly (1), of the Oklahoma Agricultural and Mechanical College, suggested that, inasmuch as *A. fruticosa* is so abundant throughout the Mississippi River Valley, its seed might serve as a source of rotenone during the war emergency. At his request the Bureau of Entomology and Plant Quarantine examined samples of seed from widely different locations for their supposed rotenone content. Although all the samples tested gave a positive Durham reaction, no rotenone or any of the rotenoids could be isolated from any of them.

However, fractionation of the chloroform extractives of the seed collected at Vermillion, S. Dak., by the Soil Conservation Service, yielded a slightly hygroscopic glycoside that melted at 151–151.5° and gave a positive Durham test. Analysis showed the compound, for which the name "amorphin" is suggested, to correspond to the formula $C_{33}H_{40}O_{16}$. It gave a positive orcinol test, but it did not reduce Fehling's solution. When warmed in concentrated hydrochloric acid, amorphin readily dissolved, and when further heated a product separated that after purification melted at 191–192°. This aglycon gave a positive Durham test, and analysis showed it to correspond to the formula $C_{22}H_{22}O_7$. This compound, tentatively designated "amorphigenin," also was obtained from the ether extractives of the seed. The acid filtrate obtained in the hydrolysis of amorphin readily reduced Fehling's solution.

It thus appears that *Amorpha fruticosa* contains a glycoside which, as well as its aglycon, behaves similarly to rotenone in the Durham color test.

EXPERIMENTAL

Extraction of seed. Belyaev (2) showed that the seed of *Amorpha fruticosa* contain considerable oil, and his findings were confirmed in this laboratory. Since large amounts of oil might inhibit the crystallization of any rotenone present in the extractive, the seed was first extracted for a short time with petroleum ether. The extractive contained a small amount of material positive to the Durham test. There remained in the marc at least two compounds that reacted positively to the Durham test. One of these compounds was soluble in ether, and both were soluble in chloroform. Because it was difficult to separate the mixture obtained by extracting only with chloroform, the following typical scheme was considered the most practical method of extraction.

The coarsely ground seed (738 grams) was extracted for 3 hours with petroleum ether (b.p. 30–60°). After removal of the solvent, the marc was finely ground and exhaustively extracted, first with ether and then with acid-free chloroform. The extracts were worked up separately.

Fractionation of petroleum ether extractive. During concentration the petroleum ether

extract partly crystallized. There separated 6.2 grams of material which gave a slightly positive Durham test. On recrystallization from methanol, 780 mg. of a colorless crystalline product was obtained, which melted at 190–191° and was negative in the Durham test. From the methanol mother liquor the neutral fraction, which was only slightly positive in the Durham test, was obtained, but nothing definite could be isolated.

Complete removal of the solvent from the original petroleum ether extract yielded 76 grams of oil. This gave a positive Durham test. The active material was extracted with methanol. The concentrated methanol extract yielded 150 mg. of a colorless crystalline product, m.p. 163–169°, which gave a negative Durham test. The neutral fraction of the mother liquor was dissolved in ether, from which 30 mg. of yellow needles crystallized. The product melted at 235–237°, with decomposition, and did not give the Durham reaction. No active material could be separated from the mother liquor, which still gave a slightly positive Durham test.

Separation of amorphigenin. After removal of the solvent, the ether extract yielded 11.9 grams of oil, which was dissolved in acetone and cooled. Some inactive amorphous material precipitated and was separated. The acetone was removed by evaporation, and the residual oil partly crystallized after solution in methanol. The amorphigenin thus obtained (200 mg.) was thrice recrystallized from methanol, and then melted at 191–192°. It gave a positive Durham test but failed to reduce Fehling's solution either before or after acid hydrolysis. It gave a negative phenol test.

Anal. Calc'd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.56; 2 OCH_3, 15.56; mol. wt., 398.

Found (avg. 2 anal.): C, 66.63; H, 5.63; OCH_3, 15.55; mol. wt. (Rast), 396, 400.

The mother liquor from methanol recrystallization yielded 45 mg. of colorless crystalline material, which melted at 218° after one recrystallization. It was positive to the Durham test, but sufficient material was not available for further study.

Separation of amorphin. After removal of the solvent under reduced pressure, the chloroform extractive weighed 5.7 grams. It was dissolved in a small amount of boiling acetone. Upon cooling, 950 mg. separated, which was boiled with chloroform and filtered while hot. The insoluble residue, upon being recrystallized twice from water and twice from methanol, yielded 450 mg. of pure amorphin, which melted to a glass at 151–151.5°. The mother liquor contained more of this compound, but was lost during further purification. Amorphin gave a positive Durham test, a positive orcinol test, and a negative phenol test. It did not reduce Fehling's solution until after acid hydrolysis. For analysis the compound was dried at 100° (0.5 mm.) for 30 minutes.

Anal. Calc'd for $C_{33}H_{40}O_{16}$: C, 57.22; H, 5.82; 2 OCH_3, 8.95.

Found (avg. 2 anal.): C, 57.44; H, 5.97; OCH_3, 8.85.

Hydrolysis of amorphin. When boiled with 1 cc. of concentrated hydrochloric acid, 50 mg. of amorphin readily dissolved; on further heating a product precipitated which was separated from the diluted and cooled reaction mixture. This aglycon was recrystallized from methanol and melted at 191–192°. When mixed with an equal part of amorphigenin obtained as described above, the melting point showed no depression.

The acid filtrate readily reduced Fehling's solution, but the sugar portion of the molecule could not be isolated.

SUMMARY

The seed of *Amorpha fruticosa* L. gives the color reaction in the Durham test which heretofore has been considered specific for rotenone and the rotenoids, but no compounds of this class could be isolated from them. The product that is responsible for the positive reaction in the Durham test is amorphigenin, $C_{22}H_{22}O_7$, the aglycon of the glycoside amorphin, $C_{33}H_{40}O_{16}$.

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