phere before its rotation was determined. A 0.05% solution in 0.01 *N* HNO_3 containing a trace of ceric ammonium nitrate gave α_{5461} + 0.13°, whence $[\alpha]^{15}_{5461}$ + 260° and $[M]^{15}_{5461}$ +2400°. The rotation in the Nad line was slightly dextro. The degree of hydration of the substance was variable owing to the use of a strong desiccant.

Anal. Calcd. for $Fe(C_{10}H_8N_2)_3(ClO_4)_3 \cdot 3H_2O$: Fe, 6.37; N, 9.59. Found: Fe, 6.28; N, 9.50.

1-Tris-2,2′-dipyridyl Iron(III) Perchlorate Trihydrate.—This was obtained in the same manner as the dextro compound, using instead *l*-tris-2,2′-dipyridyl ferrous perchlorate as a microcrystalline powder. A 0.05% solution in the same medium as above gave α_{5461} − 0.13°, whence $[\alpha]^{15}_{5461}$ −260°.

Anal. Calcd. for $Fe(C_{10}H_8N_2)_3 \cdot (ClO_4)_3 \cdot 3H_2O$: Fe, 6.37; N, 9.59. Found: Fe, 6.40; N, 9.63.

***dl*-Tris-1,10-phenanthroline Osmium(III) Chloride Monohydrate.**—*dl*-Tris-1,10-phenanthroline osmium(II) chloride octahydrate (0.2 g.) in methanol (10 ml.) at 0°, was treated with chlorine gas until the dark brown solution became bluish-red. The osmic complex was immediately precipitated with ether, and the precipitate washed first with 50% methanol ether and then ether.

The dark red micro needles were very soluble in water giving a brilliant bluish-red solution which rapidly turned brown due to reduction. The substance was more stable in the solid state.

Anal. Calcd. for $Os(C_{12}H_8N_2)_3 \cdot Cl_2 \cdot H_2O$: Os, 22.24; N, 9.83. Found: Os, 22.1; N, 9.9.

***dl*-Tris-1,10-phenanthroline Osmium(III) Perchlorate Monohydrate.**—*dl*-Tris-1,10-phenanthroline osmium(II) perchlorate dihydrate (0.5 g.) was suspended in 20 ml. of water, cooled to 0° and treated with chlorine until the substance went into solution. The deep reddish-blue solution was warmed to 20°, 10% sodium perchlorate was added until the solution became cloudy and then precipitation was brought about by cooling the mixture on ice and by scratching the sides of the vessel. The precipitate was filtered through a sintered glass filter, washed quickly first with cold absolute alcohol, then with ether and dried in warm air.

The monoclinic prisms were dark red with a grayish-blue reflex. The aqueous solutions rapidly underwent self reduction except in the presence of chlorine or acid.

Anal. Calcd. for $Os(C_{12}H_8N_2)_3(ClO_4)_3 \cdot H_2O$: Os, 18.17; N, 8.03. Found: Os, 18.3; N, 8.1.

***d*-Tris-1,10-Phenanthroline Osmium(III) Perchlorate Monohydrate.**—*d*-Tris-1,10-phenanthroline osmium(II) perchlorate was treated as the *dl*-perchlorate above. The bluish-red prisms of the active perchlorate were more soluble than the racemate. A 0.01% solution in water containing a trace of chlorine gave α = +0.04°, whence $[\alpha]^{20}_{5461}$ +400°, and $[M]^{20}_{5461}$ +4200°. No rotation was observed in the Nad line.

Anal. Calcd. for $Os(C_{12}H_8N_2)_3(ClO_4)_3 \cdot H_2O$: Os, 18.17; N, 8.03. Found: Os, 18.3; N, 8.10.

***l*-Tris-1,10-Phenanthroline Osmium(III) Perchlorate Monohydrate.**—The bluish-red prisms of this substance were prepared from *l*-tris-1,10-phenanthroline osmous perchlorate in the same manner as the *dl*-compound. A 0.01% solution in water containing chlorine gave α −0.04°, whence $[\alpha]^{20}_{5461}$ −400°.

Anal. Calcd. for $Os(C_{12}H_8N_2)_3(ClO_4)_3 \cdot H_2O$: Os, 18.17; N, 8.03. Found: Os, 18.1; N, 8.0.

SYDNEY, AUSTRALIA

NOTES

Preparation of Alkyl Isocyanates Using Alkyl Phosphates

BY THEODORE I. BIEBER[1]

RECEIVED APRIL 10, 1952

Isocyanic esters are generally prepared by the phosgenation of primary amines or by the Curtius rearrangement of acyl azides, but the alkylation of an inorganic cyanate constitutes a convenient method in some cases. Ethyl isocyanate may thus be prepared by the reaction of potassium cyanate with potassium ethyl sulfate,[2] ethyl sulfate[3] or ethyl *p*-toluenesulfonate.[3] A satisfactory yield is obtainable only with ethyl sulfate as the ethylating agent. However, the resulting ethyl isocyanate has been observed by us to polymerize very readily, even after several redistillations. It appears likely that this polymerization is catalyzed by sulfur dioxide, a known decomposition product of ethyl sulfate at the alkylation temperature used, and that distillation does not achieve the complete separation of this gas from the low-boiling ethyl isocyanate.

We have found that triethyl phosphate, a readily available substance, is capable of ethylating potassium cyanate at about 200°, affording ethyl isocyanate in good yield. The product so obtained does not polymerize on standing. It should be pointed out that triethyl phosphate is stable at its boiling point (216°), whereas ethyl sulfate boils with considerable decomposition (208°). The reaction of ethyl sulfate with potassium cyanate is rather violent and requires a moderator, like sodium carbonate[3]; the analogous reaction of triethyl phosphate, however, is smooth and unlikely to get out of control. The fact that triethyl phosphate, in contrast to ethyl sulfate, has no corroding action and is safe to handle, also deserves mention.

The ratio of phosphoric ester to potassium cyanate employed in this reaction is considerably greater than one (on a molar basis), so that the principal reaction leading to ethyl isocyanate must be

$$(C_2H_5O)_3PO + KNCO \longrightarrow (C_2H_5O)_2PO_2K + C_2H_5NCO$$

only one ethyl group of triethyl phosphate being utilized. The use of triethyl phosphate in limited amount gives unsatisfactory results.

Butyl isocyanate was similarly prepared, but in smaller yield, by the reaction of potassium cyanate with tributyl phosphate. Butyl isocyanate has previously been obtained by the Curtius rearrangement of valeryl azide but was not separated from

(1) Address correspondence concerning this paper to the author at 80-40 Lefferts Blvd., Kew Gardens 15, N. Y.

(2) A. Wurtz, *Compt. rend.*, **27**, 241 (1848); *Ann. chim.*, [3] **42**, 43 (1854).

(3) K. H. Slotta and L. Lorenz, *Ber.*, **58**, 1320 (1925).

the toluene used as solvent in the azide decomposition.[4a] The preparation of pure butyl isocyanate by the phosgenation of butylamine has been reported only recently.[5]

Experimental

Ethyl Isocyanate.—In a 500-ml. distilling flask were placed 98 g. of triethyl phosphate and 30 g. of potassium cyanate (along with a few glass beads). Potassium cyanate does not dissolve appreciably in triethyl phosphate, even at higher temperatures. The mixture was strongly heated until distillation occurred. For the next ten minutes heat was applied on and off to maintain distillation at a fairly even rate. The reaction mixture became quite viscous by the end of this time and heating was discontinued when strong white fumes due to the condensation of water vapor started to appear, the water being a result of decomposition within the viscous mass. A parallel experiment had shown that when these fumes were allowed to distil, water droplets appeared in the distillate and caused the evolution of carbon dioxide from the latter (hydrolysis of ethyl isocyanate). The viscous residue in the distilling flask set to a gel on cooling. It consisted chiefly of potassium diethyl phosphate along with some triethyl phosphate.

The distillate, a mixture of ethyl isocyanate and triethyl phosphate, was subjected to distillation, and 16.5 g. of ethyl isocyanate (a 63% yield based on potassium cyanate) was collected at 60–63°. The high-boiling liquid residue from the distillation was triethyl phosphate (16.3 g.).

An experiment employing a smaller relative amount of triethyl phosphate than used above gave a less satisfactory result, since the reaction mixture became viscous and gave rise to water vapor before much product had been collected.

Butyl Isocyanate.—The procedure is very similar to that used for ethyl isocyanate. There were employed 73 g. of tributyl phosphate and 20 g. of potassium cyanate. In this case also, when heating of the reaction mixture was continued after it had become viscous, decomposition with formation of water vapor occurred. The reaction was therefore stopped at this stage. The residue in the distilling flask, consisting chiefly of potassium dibutyl phosphate, solidified on cooling. The distillate contained butyl isocyanate and tributyl phosphate, separable by fractional distillation. After three distillations 7 g. of butyl isocyanate (a 29% yield based on potassium cyanate) boiling at 115–117° was obtained; reported b.p. 113–116°.[5]

Reaction of the butyl isocyanate prepared in this manner with *p*-toluidine in benzene solution yielded 1-butyl-3-(*p*-tolyl)-urea in very good yield, m.p. 118° after recrystallization from an alcohol–water mixture; reported m.p. 119°.[4b]

(4) (a) J. W. Boelmer, *Rec. trav. chim.*, **55**, 382 (1936); (b) **55**, 386 (1936).

(5) W. Siefken and A. Doser, U. S. Patent 2,326,501 (1943); R. J. Slocombe, E. E. Hardy, J. H. Saunders and R. L. Jenkius, THIS JOURNAL, **72**, 1890 (1950).

NICHOLS CHEMICAL LABORATORIES
NEW YORK UNIVERSITY, UNIVERSITY HEIGHTS
NEW YORK, N. Y.

Optical Enantiomorphs of Isovaline

BY CARL G. BAKER, SHOU-CHENG J. FU, SANFORD M. BIRNBAUM, HERBERT A. SOBER AND JESSE P. GREENSTEIN

RECEIVED APRIL 23, 1952

A levorotatory isomer ($[\alpha]^{20}D$ −9.10° in H_2O) was isolated by Ehrlich and Wendel[1] from the yeast fermentation of racemic isovaline (I). Fischer and

$(C_2H_5)(CH_3)C(NH_2)COOH$
I

von Grävenitz prepared the dextrorotatory isomer ($[\alpha]^{19}D$ + 11.0° in water) from the formyl compound with brucine.[1a] They did not prepare the enantiomorph. Because of this lack of concordance, there exists some uncertainty in regard to the rotation value of the isolated isomers and to their optical configuration. For these reasons, racemic isovaline was resolved into its optical enantiomorphs by the general enzymatic procedure developed in this Laboratory.[2–7] This procedure essentially depends upon the asymmetric enzymatic hydrolysis of the N-acylated derivative of the racemic amino acid, followed by the separation of the resulting L-amino acid and acyl-D-amino acid in different solvents.

Two special problems arose in the application of this procedure to the resolution of isovaline. The first of these was whether the N-acylated derivative of an amino acid which lacked a hydrogen atom on the α-carbon atom would be susceptible to the action of hog kidney acylase I.[4] N-Chloroacetyl-DL-isovaline was prepared, and found to be asymmetrically hydrolyzed at the L-isomer at a rate which, although considerably lower than that observed with either chloroacetyl-DL-valine or chloroacetyl-DL-norvaline,[4] was sufficient to serve the present purpose. The second problem was to isolate the extremely soluble L-isovaline from the resolution mixture at the end of the enzymatic reaction. This was solved by the employment of a chromatographic procedure involving a cationic exchange resin.

By these means no difficulty was encountered in preparing L-isovaline ($[\alpha]^{25}D$ +11.13°) and D-isovaline ($[\alpha]^{25}D$ −11.28°) in satisfactory yield. It would have been expected that the levorotatory isomer isolated by Ehrlich and Wendel from the fermentation mixture was D-isovaline, and our results are in accord with this assignment of configuration. The fact that our rotation values are higher in magnitude than that reported by Ehrlich and Wendel is not surprising in view of the difficulties which they encountered in their isolation and purification procedures. Our values are in good agreement with that obtained for the dextrorotatory isomer by Fischer and von Grävenitz.[1a]

Experimental Part

N-Chloroacetyl-DL-isovaline.—DL-Isovaline[8] was treated with chloroacetyl chloride and chilled NaOH in the usual manner. On acidification with concd. HCl to *p*H 1.7, N-chloroacetyl-DL-isovaline crystallized in 82% yield. It was recrystallized from water; m.p. 161.5–163.0° (cor.). A m.p. of 162° has been reported for this compound.[9]

Anal.[10] Calcd. for $C_7H_{12}O_3NCl$: C, 43.4; H, 6.3; N, 7.2; Cl, 18.3. Found: C, 43.4; H, 6.4; N, 7.2; Cl, 18.2.

Enzymatic Resolution of Chloroacetyl-DL-isovaline.—Fifty-three grams of N-chloroacetyl-DL-isovaline was dissolved in 2 liters of water and the solution brought to *p*H 7.5 with 2 *N* LiOH. Three grams of acylase I powder[4] was dissolved in the solution, and water added to bring the concentration of the racemic compound to 0.1 *M*. The enzymatic hydrolysis of the substrate could not be followed by the usual manometric ninhydrin procedure, because the

(1) F. Ehrlich and A. Wendel, *Biochem. Z.*, **8**, 438 (1908).

(1a) E. Fischer and von Grävenitz, *Ann.*, **406**, 5 (1914).

(2) J. P. Greenstein, L. Levintow, C. G. Baker and J. White, *J. Biol. Chem.*, **188**, 647 (1951).

(3) L. Levintow and J. P. Greenstein, *ibid.*, **188**, 643 (1951).

(4) S. M. Birnbaum, L. Levintow, R. B. Kingsley and J. P. Greenstein, *ibid.*, **194**, 455 (1952).

(5) D. Rudman, A. Meister and J. P. Greenstein, THIS JOURNAL, **74**, 551 (1952).

(6) D. Hamer and J. P. Greenstein, *J. Biol. Chem.*, **198**, 81 (1951).

(7) S. M. Birnbaum and J. P. Greenstein, *Archiv. Biochem. Biophys.*, **39**, 108 (1952).

(8) P. A. Levene and R. Steiger, *J. Biol. Chem.*, **76**, 299 (1928).

(9) K. W. Rosenmund, *Ber.*, **42**, 4473 (1909).

(10) Analyses by R. J. Koegel and staff of this Laboratory.

liberated amino acid does not yield quantitative amounts of carbon dioxide, and therefore the nitrous acid method was employed. The rate of hydrolysis of the susceptible L-isomer of N-chloroacetyl-DL-isovaline by acylase I is 38 micromoles per hour per mg. protein N. The digest was treated with a few drops of toluene, and allowed to incubate at 38° for 24 hours. Analyses on an aliquot of the digest revealed that the hydrolysis of the compound had proceeded to 50%. Another gram of the enzyme was added, and the digest allowed to stand for 12 hours longer. Analysis again revealed 50% hydrolysis. Acetic acid was added to *p*H 5, and the protein filtered off with the aid of Norit. The filtrate was evaporated at 40° *in vacuo*, and the small amount of protein which flocculated was again removed by filtration. The filtrate contained L-isovaline, chloroacetic acid and chloroacetyl-D-isovaline. Treatment with excess ethanol in the usual manner[2,7] failed to bring about the separation of the highly soluble L-isovaline. Treatment with concd. HCl to *p*H 1.7 led to the separation in 50% yield of chloroacetyl-D-isovaline. After recrystallization from acetone–ether, the m.p. was 158° (cor.), and $[\alpha]^{25}D$ −9.0° for a 2% solution in absolute ethanol. In 2% aqueous solution, the rotation of the compound was imperceptible.

Anal. Calcd. for $C_7H_{12}O_3NCl$: N, 7.2. Found: N, 7.1.

Chromatographic Separation of the Enzymatic Products.—A general chromatographic procedure for the separation of the amino acid products obtained by the enzymatic resolution method has been developed in this Laboratory and will be described more fully in a subsequent publication.[11] A brief description of the procedure as it applied to the present problem is as follows. A 100-ml. aliquot of a deproteinized and concentrated isovaline resolution mixture (corresponding to 25.8 g. of chloroacetyl-DL-isovaline in the original digest) was poured onto the top of a column 87 cm. high and 6.5 cm. in diameter composed of 20 to 50 mesh Dowex 50 resin in the acid phase.[12]

Elution with water was carried out at a flow rate of 40 to 60 ml. per hour. Chloroacetyl-D-isovaline appeared in the effluent after approximately 250 ml. of water had passed through the column, as indicated by a fall in *p*H from about 7 to about 3. Aliquots taken from the hour-long fractions were hydrolyzed in 2 *N* HCl for 2 hours and tested for color development with ninhydrin. By this means it was demonstrated that the N-acyl derivative was eluted in approximately 3 liters of effluent. No free isovaline was present in the fractions collected during this interval since ninhydrin tests on unhydrolyzed aliquots were all negative. After further washing of the column with an additional 1.5 liters of water, elution was begun with 2.5 *N* HCl. L-Isovaline began to appear after about 4 liters of solution had passed through the column, as shown by positive ninhydrin tests. The entire L-isovaline was eluted after an additional 3800 ml. of solution had passed through the column.

All the fractions containing chloroacetyl-D-isovaline were combined and evaporated to dryness *in vacuo*, and the residue was taken up in absolute ethanol to remove sodium chloride[13] and any residual protein. The ethanol was evaporated and the residue taken up in acetone and filtered to ensure further the absence of any L-isovaline or sodium chloride. The chloroacetyl-D-isovaline was then isolated by evaporation of the acetone and crystallization from acetone–ether; m.p. 158° (cor.); yield 55% of theory, based on the original amount of chloroacetyl-DL-isovaline; $[\alpha]^{25}D$ −9.0° for a 2% solution in absolute ethanol.

Anal. Calcd. for $C_7H_{12}O_3NCl$: N, 7.2. Found: N, 7.2.

Thus the chloroacetyl-D-isovaline isolated from the column was identical in properties with that obtained by acidification of the resolution mixture. Five grams of chloroacetyl-D-isovaline was refluxed for 2 hours with 100 cc. of 2 *N* HCl. The solution was decolorized with Norit, and the filtrate evaporated *in vacuo* to dryness. The residue was dissolved in 100 cc. water and the solution treated with a slight excess of silver carbonate. The silver chloride was filtered off, and the filtrate saturated with hydrogen sulfide gas. The final filtrate was evaporated to dryness *in vacuo* and the residual D-isovaline taken up in a little water, the solution filtered, and acetone added in excess to the clear filtrate. The D-isovaline crystallized as long needles in nearly quantitative yield, $[\alpha]^{25}D$ −11.28° for a 5% solution in water.

Anal. Calcd. for $C_5H_{11}O_2N$: C, 51.2; H, 9.4; N, 12.0. Found: C, 51.0; H, 9.5; N, 12.0.

The combined fractions containing the L-isovaline were evaporated to dryness *in vacuo*, and the residue taken up in absolute ethanol and filtered to remove sodium chloride.[13] The ethanol was evaporated, and the residue treated successively with silver carbonate and hydrogen sulfide as described for the D-enantiomorph. The yield after crystallization from water with excess acetone was 77% of the theoretical, based on the original amount of chloroacetyl-DL-isovaline; $[\alpha]^{25}D$ +11.13° for a 5% solution in water.

Anal. Calcd. for $C_5H_{11}O_2N$: C, 51.2; H, 9.4; N, 12.0. Found: C, 51.0; H, 9.5; N, 12.2.

NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTES OF HEALTH
U. S. PUBLIC HEALTH SERVICE
BETHESDA, MARYLAND

(11) C. G. Baker and H. A. Sober, in preparation.

(12) Cationic exchange resin from the Dow Chemical Company. The resin was regenerated by two cycles of washing with 5 *N* HCl, water, 1 *N* NaOH and water, followed by a final 5 *N* HCl and water wash.

(13) Large volumes of water were used for the final wash of the resin during its regeneration. However, even after the effluent was neutral to phenolphthalein, additional sodium chloride was obtained. The coarse mesh resin employed probably requires a longer equilibration period than does the resin of a finer mesh.

Some Alkyl Benzenesulfonates[1,2]

BY BERTIN L. EMLING

RECEIVED MAY 12, 1952

Six alkyl benzenesulfonates and their pyridinium salts have been synthesized. Their physical properties and yields are given in Tables I and II. None of these compounds has been reported previously in the chemical literature, although a commercial grade of *n*-butyl benzenesulfonate is produced by the Wyandotte Chemicals Corporation.

Attempts to synthesize *t*-butyl arylsulfonates were unsuccessful. Besides the method used to make the normal alkyl sulfonates, the addition reaction of isobutylene with a sulfonic acid was tried, but the *t*-butyl esters could not be isolated. *t*-Butyl alcohol was produced when water was present, while dimers and trimers of isobutylene were obtained under anhydrous conditions.

Experimental

n-Alkyl Benzenesulfonates.—The sulfonates listed in Table I were prepared from benzenesulfonyl chloride, pyridine and the appropriate alcohol according to the procedure of Sekera and Marvel.[3] The pyridinium salts, listed

TABLE I

n-ALKYL BENZENESULFONATES, $C_6H_5SO_3$-R

R	B.p. °C.	Mm.	Yield, %	$n^{25}D$	d^{25}_4	S analyses, % Calcd.	Found
C_4H_9	147–149	4	65	1.4997	1.148	14.97	15.15
C_5H_{11}	136–138	1	75	1.4969	1.119	14.04	13.96
C_6H_{13}	135–136	0.5	58	1.4952	1.099	13.23	13.36
	M.p.						
$C_{14}H_{29}$	25–25.5		63			9.04	8.82
$C_{16}H_{33}$	35–36		79			8.38	8.45
$C_{18}H_{37}$	45–46		85			7.81	7.80

(1) Based on a paper presented, March 26, 1952, at the 121st Meeting of the American Chemical Society, Buffalo, N. Y.

(2) The author wishes to acknowledge the assistance of John Palkiewicz and Carl Miskowicz of King's College; of Jane Furikawa, Mary Wassel and Joan Boersig of Marian College; of Maragret Jevnik of Caldwell College; and of Paul Mosso and Arthur Marcozzi of St. Vincent College.

(3) V. C. Sekera and C. S. Marvel, THIS JOURNAL, **55**, 346 (1933).

in Table II, were synthesized by heating the sulfonates with dry pyridine at 130–140°.[3]

TABLE II

N-*n*-ALKYLPYRIDINIUM BENZENESULFONATES, $C_5H_5NRC_6H_5SO_3$

R	M.p., °C.	Yield, %	Sulfur, % Calcd.	Sulfur, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Butyl	86–87	42	10.9	10.7	..	..
Amyl	95–96	50	10.43	10.30	..	..
Hexyl	105–106	50	9.97	9.98	..	..
Tetradecyl	117–118	90	7.39	7.12	3.21	3.15
Hexadecyl	118–118.5	88	6.94	6.88	3.03	2.96
Octadecyl	120.5–121.5	80	6.55	6.58	2.86	2.87
Butyl[a]	63–64	70	10.43	10.59	4.56	4.53
Butyl[b]	81–82	35	10.43	10.77	4.56	4.42

[a] γ-Picolinium benzenesulfonate. [b] α-Picolinium benzenesulfonate.

Reaction of Isobutylene and *p*-Toluenesulfonic Acid.—Twenty grams of *p*-toluenesulfonic acid monohydrate (Eastman Kodak Co. Reagent Grade) dissolved in 9 g. of water was placed in the pressure bottle of a Parr low pressure gas apparatus, and isobutylene was passed in at room temperature at 19–28 lb. gage pressure with continuous agitation. The reaction mixture was made strongly basic with potassium hydroxide and extracted with ether. The ether extract was dried over anhydrous potassium carbonate and distilled through a 10 in. helix packed partial take-off column. Sixteen and one-half grams of *t*-butyl alcohol was obtained; b.p. 78–81°, $n^{25}D$ 1.3870. There was no sulfur present in the ether extract.

Reaction of Isobutylene with Benzenesulfonic Acid.—Fifteen grams of reagent grade benzenesulfonic acid was dehydrated by heating at 135° for five hours and was then distilled at 147–149° at 2 mm. The acid was dissolved in 20 ml. of dry dioxane, placed in a Parr pressure bottle and exposed with shaking to C.P. isobutylene at 10–20 lb. gage pressure for 13 hours at room temperature. Two layers formed, a lower water-soluble layer and an insoluble layer. The upper layer was separated, washed with water and saturated potassium carbonate solution, dried over calcium sulfate and distilled through a two-foot helix-packed partial take-off column. Two principal fractions were obtained boiling at 99.5–100.2° (16 g.), and 175.3–175.6° (31 g.) at 725 mm. The first fraction was diisobutylene, and the second triisobutylene.[4] The first fraction had a molecular weight of 116 (cryoscopic method in benzene); calcd. for C_8H_{12}, mol. wt., 112.

Acknowledgment.—We wish to thank the Research Corporation for a Frederick Gardner Cottrell grant-in-aid in support of this work.

(4) C. O. Tongberg, J. D. Pickens, M. R. Fenske and F. C. Whitmore, THIS JOURNAL, **54**, 3706 (1932); F. C. Whitmore, *et al.*, *ibid.*, **63**, 2035 (1941).

DEPARTMENT OF CHEMISTRY
ST. VINCENT COLLEGE
LATROBE, PENNA.

The Conversion of α-Diazo-*o*-methoxyacetophenone to Coumaranone

BY AJAY KUMAR BOSE AND PETER YATES

RECEIVED APRIL 3, 1952

Marshall, Kuck and Elderfield[1] have reported that coumaranone is formed when α-diazo-*o*-methoxyacetophenone is treated with cold acetic acid. In connection with a general study of the reactions of diazoketones we have investigated further the details of this interesting ring closure and have found that the reaction proceeds in the presence of a catalytic amount of hydrochloric acid. It seems hardly likely that α-chloro-*o*-methoxyacetophenone is an intermediate in the reaction under these conditions in view of the stability of α-chloro-*o*-methoxyacetophenone in acetic acid.[2]

α-Diazo-*o*-methoxyacetophenone was prepared by the slow addition of a cold ethereal solution of *o*-methoxybenzoyl chloride to a large excess (about 4 molar equivalents) of ethereal diazomethane, thus minimizing the formation of any chloroketone.[3] A measured volume of standard hydrochloric acid was added to an aqueous suspension of the diazoketone and the nitrogen evolved was measured.

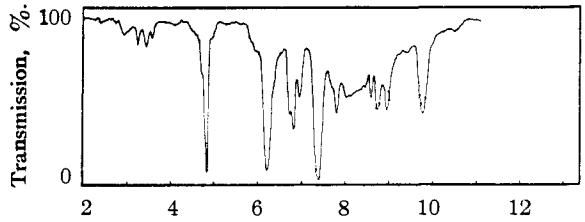


Fig. 1.—Infrared spectrum of α-diazo-*o*-methoxyacetophenone in chloroform solution.

The addition of only 0.05 molar equivalent of acid led to the evolution of one molar equivalent of nitrogen and to the separation of crystalline coumaranone, which was obtained by filtration in 86.5% yield. The identity of the coumaranone was established by a mixed melting point and comparison of the infrared spectrum[4] (Fig. 2) with that of an authentic sample prepared by the action of sodium acetate on α-chloro-*o*-hydroxyacetophenone.[5]

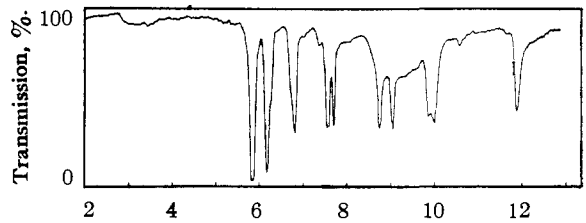


Fig. 2.—Infrared spectrum of coumaranone in chloroform solution

In view of the fact that only a fraction of an equivalent of acid is required to liberate one molar equivalent of nitrogen, a reaction scheme compatible with the catalytic nature of the acid is formulated as

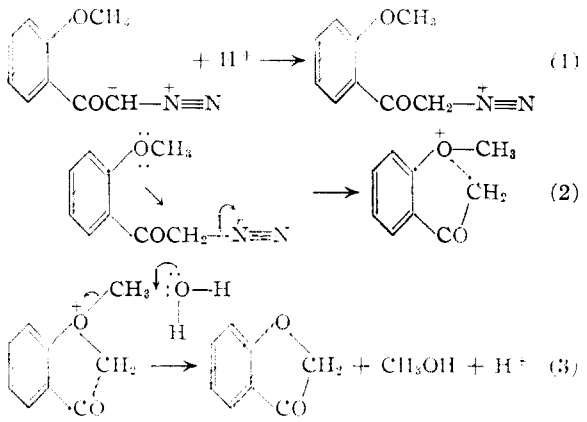
(1) E. R. Marshall, J. A. Kuck and R. C. Elderfield, *J. Org. Chem.*, **7**, 444 (1942).

(2) K. v. Auwers, *Ber.*, **59**, 2899 (1926).

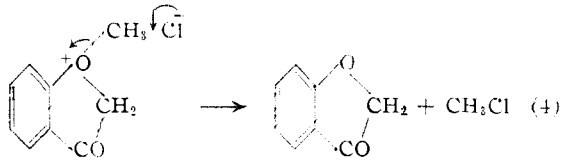
(3) The absence of appreciable amounts of chloroketone is demonstrated by the weakness of the 5.95μ band in the infrared spectrum (Fig. 1): the band at 4.83μ and the displacement of the carbonyl band to *ca.* 6.2μ are characteristic of aliphatic diazoketones (P. Yates, to be published).

(4) It is interesting to note that the spectrum of coumaranone exhibits two peaks of equal intensity in the carbonyl region.

(5) We are grateful to Mr. Edward Trachtenberg for making available to us a sample of coumaranone prepared by this method and its infrared spectrum.



In reaction (2) the nucleophilic methine carbon of the diazoketone is attacked by a proton to give an aliphatic diazonium ion[6] which then loses nitrogen by a displacement reaction on carbon involving an unshared electron pair on oxygen (equation (2)).[7] The oxonium ion thus formed is then attacked by the solvent water to give coumaranone and methanol and at the same time the proton is regenerated. Reactions (2) and (3) might well be concerted. Although this scheme conforms with the catalytic nature of the action of the hydrochloric acid, the acid will be partially consumed by an alternative final step—the attack of a chloride ion on the oxonium intermediate



However, this will only occur as a side reaction since the presence of water in large excess ensures much more frequent attack by solvent than by chloride ion.

It is of interest in connection with the present work to consider a recent report by Seth and Deshapande[8] that α-diazo-*o*-methoxyacetophenone decomposes spontaneously with the evolution of nitrogen to give a crystalline solid, m.p. 104°. This substance was assigned the molecular formula $C_9H_8O_2$ and two derivatives were described but no structure assignation was made. The properties of this product (Table I) and its source suggested to us that it might be coumaranone. Our sample of α-diazo-*o*-methoxyacetophenone, however, gave no visible evidence of decomposition on standing at 25–28° for six days; furthermore, the intensity and position of bands in the infrared spectrum of the diazoketone before and after storage were identical in every respect, confirming that pure α-diazo-*o*-methoxyacetophenone does not decompose spontaneously.[9]

(6) *Cf.* J. F. Lane and R. L. Feller, THIS JOURNAL, **73**, 4230 (1951).

(7) The geometry of the system favors this reaction rather than direct attack on the diazonium ion by the solvent, as in the case of simple diazoketones (*cf.* ref. 6).

(8) U. S. Seth and S. S. Deshapande, *J. Ind. Chem. Soc.*, **27**, 429 (1950).

(9) It is noteworthy that neither Marshall, Kuck and Elderfield[1] nor P. Pfeiffer and E. Enders, *Ber.*, **84**, 247 (1951), report any spontaneous decomposition of their samples of this diazoketone.

TABLE I

	Seth and Deshapande's product	Coumaranone
Melting point, °C.	104	101–102[a]
Analysis:	$C_9H_8O_2$ requires:	$C_8H_6O_2$ requires:
Found:		
C, 72.5; H, 4.7	C, 73.0; H, 5.4	C, 71.6; H, 4.5
Molecular weight:		
Found: 140	148	134
Semicarbazone:		
Melting point, °C.	220	231[b]
Analysis:	$C_{10}H_{11}O_2N_3$ requires	$C_9H_9O_2N_3$ requires
Found: N, 21.2	N, 20.5	N, 22.0
Product with bromine:		
Melting point, °C.	147	142[c]
Analysis:	$C_9H_8O_2Br_2$ requires	$C_8H_6O_2Br_2$ requires
Found: Br, 53.1	Br, 52.0	Br, 54.8

[a] D. A. Clibbens and M. Nierenstein, *J. Chem. Soc.*, 1493 (1915). [b] R. Stoermer and F. Bartsch, *Ber.*, **33**, 3178 (1900). [c] K. Fries and W. L. Pfaffendorf, *ibid.*, **45**, 161 (1912).

Experimental

α-Diazo-*o*-methoxyacetophenone.—An ethereal solution of 3 g. of *o*-methoxybenzoyl chloride[10] was added drop by drop with thorough shaking to an ethereal solution of a large excess (about 4 molar equivalents) of diazomethane at 0°. After a brief induction period nitrogen was evolved vigorously. The reaction mixture was allowed to stand overnight at room temperature and was then filtered to remove a small amount of solid that had separated. After removing the excess diazomethane and ether by distillation under reduced pressure at 30–40° a golden yellow oil (3.1 g., quantitative yield) was obtained. A sample on standing at room temperature (25–28°) for six days showed no visible sign of decomposition and its infrared spectrum was found to be identical with that of the freshly prepared material.

Coumaranone.—In a flask fitted with a calibrated dropping funnel and connected to a gas buret were placed 1 g. of α-diazo-*o*-methoxyacetophenone and 5 ml. of distilled water. To this was added by means of the dropping funnel, 0.1 ml. of 1.13 *N* hydrochloric acid during vigorous stirring with a magnetic stirrer; a steady evolution of gas was observed. A second 0.1 ml. of acid was added after 1 hour, when the gas evolution had slackened. The reaction was complete in three hours with the evolution of one molar equivalent of nitrogen. Further addition of acid was without effect. The crystalline solid that had separated was collected by filtration and dried. A light yellow solid (0.65 g., 86.5%), m.p. 95–97°, was thus obtained. Purification by sublimation at 1 mm. gave an almost colorless crystalline powder of m.p. 100–101.5°, undepressed on admixture with an authentic sample of coumaranone.

(10) J. T. Marsh and H. Stephen, *J. Chem. Soc.*, 1635 (1925).

CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY
CAMBRIDGE, MASS.

The High Field Conductance of Copper Sulfate Relative to Potassium Chloride at 25°[1]

BY DANIEL BERG AND ANDREW PATTERSON, JR.

RECEIVED APRIL 25, 1952

The high field conductance of magnesium sulfate has been determined by Bailey and Patterson.[2] It was found that the high field conductance was insensitive to change of temperature over the range 5–55° when plotted as the fractional high field conductance quotient, $\Delta\lambda/\lambda_0(\%)$, although the actual conductance varied markedly with temperature. It was also found that the experimental results were decidedly larger than the values pre-

(1) Contribution No. 1100 from the Department of Chemistry, Yale University.

(2) F. E. Bailey and A. Patterson, THIS JOURNAL, **74**, 4426 (1952).

dicted by the Onsager–Wilson theory[3]: the difference at 200 kv./cm. between the theoretical and experimental results was 1.5. A similar determination of high field conductance of a zinc sulfate solution showed a larger change of conductance with increasing field and the same type of disparity between the theoretical and experimental results: the difference at 200 kv./cm. was 1.7.[4] Bailey and Patterson[5] found it possible to make a correction for the "weakness" of the two 2–2 electrolytes on the assumption that ion pairs were present which had a calculable Wien effect characteristic of a weak electrolyte. The agreement between the corrected theory and the experimental results was gratifying.

In order to check the high field conductance of another 2–2 electrolyte and the success of the corrected theory[5] in the computation of the Wien effect for such an electrolyte, copper sulfate was chosen since the low field conductance data, required for the correction, were available for it.[3] The measurement was made at 25° only since in view of the results with magnesium sulfate[2] it was deemed unnecessary to study other temperatures.

Determinations of high field conductance were made on two different copper sulfate solutions, having very nearly the same concentration, approximately 1.77×10^{-4} molar. The concentration of the potassium chloride reference solution was 3.18×10^{-4} molar. Both salts were purified by repeated crystallizations from conductivity water and made up in strong stock solutions in conductivity water. The solutions for actual conductance measurement were made by weight dilution of the strong solutions to give suitable resistance values in the conductance cells: R_0 ($CuSO_4$) = 1026.0 ohms; R_0 (KCl) = 921.5 ohms. The concentration of the potassium chloride stock solution was determined from the weight of fused potassium chloride and water used; the concentration of the copper sulfate stock solution was obtained from low field conductance measurements. The determination of high field conductance was done in exactly the same manner as described by Gledhill and Patterson.[4] The results are given in Fig. 1.

Figure 1 shows the computed Onsager–Wilson theory relative to potassium chloride, uncorrected, on the lowest curve and the corrected Onsager theory on the highest curve. The experimental results for copper sulfate are shown as open and filled circles for the two separate determinations. The increase in conductance with field is greater for zinc sulfate than for magnesium sulfate, and greater for copper sulfate than for zinc sulfate, as would be expected from the successively decreasing values of $K(O)$ for the three electrolytes. It will be observed that the agreement between theory and experiment is greatly improved by the correction for the weakness of the electrolyte. The computation was made with values for $K(O)$ = 0.0043 and Λ^0 = 133.6 for copper sulfate[3]; the value 0.88 was used for $\gamma_\pm$ at zero field, obtained from a plot of data from Harned and Owen.[3] Whereas the disparity between the values of $\Delta\lambda/\lambda_0$ (%) at 200 kv./cm. for the experimental results and the uncorrected theory is 2.25, the theory being the lower, this difference is reduced to 0.25 in the case of the corrected theory, the theory being higher. It was found[5] that the corrected theory for both magnesium sulfate and zinc sulfate lay above experiment, a fact attributed to uncertainty in the value of $K(O)$. The agreement in the case of copper sulfate is better than for either magnesium or zinc sulfate; this is probably more or less accidental, depending upon the value of $K(O)$ chosen as a result of extrapolation of low field conductance data. There is no obvious physical interpretation to be placed on the fact that all three salts show the same effect, with the corrected theoretical curves falling slightly above the experimental.

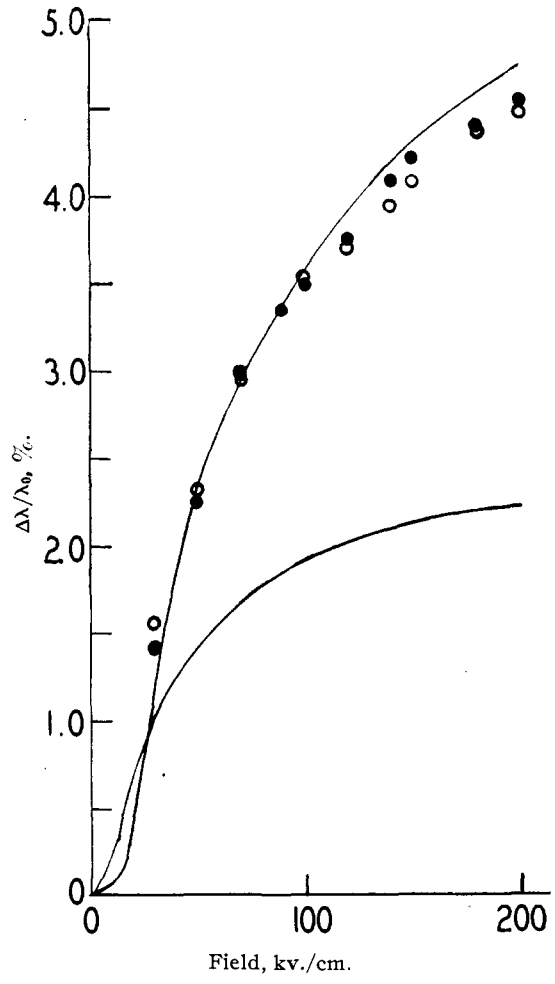


Fig. 1.—The high field conductance of copper sulfate (1.77×10^{-4} molar) relative to potassium chloride at 25°; highest curve, corrected Onsager–Wilson theory; lowest curve, uncorrected Onsager–Wilson theory; closed and open circles, experimental results on two separate solutions of very nearly same concentration.

(3) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 2nd ed., Reinhold Publishing Corp., New York, N. Y., 1950.

(4) J. A. Gledhill and A. Patterson, *J. Phys. Chem.*, scheduled for publication, December, 1952.

(5) F. E. Bailey and A. Patterson, THIS JOURNAL, **74**, 4428 (1952).

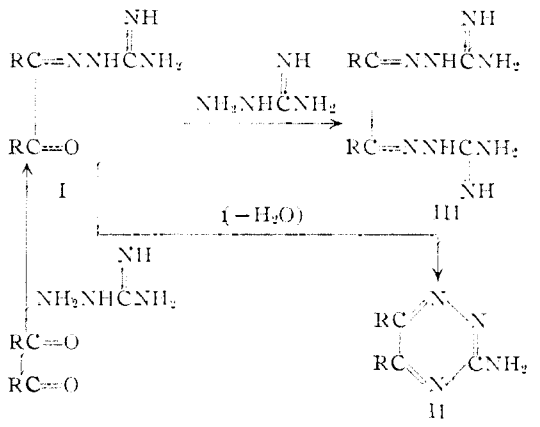
DEPT. OF CHEMISTRY, YALE UNIVERSITY
NEW HAVEN, CONN.

3-Amino-*as*-triazines

BY JOHN G. ERICKSON[1]

RECEIVED APRIL 19, 1952

Thiele and Dralle[2] have studied the reactions of aliphatic 1,2-dicarbonyl compounds with certain aminoguanidine salts. Using glyoxal, biacetyl and dioxytartaric acid with aminoguanidine hydrochloride or nitrate in aqueous solution, they obtained no ring compounds. The monoguanylhydrazones (I), rather than cyclizing to *as*-triazines (II), reacted with a second mole of aminoguanidine and only osazone-like compounds (III) were isolated.



We have found that glyoxal and biacetyl react readily with aminoguanidine bicarbonate in aqueous medium at room temperature. 3-Amino-*as*-triazine (II, R = H) and 3-amino-5,6-dimethyl-*as*-triazine (II, R = CH_3) were obtained in this manner in good yields. These successful results are no doubt due to a difference between aminoguanidine bicarbonate and the hydrochloride and nitrate. The bicarbonate is relatively insoluble in water; its solutions therefore contain much lower concentrations of aminoguanidine salt than was the case with the hydrochloride or nitrate. As a result, monoguanylhydrazones are given a greater chance to cyclize before reacting further with aminoguanidine to form the osazones.

3-Amino-*as*-triazine appears to be the simplest *as*-triazine known.

Acknowledgment.—Analyses were performed by the Microanalytical Group of these laboratories.

Experimental

3-Amino-*as*-triazine.—Thirty per cent. glyoxal solution in water (80 g., 0.41 mole of glyoxal) was added to a suspension of aminoguanidine bicarbonate (76.5 g., 0.56 mole) in 1200 ml. of water at 25°. The evolution of carbon dioxide began almost immediately. The mixture was stirred for two hours; at the end of this period the evolution of gas had virtually ceased. After standing overnight, the mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was extracted with 1 liter of cold methanol. The methanol solution was filtered, evaporated to 100 ml., chilled and filtered again, yielding 24.0 g. (60.3%) of crude product as brown crystals. Recrystallization from acetonitrile gave fine, white needles, m.p. 171.5–172.5° (cor.), soluble in water.

Anal. Calcd. for $C_3H_4N_4$: C, 37.50; H, 4.19; N, 58.31. Found: C, 38.03, 38.03; H, 4.35, 4.30; N, 58.44, 58.05.

3-Amino-5,6-dimethyl-*as*-triazine.—A solution of biacetyl (64.4 g., 0.75 mole) in 250 ml. of water was added to a suspension of aminoguanidine bicarbonate (102 g., 0.75 mole) in 1250 ml. of water at 25°. The reaction was slow at first but carbon dioxide began gradually to be evolved. After standing for 22 hours at 25°, the mixture was warmed to 50° for an hour, then chilled and filtered, yielding 60.6 g. of nearly white solid, m.p. 208–210° (cor.). Concentration of the filtrate to 400 ml., followed by chilling and filtration, gave an additional 6.2 g. of product; total yield of crude product, 66.8 g. (82.6%). Recrystallization from toluene–ethanol (3:1 by volume) gave a very light yellow product, m.p. 211–212° (cor.). It is approximately 1% soluble in water at 25°.

Anal. Calcd. for $C_5H_8N_4$: C, 48.37; H, 6.50; N, 45.13. Found: C, 48.25, 48.52; H, 6.46, 6.73; N, 45.13, 45.13.

STAMFORD RESEARCH LABORATORIES
AMERICAN CYANAMID CO.
STAMFORD, CONN.

(1) Research Dept., General Mills, Inc., Minneapolis, Minn.

(2) J. Thiele and E. Dralle, *Ann.*, **302**, 275 (1898).

Preparation of N-Bis-(2-cyanoethyl)-acetamide[1]

BY HENRY FEUER AND STANLEY M. PIER

RECEIVED FEBRUARY 25, 1952

In the course of certain researches carried on in this Laboratory, a quantity of N-bis-(2-cyanoethyl)-acetamide was required. A search of the literature revealed two reports of this compound. In an attempt to characterize β,β'-iminodipropionitrile, Kost[2] reported the preparation of the acetyl derivative, N-bis-(2-cyanoethyl)-acetamide, and indicated a melting point of 146°. No details of the method of preparation are given, but it must be concluded from our findings that the reaction used was that between β,β'-iminodipropionitrile and acetyl chloride, inasmuch as the compound actually obtained was the hydrochloride[3] and not the acetyl derivative of β,β'-iminodipropionitrile.

In a patent[4] by McQueen, a preparation of N-bis-(2-cyanoethyl)-acetamide is described which involves the base-catalyzed reaction of acetamide and acrylonitrile.[5] The product was isolated as a liquid boiling at 210–225° and 2 mm., but no other physical constants are given. Several attempts to repeat the reaction in this Laboratory by adding acrylonitrile dropwise to a stirred solution of acetamide and catalytic amounts of Triton B in dioxane at about 30° were unsuccessful. The acetamide was recovered and a polymer of acrylonitrile was isolated.

We have obtained N-bis-(2-cyanoethyl)-acetamide as a solid (m.p. 50°) using very slightly more than two moles of amine to one mole of acid chloride. The excess amine permits complete reaction of the acid chloride by accepting the hydrogen chloride generated in the reaction.

(1) Financial support of this research was supplied by the United States Office of Naval Research.

(2) A. N. Kost, *Vestnik, Moskov. Univ.*, No. 2, 141 (1947); *C. A.*, **42**, 3722 (1948).

(3) In a subsequent publication, the preparation of the hydrochloride of β,β'-iminodipropionitrile was reported, and its melting point was listed as 147–148°. No remark was made of the earlier erroneous report of the constants for the supposed acetyl derivative. See A. P. Terent'ev, *et al.*, *Zhur. Obschei Khim.*, **20**, 1073 (1950); *C. A.*, **44**, 9349 (1950); **45**, 1968 (1951).

(4) D. M. McQueen, U. S. Patent 2,424,664 (1947).

(5) In the review article on "Cyanoethylation," by H. A. Bruson, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 79 *et seq.*, the reaction is represented as giving a 72% yield. However, no indication is given of the low conversion, 24%, reported by McQueen.

Experimental

N-Bis-(2-cyanoethyl)-acetamide.—A solution of 25 g. (0.203 mole) of β,β′-iminodipropionitrile in 30 ml. of chloroform was cooled and rapidly stirred during the addition of 7.85 g. (0.1 mole) of acetyl chloride. A vigorous reaction set in instantly, causing the precipitation of a white solid. After stirring for about one hour, the solid was removed by suction filtration. The solid melted at 147°, the melting point of the hydrochloride of β,β′-iminodipropionitrile, and it was obtained in 95–100% of the theoretical amount. The filtrate was a clear yellow solution, and when hydrogen chloride gas was bubbled through it, more of the hydrochloride formed. In addition, the yellow color was discharged, giving rise to a yellow gum and a water-white solution. The solid and gum were removed by filtration, and the chloroform solvent was evaporated from the clear filtrate. A solid began to crystallize out, and even before the entire product had solidified, it was poured into boiling ethyl acetate. Upon cooling, white plates crystallized slowly; a dried sample of this material melted at 50° (cor.). The yield of product was 82%.

Anal. Calcd. for $C_8H_{11}N_3O$: C, 58.16; H, 6.71; N, 25.44. Found: C, 58.32; H, 6.65; N, 25.37.

β,β′-Iminodipropionitrile Hydrochloride.—Dry hydrogen chloride was passed into a solution of β,β′-iminodipropionitrile in chloroform and a white solid precipitated immediately. The needles were filtered off, washed with chloroform and ethanol, and then dried in a vacuum desiccator. A sample of this solid melted at 147–148°, and recrystallization from methanol did not raise the melting point. A determination of the melting point of a mixture consisting of the pure hydrochloride and a sample of the white solid obtained during the preparation of N-bis-(2-cyanoethyl)-acetamide showed no depression.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

Preparation and Chlorinolysis of α-Mercaptodiethylacetic Acid

BY LAMAR FIELD AND ROBERT O. BEAUCHAMP, JR.

RECEIVED MARCH 20, 1952

A recent oxidation of thioglycolic acid to chlorosulfonylacetic acid with chlorine[1] suggested the possibility of obtaining α-chlorosulfonyldiethylacetic acid, desired for synthetic purposes, in this way. The action of chlorine on α-mercaptodiethylacetic acid resulted, however, in the formation of dichloro-α-ethylbutyric acid (apparently the α,β-isomer), α-ethylcrotonic acid and sulfuric acid as the only isolable products.[2] These observations may be helpful in suggesting the nature of products obtained from the chlorine oxidation of other sulfur compounds.

Experimental[3]

α-Bromodiethylacetic Acid (I).—A modification of the general method of Marvel[4] was used. A mixture of 288.7 g. of diethylacetic acid, 435 g. of dry bromine and 4.4 ml. of phosphorus trichloride was heated at 70–80° for ten hours. Additional bromine (23 g.) was added and heating continued for six hours. Distillation using a 15-cm. Vigreux column gave 370 g. (76%) of I, b.p. 98.5–103.5° (0.9 mm.); m.p. 20–21.5°; $n^{25}D$ 1.4743; reported[5] b.p. 130–133° (18 mm.); m.p. 20°; Br found, 40.73 (calcd., 40.97).

I reacts rapidly with two equivalents of 0.1 *N* sodium hydroxide upon titration in the usual way. Thus, while rapidly fading end-points corresponding to neut. equiv. of 170–192 (calcd. 195) were observed, end-points stable for one-half hour corresponded to neut. equiv. 97.9 (calcd. for I/2 97.5).

This neutralization of I with two equivalents of alkali was found to involve both elimination and substitution reactions. Addition of 4.1 g. of sodium hydroxide in 23 ml. of water to 10 g. of I with cooling, followed by acidification and extraction gave solid and oil which were separated. Short-path distillation of the solid gave 0.5 g. (8%) of α-hydroxydiethylacetic acid, m.p. 78–79.5° (reported[6] 80°); neut. equiv., 133 (calcd., 132). Short-path distillation of the oil gave 0.83 g. (14%) of the liquid form of α-ethylcrotonic acid (II), $n^{25}D$ 1.4441; neut. equiv., 112 (calcd., 114); this form of II upon heating with hydrobromic acid[7] gave the solid form, m.p. 39.5–40° (reported[8] 41–42°).

In order to substantiate the α-position of bromine in the presumed I, a portion of the bromo acid was converted with silver oxide in water to α-hydroxydiethylacetic acid, m.p. 78°.

α-(Ethylxantho)-diethylacetic Acid (III).—III was prepared using a procedure based on one of Biilmann.[9] A solution of 600 g. of potassium ethyl xanthate[10] in 950 ml. of water containing 347 g. of I was allowed to stand for two days. Oil which separated was removed with ether and the aqueous layer was treated with 360 ml. of 30% hydrochloric acid. An ether extract of the oily product on partial evaporation and chilling gave 192.0 g. (46%) of III as white crystals, m.p. 108–112° (uncor.), which after recrystallization from aqueous ethanol had a constant m.p. of 114.5–115°.

Anal. Calcd. for $C_9H_{16}O_3S_2$: C, 45.74; H, 6.82; S, 27.13; neut. equiv., 236. Found: C, 46.07; H, 6.67; S, 27.04; neut. equiv., 236.

α-Mercaptodiethylacetic Acid (IV).[11]—III was converted to IV by a method similar to one of Biilmann.[9] A flask completely filled with 192 g. of III, 332 ml. of 25% ammonium hydroxide and 638 ml. of absolute alcohol, was allowed to stand closed for four days. The mixture was then heated at the reflux temperature for three hours, after which excess alcohol and ammonia were removed by distillation. The residue was adjusted with concentrated ammonium hydroxide to about *p*H 10, extracted with ether, and then brought to about *p*H 3 with concentrated hydrochloric acid (137 ml.). An ether extract of the resulting oil was dried over anhydrous sodium sulfate, and the IV obtained therefrom was purified by distillation; yield 56.9 g. (47%), b.p. 85–118° (1 mm.). Redistillation gave IV having b.p. 113–117° (5 mm.); m.p. 26–28.5°; $n^{25}D$ 1.4768; d^{25}_4 1.0718; M_D calcd. 39.14, found 39.06.

Anal. Calcd. for $C_6H_{12}O_2S$: C, 48.62; H, 8.16; S, 21.63; neut. equiv., 148. Found: C, 48.55; H, 8.04; S, 21.44; neut. equiv., 148.

Chlorinolysis of IV.—Chlorine gas was passed through a solution of 10 g. of IV in 10 ml. of water and 25 ml. of acetic acid cooled to −15°. The temperature rose initially to 15° but could soon be maintained at −15° during one hour of chlorination; 16.4 g. of chlorine was absorbed. After addition of ice-water, a benzene extract was dried and concentrated with gentle heating under reduced pressure to an oil from which 0.7 g. (6%) of a dichloro-α-ethylbutyric acid slowly separated, m.p. 99–103.5°. Recrystallization from petroleum ether–benzene (5:1) gave the pure dichloro acid, m.p. 111–112°, an aqueous solution of which was strongly acidic.

(1) J. B. Dickey, U. S. Patent 2,466,396 (1949) [*C. A.*, **43**, 4868 (1949)].

(2) Dr. E. Campaigne of Indiana University has informed us that an attempted synthesis of ethyl α-chlorosulfonylisobutyrate by the wet chlorine oxidation of the isothiuronium salt of ethyl α-bromoisobutyrate resulted in the evolution of sulfur dioxide upon working up the product.

(3) Melting points are corrected and boiling points are uncorrected. Most of the analyses are by the Clark Microanalytical Laboratory, Urbana, Ill.

(4) C. S. Marvel, *Org. Syntheses*, **20**, 106 (1940).

(5) K. W. Rosenmund, *Ber.*, **42**, 4472 (1909). *Cf.* M. S. Newman, THIS JOURNAL, **57**, 732 (1935).

(6) F. Tiemann and L. Friedländer, *Ber.*, **14**, 1974 (1881).

(7) E. Blaise and P. Bagard, *Ann. chim. phys.*, [8] **11**, 120–131 (1907).

(8) K. von Auwers, *Ann.*, **432**, 76 (1923).

(9) E. Biilmann, *ibid.*, **348**, 128 (1906).

(10) Prepared by Frey's procedure as given by C. Bruchhold, *Eng. Mining J.*, **125**, 338 (1928).

(11) The preparation of IV by another method was reported by E. Clemmensen and A. H. C. Heitman, *Am. Chem. J.*, **40**, 298 (1908); no physical constants were given.

Anal. Calcd. for $C_6H_{10}O_2Cl_2$: C, 38.94; H, 5.45; Cl, 38.32; neut. equiv., 185. Found: C, 39.01; H, 5.18; Cl, 37.99; neut. equiv., 186.

This acid is presumed to be α,β-dichloro-α-ethylbutyric acid (V), since heating a dioxane solution under reflux with zinc dust gave the solid form of II, m.p. 38.5–41°.

A similar experiment in which chlorination was effected at −3° gave 7.6 g. of oil, which after four distillations from a modified Claisen flask gave 1.45 g. (19%) of II; b.p. 91.5–94° (3 mm.); $n^{25}D$ 1.4451 (*cf.* above); b.p. reported[7] 107–108° (10 mm.); rapid decolorization of aqueous potassium permanganate and bromine in carbon tetrachloride (with hydrogen bromide evolution). The identity of the presumed II was confirmed by conversion as described above to the stable form, m.p. 38–40.5°, and by formation of the β-naphthylamide, m.p. 92–95° (reported[7] 96°).

Concentration of the benzene-extracted aqueous layer from another chlorination gave a hygroscopic viscous liquid which was strongly acidic (neut. equiv. 98) and gave a heavy precipitate with barium chloride but none with silver nitrate; it apparently consisted in large part of sulfuric acid. Neutralization with sodium hydroxide followed by evaporation and recrystallization of the resulting solid gave sodium sulfate; Na, 31.6 (calcd. 32.4).

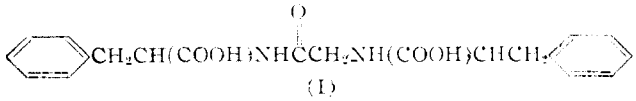
DEPARTMENT OF CHEMISTRY
VANDERBILT UNIVERSITY
NASHVILLE 4, TENNESSEE

N,N′-(Oxoethylene)-bis-(DL-β-phenylalanine)

BY WILLIAM S. FONES

RECEIVED APRIL 11, 1952

In the course of the preparation of N-bromoacetyl-DL-β-phenylalanine by the conventional Schotten–Baumann reaction between DL-β-phenylalanine and bromoacetyl bromide there was isolated in addition to the desired product a substance insoluble in dilute mineral acid, ethyl acetate or acetone. The same material could be obtained in somewhat larger yield if only one-half molar amounts of bromoacetyl bromide were used. This fact, together with the analyses for carbon, hydrogen and nitrogen, indicated that the substance was N,N′-(oxoethylene)-bis-(DL-β-phenylalanine) (I).



(I)

That this was the correct formulation was shown in two ways. First, the compound was also prepared by the condensation of N-bromoacetyl-DL-β-phenylalanine methyl ester with DL-β-phenylalanine ethyl ester, followed by basic hydrolysis and acidification. Second, (I) was hydrolyzed with concentrated hydrochloric acid to DL-β-phenylalanine and DL-β-phenylalanine-N-acetic acid.[1] The latter compound was isolated from the hydrolysate and identified by its analysis and by conversion to the known hydrochloride.[2] The presence of β-phenylalanine in the hydrolysate was shown by paper chromatography utilizing an alcohol–water solvent (77% alcohol). No ninhydrin reacting materials other than the two substances mentioned were observed in the developed chromatogram.

The author is indebted to Dr. H. A. Sober of this Laboratory for the chromatographic analysis.

(1) D. A. Hahn and A. Lützinger, THIS JOURNAL, **54**, 4665 (1932).

(2) D. A. Hahn and M. M. Endicott, *ibid.*, **60**, 1040 (1938).

Experimental[3]

N-Bromoacetyl-DL-β-phenylalanine Methyl Ester.—To a 10% excess of diazomethane[4] in 200 ml. of ether there was added in small portions 21.5 g. of N-bromoacetyl-DL-β-phenylalanine.[5] After one-half hour the excess diazomethane was destroyed with dilute hydrochloric acid following which the ethereal solution was washed with sodium bicarbonate solution and saturated sodium chloride. After drying over sodium sulfate the ether was concentrated and petroleum ether (b.p. 35–70°) was added. There was thus obtained 18.0 g. (80%) of ester, m.p. 80–82°. The melting point was not changed by recrystallization from the same solvents.

Anal.[6] Calcd. for $C_{12}H_{14}O_3NBr$: C, 48.0; H, 4.7; N, 4.7; Br, 26.6. Found: C, 48.0; H, 4.9; N, 4.8; Br, 26.6.

N,N′-(Oxoethylene)-bis-(DL-β-phenylalanine) (I). **Method (A).**—In a 500-ml. three neck round-bottomed flask, cooled by an ice-bath and equipped with a stirrer and two addition funnels there was placed 33 g. of DL-β-phenylalanine and 100 ml. of 2 *N* sodium hydroxide. To the stirred solution, kept below 5° there was added dropwise from one funnel 20 g. of bromoacetyl bromide and from the other funnel 2 *N* sodium hydroxide was added at such a rate as to just keep the solution alkaline. After the addition was complete the ice-bath was removed and the reaction mixture stirred for three hours.

At the end of this period acetic acid (50 ml.) was added and the resulting precipitate collected by filtration. This was taken up in sodium bicarbonate solution and again precipitated with acetic acid to give 15 g. of material m.p. 210–215° dec. After two more precipitations from bicarbonate by the addition of acetic acid followed by washing of the precipitate with ethanol and ether, there was obtained 9.5 g. (26%) of N,N′-(oxoethylene)-bis-(DL-β-phenylalanine), m.p. 224–227° dec.

Anal.[6] Calcd. for $C_{20}H_{22}O_5N_2$: C, 64.8; H, 5.9; N, 7.6. Found: C, 64.8; H, 6.2; N, 7.6.

Method B.—Eleven and one-half grams of DL-β-phenylalanine ethyl ester hydrochloride was treated with a slight excess of alkali and the free ester was extracted into 150 ml. of ether. To this ethereal solution there was added a solution of 7.5 g. of N-bromoacetyl-DL-β-phenylalanine methyl ester in 150 ml. of ether. Seventy-five ml. of ethyl acetate was then added and most of the ether was removed by boiling, following which the mixture was allowed to stand overnight.

The solvent was removed in a stream of air and the residue triturated with ether. The solid amine hydrobromide was collected by filtration and the ether removed from the filtrate *in vacuo* following which the oily residue was dissolved in 50 ml. of ethanol and treated overnight at room temperature with 2.5 g. of sodium hydroxide in 50 ml. of water. The acid was precipitated by the addition of acetic acid to give 5.9 g. of material, m.p. 200–220° dec. After one precipitation by dilute hydrochloric acid and one by acetic acid from sodium bicarbonate solution, 4.2 g. (45%) of N,N′-(oxoethylene)-bis-(DL-β-phenylalanine), m.p. 224–227° was obtained. A mixed melting point with I from A showed no depression.

Hydrolysis of N,N′-(Oxoethylene)-bis-(DL-β-phenylalanine).—One and eight-tenths grams of I (from A) was refluxed for 6 hr. in 50 ml. of concentrated hydrochloric acid following which the solution was taken to dryness *in vacuo*. Most of the hydrochloric acid was removed by taking the residue up in 50-ml. portions of water and evaporating to dryness *in vacuo* three times. After the third evaporation the residue was taken up in 10 ml. of water and treated with excess aniline to remove bound hydrogen chloride. An equal volume of alcohol was added and the solution placed in the refrigerator overnight. Filtration gave 1.5 g. of crystals, m.p. 195° (dec.). Two recrystallizations from water gave 0.1 g. of DL-β-phenylalanine-N-acetic acid, m.p. 233–236° dec. (lit.[2] 225–226°).

Anal. Calcd. for $C_{11}H_{13}O_4N$: C, 59.2; H, 5.8; N, 6.3. Found: C, 59.2, 58.9; H, 5.9, 5.8; N, 6.0, 6.0.

(3) All melting points are corrected.

(4) "Organic Syntheses," Coll. Vol. II, J. Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(5) E. Abderhalden and F. Schweitzer, *Fermentforschung*, **11**, 224 (1930).

(6) Analyses by R. J. Koegel and staff of this Laboratory.

The filtrate from the first precipitation was chromatographed on filter paper using 77% ethanol as solvent to show the presence of DL-β-phenylalanine in the hydrolysate.

DL-β-Phenylalanine-N-acetic Acid Hydrochloride.—Sixty mg. of the DL-β-phenylalanine-N-acetic acid was converted to the hydrochloride[2] to give 50 mg. of material, m.p. 203–206° dec. (lit.[2] 200–201°).

NATIONAL CANCER INSTITUTE
NATIONAL INSTITUTES OF HEALTH[7]
BETHESDA, MARYLAND

(7) Federal Security Agency, Public Health Service.

A Note on the Occurrence of Panstroside[1]

BY ROBERT FOPPIANO AND M. R. SALMON

RECEIVED MARCH 19, 1952

v. Euw and Reichstein[2] have reported on the glycoside content of the seeds of *Strophanthus petersianus*, Klotzsch, from which they isolated sarmentocymarin, sarmentogenin and three new substances identified as No. 792, 793 and 794. We find that in addition the seeds of this species contain panstroside which we isolated in a crude yield of 0.035%.

The seeds were received from Mr. P. Topham, Nyasaland, Africa, through the courtesy of the New York Botanical Garden. A flowering specimen and a mericarp sent as botanical vouchers for the seeds were identified as *S. petersianus* at the New York Botanical Gardens. We wish to thank Mr. Topham for the collection and Mr. Joseph Monachino for the botanical examination of this sample.

Panstroside frequently crystallizes slowly or not at all[3] and may be easily overlooked. When the presence of this glycoside is suspected we regularly crystallize the chloroform extract from acetone from which panstroside crystallizes more readily than from methanol and ether.

Experimental

The seeds (1111 g.) were extracted as previously described.[4] The chloroform extract on concentration gave 2.58 g. (0.23%) of crude total glycoside. This was dissolved in about 10 cc. of acetone, and allowed to crystallize in the refrigerator. We obtained 366 mg. of crude panstroside, $[\alpha]_D$ +25°; m.p. 210–219°. An additional 19 mg. was isolated by chromatography of the mother liquors.

Recrystallization of this panstroside gave preparations that agreed in rotation and melting point with our former preparations but the absorption spectrum showed that a small amount of impurity was retained tenaciously. It was accordingly chromatographed on alumina, and from the eighth and ninth fractions eluted with chloroform and chloroform–methanol (99:1), 193 mg. of panstroside was obtained after crystallization from methanol; $[\alpha]_D$ +27°. Panstroside was recrystallized three times and yielded 154 mg.; $[\alpha]_D$ +31.0°; m.p. 222–228°; Keller–Kiliani test negative; legal test positive. Color test with 84% sulfuric acid pink becoming red in 2 min., developing a blue edge in 3 min., and becoming blue in 20 min. The mixed melting point with panstroside from *S. intermedius* showed no depression. Ultraviolet absorption spectrum maximum at 218 mμ, log ε 4.23; plateau at 265–280 mμ, log ε 1.93.

Anal. Calcd. for $C_{30}H_{44}O_{11}$: C, 62.06; H, 7.64. Found: C, 61.84, 61.63; H, 7.43, 7.61.

(1) J. v. Euw, H. Hess, P. Speiser and T. Reichstein, *Helv. Chim. Acta*, **34**, 1821 (1951).

(2) J. v. Euw and T. Reichstein, *ibid.*, **33**, 1551 (1950).

(3) See for example J. v. Euw and T. Reichstein, *ibid.*, **33**, 2153 (1950).

(4) M. R. Salmon, Eric Smith and W. G. Bywater, THIS JOURNAL, **73**, 3824 (1951).

We wish to thank Dr. W. G. Bywater for advice and suggestions and the Upjohn Company for encouragement and support.

RESEARCH DIVISION
S. B. PENICK AND CO.
JERSEY CITY 6, N. J.

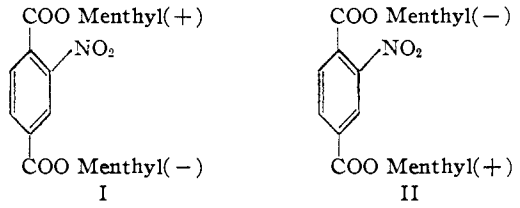
Active (+) Menthyl (−) Menthyl Nitroterephthalates

BY P. J. HEARST AND C. R. NOLLER

RECEIVED APRIL 25, 1952

Compounds containing two like asymmetric groups of opposite configuration, A(+) and A(−), and no other asymmetric groups, but which nevertheless have molecular asymmetry, are of interest in that they have some bearing on the entrenched idea of internal compensation. It might be argued that the rotation of A(+) should cancel that of A(−) or that, if it did not, the rotation of the compound would be small. An example of such compounds would be those of the type (+)A-Z-X-Y-Z-A(−) and (−)A-Z-X-Y-Z-A(+), where X, Y and Z are not asymmetric. It is difficult to be certain that this type of compound has not been discussed or prepared previously, but an examination of several available books on stereochemistry and a search of the literature for likely specific compounds have not revealed a reference to this aspect of the problem.

We have prepared one pair of enantiomorphs of this type, namely, the 1-(+)menthyl 4-(−)menthyl 2-nitroterephthalate (I) and the 1-(−)menthyl 4-(+)menthyl 2-nitroterephthalate (II). These compounds have specific rotations in benzene solution of +59.1 and −59.7°, respectively. Thus the molecular asymmetry not only confers activity on these compounds, but the rotation is appreciable.



Experimental

Nitroterephthalic acid was prepared from terephthalic acid in 78% yield by a procedure essentially the same as that of Wegscheider[1] except that 70% nitric acid and 30% fuming sulfuric acid were used instead of fuming nitric acid and pyrosulfuric acid. It was converted to the (−)**menthyl ester** by the procedure of Cohen and de Pennington[2] except that, in the preparation of the acyl chloride, twice the calculated amount of phosphorus pentachloride was used and a small amount of phosphorus oxychloride was added to start the reaction. The purified ester, obtained in over-all yield of 59%, melted at 86–88°; $[\alpha]^{25}_D$ −159° (*c* 1.996 in benzene).

1-(−)**Menthyl 2-nitroterephthalate** was obtained in 42% yield by the partial saponification of the (−)menthyl ester.[2] After crystallization from aqueous ethyl alcohol, it melted at 73.5–75°, compared to the 75° previously reported. Recrystallization from hexane, however, raised the melting point to 128.5–129.5°. A determination of neutralization equivalents showed that the product melting at 75° contains one molecule of water of crystallization, whereas that melt-

(1) R. Wegscheider, *Monatsh.*, **21**, 621 (1900).

(2) J. B. Cohen and H. S. de Pennington, *J. Chem. Soc.*, **113**, 57 (1918).

ing at 129° is anhydrous; $[\alpha]^{25}D$ −128° (*c* 2.029 in 95% alcohol). In addition to the half menthyl ester, the half methyl ester, presumably formed by ester exchange from the methanolic potassium hydroxide solution, was isolated in 15% yield.

1-(−)Menthyl 4-(+)menthyl 2-nitroterephthalate was prepared by refluxing 3.49 g. of 1-(−)menthyl 2-nitroterephthalate with 5 cc. of pure thionyl chloride for one hour and removing the excess thionyl chloride at reduced pressure. To the residue was added 1.56 g. of (+)menthol[3] in 25 cc. of pyridine. After 24 hours the mixture was worked up in the usual way, and gave 4.09 g. of product that crystallized on standing. Recrystallization to constant melting point from 95% alcohol gave 2.76 g., m.p. 99.5–100.5°; $[\alpha]^{25}D$ −59.7° (*c* 2.011 in benzene).

Anal. Calcd. for $C_{28}H_{41}O_6N$: C, 68.97; H, 8.48. Found: C, 69.08, 69.29; H, 8.53, 8.40.

(+)Menthyl 2-nitroterephthalate was prepared by the same procedure used to make the (−)menthyl ester. It melted at 86–88°; $[\alpha]^{25}D$ +158° (*c* 2.031 in benzene). It was converted to the half ester, **1-(+)menthyl 2-nitroterephthalate**, m.p. 127.5–128.5°; $[\alpha]^{25}D$ +127° (*c* 2.00 in 95% alcohol). The half ester was converted to **1-(+)menthyl 4-(−)menthyl 2-nitroterephthalate**, m.p. 99.5–100.5°; $[\alpha]^{25}D$ +59.1° (*c* 2.006 in benzene).

Anal. Calcd. for $C_{28}H_{41}O_6N$: C, 68.97; H, 8.48. Found: C, 69.03, 69.02; H, 8.48, 8.45.

A mixture of equal amounts of the two enantiomorphic esters melted at 80–87°.

(3) J. Read and W. J. Grubb, *J. Soc. Chem. Ind.*, **51**, 329T (1932).

DEPARTMENT OF CHEMISTRY
STANFORD UNIVERSITY
STANFORD, CALIFORNIA

Effect of Nearest Neighbor Substrate Interactions on the Rate of Enzyme and Catalytic Reactions

BY TERRELL L. HILL

RECEIVED JUNE 25, 1952

The object of this note is to illustrate with a simple example an approximate method of taking into account explicitly the effect of substrate interactions on the rate of surface-catalyzed reactions.

Let us consider nearest neighbor interactions on a surface with a large number B of equivalent adsorption sites. The problem of a linear enzyme, with B not necessarily large, has been discussed by Botts and Morales.[1] Consider the system (S is the substrate, S′ the product)

$$\mathrm{S}\begin{pmatrix}\text{solution, concentration } c;\\ \text{or gas, pressure } p\end{pmatrix} \underset{k_{-1}^\circ}{\overset{k_1^\circ}{\rightleftharpoons}} \mathrm{S\ (adsorbed)} \quad (1a)$$

$$\mathrm{S\ (adsorbed)} \xrightarrow{k_2^\circ} \mathrm{S'\ (solution;\ or\ gas)} \quad (1b)$$

The desorption of S′ is assumed fast enough that the number of S′ molecules on the surface is negligible.

In the absence of interactions we write the rates of the separate reactions as

$$v_1^\circ = k_1^\circ c(1-\theta) \quad (2)$$

$$v_{-1}^\circ = k_{-1}^\circ\theta,\ v_2^\circ = k_2^\circ\theta$$

where $\theta = N/B$ and N is the number of adsorbed S molecules. Let the interaction free energy[2] between nearest neighbor S molecules be w_a, and between S and S′ nearest neighbors w_a'. At steady state, with N adsorbed S molecules, we assume that the probabilities of the various possible configurations of the adsorbed phase are given by a Boltzmann distribution (*i.e.*, the *adsorbed phase* is in *internal* equilibrium); the quasi-chemical approximation[3] is used to represent this equilibrium.

A consequence of the quasi-chemical approximation is the following: of the z sites nearest neighbor to a filled site, the probability that j will be filled is

$$P_j^{(f)} = \frac{z!}{j!(z-j)!}\,p^{z-j}(1-p)^j \quad (3)$$

where

$$p = 2(1-\theta)/(\beta+1) \quad (4)$$

$$\beta^2 = 1 - 4\theta(1-\theta)[1-\exp(-w_a/kT)]$$

Also, the probability that next to an empty site j will be filled is

$$P_j^{(e)} = \frac{z!}{j!(z-j)!}\,r^{z-j}(1-r)^j \quad (5)$$

where

$$r = (\beta+1-2\theta)/(\beta+1) \quad (6)$$

We assume that the rate constant for an S molecule being adsorbed onto an empty site with j nearest neighbor filled sites can be written as

$$k_1(j) = k_1^\circ \exp(-jw_b/kT) \quad (7)$$

That is, the increase in the free energy of activation per nearest neighbor is w_b. Then the rate constant for an S molecule leaving a site with j nearest neighbor filled sites is

$$k_{-1}(j) = k_{-1}^\circ \exp[j(w_a - w_b)/kT] \quad (8)$$

Similarly, the rate constant for an S′ molecule leaving a site with j nearest neighbor filled (with S) sites is written as

$$k_2(j) = k_2^\circ \exp[j(w_a' - w_b')/kT] \quad (9)$$

The over-all rates in the presence of interactions are then

$$v_1 = c(1-\theta)\sum_{j=0}^{z} k_1(j)P_j^{(e)} \quad (10)$$

$$v_{-1} = \theta\sum_{j=0}^{z} k_{-1}(j)P_j^{(f)} \quad (11)$$

$$v_2 = \theta\sum_{j=0}^{z} k_2(j)P_j^{(f)} \quad (12)$$

Equation (12) gives the desired rate of formation of product. Implicit in writing eq. (12) is the assumption that an S′ molecule, once formed, leaves the surface before the local nearest neighbor distribution determined by S–S interactions has time to readjust to S–S′ interactions. When simplified, eq. (12) leads to

$$v_2(\theta) = k_2^\circ\theta\left[\frac{2(1-\theta)}{\beta+1-2\theta}\right]^z\left(1 + \frac{2\theta\{\exp[(w_a' - w_b' - w_a)/kT] - 1\}}{\beta+1}\right)^z \quad (13)$$

The other rates become

$$v_1 = k_1^\circ c(1-\theta)f(\theta) \quad (14)$$

$$v_{-1} = k_{-1}^\circ\theta\left[\frac{2(1-\theta)}{\beta+1-2\theta}\right]^z f(\theta) \quad (15)$$

$$f(\theta) = \left\{1 + \frac{2\theta[\exp(-w_b/kT) - 1]}{\beta+1}\right\}^z$$

(1) D. J. Botts and M. F. Morales, to be published.

(2) E. A. Guggenheim, *Trans. Faraday Soc.*, **44**, 1007 (1948).

(3) R. H. Fowler and E. A. Guggenheim, "Statistical Thermodynamics," Cambridge University Press, 1939, Chap. 10.

Although eq. (13) gives $v_2(\theta)$, to obtain $v_2(c)$ we need also $c(\theta)$. The steady state condition

$$v_1 = v_{-1} + v_2 \qquad (16)$$

gives

$$c(\theta) = \frac{\theta}{1-\theta}\left[\frac{2(1-\theta)}{\beta+1-2\theta}\right]^z \frac{k_{-1}^\circ}{k_1^\circ} + \frac{k_2^\circ}{k_1^\circ}\left[\frac{\beta+1+2\theta\{\exp[(w_a'-w_a'-w_a)/kT]-1\}}{\beta+1+2\theta\{\exp(-w_b/kT)-1\}}\right]^z \qquad (17)$$

When $k_2^\circ = 0$, eq. (17) reduces to the quasi-chemical equilibrium adsorption isotherm,[3] as expected. When $w_a' - w_a' - w_a = -w_b$, the $k_2^\circ = 0$ result is again obtained except k_{-1}° is replaced by $k_{-1}^\circ + k_2^\circ$.

One complication should be mentioned. Suppose w_a/kT and θ, at steady state, have values such that the adsorbed S molecules split into two surface phases[3] (determined by equal surface pressure and chemical potential in the two phases—since equilibrium within the adsorbed phase or phases has been assumed). Let θ_1 and θ_2 refer to the two different phases. Using eq. (13), (14) and (15), let us write the left-hand side of eq. (16) as $c\varphi_L(\theta)$ and the right-hand side as $\varphi_R(\theta)$. Then it is easy to show that in the region of phase splitting $c(\theta)$ is given by

$$c(\theta) = \frac{(\theta_2-\theta)\varphi_R(\theta_1) + (\theta-\theta_1)\varphi_R(\theta_2)}{(\theta_2-\theta)\varphi_L(\theta_1) + (\theta-\theta_1)\varphi_L(\theta_2)} \qquad (18)$$

The present treatment applies to one, two or three dimensional lattices, the two dimensional case being the most important. The quasi-chemical method is exact in one dimension for B large, it may be recalled (Ising model).

This problem suggested itself in conversations with Drs. D. J. Botts and M. F. Morales concerning their work mentioned above.[1]

NAVAL MEDICAL RESEARCH INSTITUTE
BETHESDA, MARYLAND

Degradation of D-Glucose, D-Fructose and Invert Sugar in Carbonate-buffered Water Solutions

BY LAWRENCE J. HEIDT AND CATHERINE M. COLMAN[1]

RECEIVED APRIL 11, 1952

D-Glucose (dextrose), D-fructose (levulose) and the equimolar mixture of these sugars (invert sugar) have been found to be degraded completely into non-reducing substances under conditions commonly believed to result mainly in Lobry de Bruyn–van Ekenstein rearrangement into an equilibrium mixture of D-glucose, D-fructose and D-mannose[2] without the degradation of a large fraction of the sugars into non-reducing substances.[3] D-Fructose, for example, has been reported to establish in water at 100° and *p*H 7 to 12 an equilibrium value for the reducing power of the solution equal to about 93% of the initial value.[4]

The rate of degradation of the sugars to non-reducing substances in carbonate-buffered solutions at 100° is shown in Fig. 1. The reducing power decreases to about 10% of its initial value in 90 min. at *p*H 9.3 and in 16 min. at *p*H 10 in accord, for the most part, with the kinetics of a first order reaction with respect to the sugar and hydroxyl ion when the latter is estimated from the *p*H at 25° at constant total formal concentration of carbonate and bicarbonate. There is a slight induction period which is the longest in the case of D-glucose as is evident from Fig. 1. The small decrease in reducing power observed in earlier work[2a,4] at this temperature and over this range of *p*H may have been caused by a lowering of the *p*H by the acid produced in the reaction to the point where the rate of degradation became negligible before much of the sugar had been degraded.

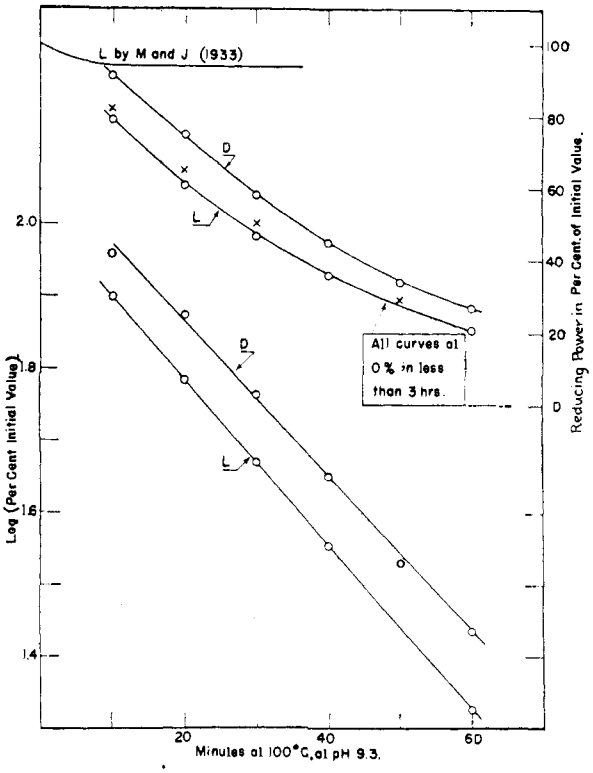


Fig. 1.—Rate of degradation at 100° of D-glucose (D), D-fructose (L) and invert sugar (X) to non-reducing material in water buffered with sodium carbonate and bicarbonate at 0.4 *M*. The solutions were initially 0.0042 *M* in hexose. The half-life of D-fructose at 100° is 6 min. at *p*H 10 and 28 min. at *p*H 9.3. Near the top of the figure is given the results reported by Mathews and Jackson[4] for D-fructose at 100° in water solution at *p*H 7 to 12.

The degradation of the sugars is accompanied by browning as is well known. The absorption spectra of the products have been found to exhibit a maximum which shifts from 2800 ± 25 Å. in the first stage of the reaction to 2650 ± 25 Å. as the reaction proceeds. This is shown in Fig. 2 which depicts the behavior of a solution of invert sugar 0.0042 *M* in hexose. Essentially the same results were obtained with D-glucose and D-fructose. The optical densities of the untreated solutions were negligible by comparison.

(1) The authors are indebted to the Sugar Research Foundation, Inc., for a grant-in-aid in support of this work.

(2) (a) C. A. Lobry de Bruyn and W. Alberda van Ekenstein, *Rec. trav. chim.*, **14**, 203 (1895); (b) W. L. Evans, *Chem. Revs.*, **31**, 537 (1942).

(3) Some of the most convincing evidence supporting the rearrangement has been published by M. L. Wolfrom and W. L. Lewis, THIS JOURNAL, **50**, 837 (1928). Their results were obtained, however, under much milder conditions than we have employed.

(4) J. A. Mathews and R. F. Jackson, *Bur. Standards J. Research*, **11**, 619 (1933).

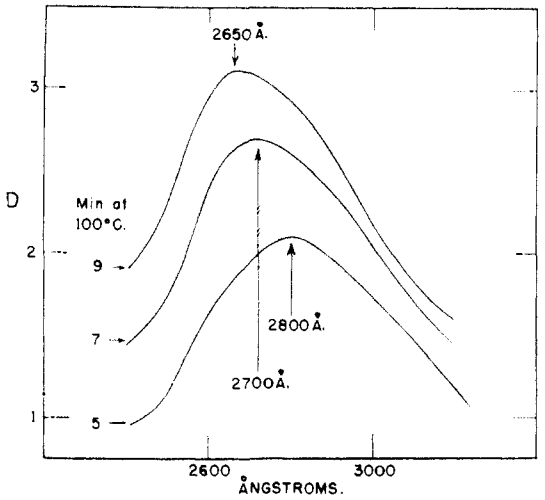


Fig. 2.—Change with time in the absorption spectrum of the products of degradation at 100° of invert sugar in water buffered with carbonate at *p*H 10. The solution was initially 0.0042 *M* in hexose. The absorbance, *D*, is based on a light path of one cm. in the solution.

Average values of the extinction coefficients have been calculated at the wave length of maximum absorption by dividing the optical density, *D*, per cm. by the moles of hexose decomposed, H_d, per liter after correcting *D* for the optical density of the untreated solution. The fractional degradation of the hexose was taken as equal to the difference between the initial and prevailing values of the reducing power of the solution divided by the initial value corrected for the cuprous oxide lost in the analytical procedure. The average values of $D/(H_d)$ calculated in this way are presented in Fig. 3; they increase rapidly as much as fivefold until about 70% of the hexose has been degraded to non-reducing material which occurs at 100° during the first ten min. at *p*H 10 and during the first 40 min. at *p*H 9.3. There is a further increase in $D/(H_d)$ of only 10 to 20%. The optical density between 2400 and 3600 Å. and the color of the solutions increase less than 5% after the reducing power has fallen below 1% of the initial value when allowance is made for loss of water by evaporation. The value reached by $D/(H_d)$ is about the same for all these sugars, but it increases with the initial concentration of the sugar nearly in proportion to the square root of this concentration.

Levulinic acid under the same conditions has an absorption curve similar to the one eventually reached in these solutions, and the value of the extinction coefficient at the peak at 2650 Å. is 27; consequently if it were responsible for the optical density in the case of Line 3, Fig. 3, 600/27 or 22 moles of it would be produced from one mole of hexose which is, of course, impossible. In a similar manner one can eliminate as products contributing largely to the optical density such compounds as lactic acid, methyl glyoxal, and the sugars and degradation products mentioned by Evans.[2b] The large value of the optical density can be attributed to compounds containing a conjugated system of alternating single and double bonds. These are not β-ketonic acids or their enolic forms because they

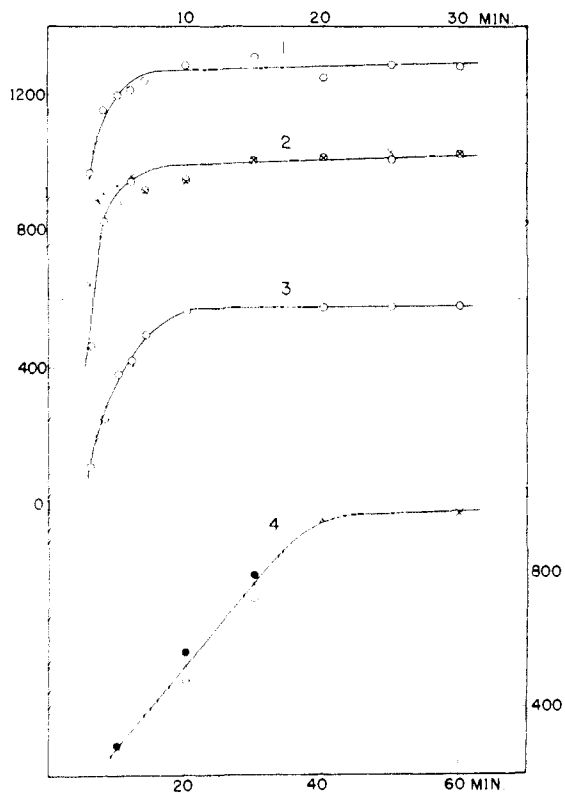


Fig. 3.—Optical density per cm. per mole of hexose degraded at 100° to non-reducing material per liter at the wave length of maximum absorbance. The value of this wave length was 2650 Å. in the case of the results represented by line 4 and by the parts of lines 1, 2 and 3 for heating periods of 10 min. or longer; the value ranged from 2830 to 2650 Å. for the other parts of lines 1, 2 and 3 in the way depicted in Fig. 2. The ordinate in every case gives the value of $D/(H_d)$. Circles, dots and crosses represent the results with D-glucose, D-fructose and invert sugar, respectively.

Line	*p*H	(Hexose)	Abscissa	Ordinate
1	10	0.0126	Upper	Left
2	10	.0042	Upper	Left
3	10	.0014	Upper	Left
4	9.3	.0042	Lower	Right

are unstable when boiled in dilute acid, whereas the optical densities of the degraded solutions obtained in this research are unaffected by this treatment.

The results presented in the figures are for aqueous solutions containing 0.0014, 0.0042 or 0.0126 mole of hexose per liter and a total concentration of sodium carbonate and sodium bicarbonate equal to 0.4 mole per liter.

The *p*H values were measured with a glass electrode at 25° both before and after the heat treatment; they were found to remain constant within 0.04 at *p*H 10 and to increase up to 0.4 unit in solutions initially at *p*H 8.9.

The reducing power was determined from measurements of the amount of cuprous oxide produced in a method[5] which employs in every analysis 5 ml. of a carbonate-buffered cupritartrate macro analytical reagent in a total volume of 10 ml.

The optical densities were measured at 20° in quartz cells by means of a Cary Record-

[5] L. J. Hoch and F. W. Southam, THIS JOURNAL, **72**, 589 (1950).

ing Spectrophotometer whose wave length and optical density scales had been calibrated.

CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE, MASSACHUSETTS

Paper Chromatography of Bile Acids[1]

BY DAVID KRITCHEVSKY AND MARTHA R. KIRK

RECEIVED MAY 5, 1952

The separation of bile acids by paper chromatography has been investigated in this Laboratory and two solvent systems which give different, reproducible R_f values for several acids have been found. The two systems are *n*-propyl alcohol–ammonia–water 90:2:8 and *n*-propyl alcohol–ethanolamine–water 90:5:5. Of the two systems, the latter concentrates the moving material into a smaller area and is, therefore, preferable for identification or separation.

Using this solvent mixture, we have been able to achieve separation of various mixtures of these bile acids. Although the R_f values of dehydrocholic, cholic and norcholic acids are close together, we have been able to separate mixtures of desoxycholic, dehydrocholic and cholic acids, and of desoxycholic, dehydrocholic and norcholic acid. In these experiments we have generally observed two distinct spots of the two acids whose R_f values are close together; in some cases, however, they merge to give one spot. All experiments were carried out using 50 γ of material; mixtures contained 50 γ of each component.

For identification of the bile acids, a 15% phosphoric acid spray, slightly different from that originally proposed by Neher and Wettstein,[2] was used. The acids appeared as brown or red spots in white light, or displayed a greenish-yellow or pink fluoresence in ultraviolet light.

The results are given in Tables I and II.

TABLE I

R_f VALUES FOR BILE ACIDS

Acid	P–M–W[a] 90:5:5	P–A–W 90:2:8	E–A–W 90:2:8	P–A–W 5:2:3
Desoxycholic	0.92	0.74	0.66	0.95
Dehydrocholic	.65	.47	.65	.89
Cholic	.71	.52	.71	.94
Norcholic	.69	.51	.70	.94
Triformylnorcholic	.92	.68	.75	.94

[a] P, *n*-propyl alcohol; M, monoethanolamine; A, ammonia; W, water.

TABLE II

SEPARATIONS

Mixture	R_f values
Desoxycholic/dehydrocholic/cholic	0.95/0.65/0.72
Desoxycholic/dehydrocholic/norcholic	0.92/0.62/0.73

Experimental

The organic solvents were distilled prior to use. All mixtures are by volume as given. Whatman #1 paper was used throughout.

The material to be chromatographed was applied to a spot about 2 cm. in diameter on a 4 × 40-cm. strip of filter paper. Descending chromatography was used and after the solvent front had advanced 25–35 cm. from the origin, the strips were removed from the chromatographic chamber (a 7 × 50-cm. test-tube) and air-dried. Prior to spraying, the strips were dried at 80° for 15 minutes. The spray solution was prepared by mixing 10 parts of 85% phosphoric acid with 25 parts each of water and 95% ethanol. After the papers were sprayed, they were kept at 90° for 20 minutes. Generally, cholic and norcholic acids showed up as red or brick colored spots and occasionally one of the other acids appeared as a red spot. In ultraviolet light (Model SL Mineralight, Ultra-Violet Products, Inc., South Pasadena, California) desoxycholic acid exhibited a pink fluorescence and the other acids exhibited a greenish-yellow fluorescence. When larger quantities of these acids were used (100–200 γ) they all gave colored spots in white light as well as appearing more readily in the ultraviolet.

The R_f values were measured from the foremost point of the origin to the leading edge of the spot. The solvent mixtures which included ammonia tended to give some streaking, whereas with ethanolamine spots about 15 mm. in diameter were obtained.

All R_f values represent the average of a number of experiments.

Acknowledgment.—The authors wish to thank Dr. J. G. Buchanan for several helpful discussions and Dr. R. M. Lemmon for generous gifts of norcholic and triformylnorcholic acids.

RADIATION LABORATORY
UNIVERSITY OF CALIFORNIA
BERKELEY 4, CALIFORNIA

(1) The work described in this paper was sponsored by the United States Atomic Energy Commission.

(2) R. Neher and A. Wettstein, *Helv. Chim. Acta*, **34**, 2278 (1951).

A Redetermination of the Kinetic Constants for the System α-Chymotrypsin–Nicotinyl-L-tryptophanamide[1]

BY H. T. HUANG AND CARL NIEMANN[2]

RECEIVED MARCH 29, 1952

In previous studies of the kinetics of the α-chymotrypsin catalyzed hydrolysis of simple specific substrates[3–8] the enzyme preparations used were obtained from a single source, *i.e.*, Armour and Co., although it is true that care was taken to use preparations of different lot numbers in several of the investigations.[4,6] While it has been possible in one instance[4] to compare the K_S and k_3 values of acetyl L-tyrosinamide obtained in these laboratories with those obtained elsewhere[9–13] with different enzyme preparations the fact that differences in the reaction systems and analytical procedures were also involved in the above comparison suggested the desirability of a comparison in which the source of the enzyme preparation was the only variable.

The Armour preparation used most frequently in our previous investigations bore the lot no. 90402. This preparation had been used at three different concentrations in a total of twenty-eight separate experiments to evaluate the

(1) Supported in part by a grant from Eli Lilly and Co.

(2) To whom inquiries regarding this article should be sent.

(3) H. T. Huang and C. Niemann, THIS JOURNAL, **73**, 1541 (1951).

(4) D. W. Thomas, R. V. MacAllister and C. Niemann, *ibid.*, **73**, 1548 (1951).

(5) R. J. Foster and C. Niemann, *ibid.*, **73**, 1552 (1951).

(6) H. T. Huang, R. V. MacAllister, D. W. Thomas and C. Niemann, *ibid.*, **73**, 3231 (1951).

(7) H. J. Shine and C. Niemann, *ibid.*, **74**, 97 (1952).

(8) H. T. Huang, R. J. Foster and C. Niemann, *ibid.*, **74**, 105 (1952).

(9) S. Kaufman and H. Neurath, *Arch. Biochem.*, **21**, 245 (1949).

(10) S. Kaufman and H. Neurath, *J. Biol. Chem.*, **180**, 181 (1949).

(11) G. W. Schwert and S. Kaufman, *ibid.*, **180**, 517 (1949).

(12) S. Kaufman and H. Neurath, *ibid.*, **181**, 623 (1949).

(13) H. Neurath and J. A. Gladner, *ibid.*, **188**, 407 (1951).

K_S and k_3 values of nicotinyl-L-tryptophanamide at 25° and *p*H 7.9 in aqueous systems 0.02 *M* in respect to the amine component of a tris-(hydroxymethyl)-aminomethane–hydrochloric acid buffer.[3] Thus with these relatively precise values at hand and also because this specific substrate had been used in inhibition experiments to evaluate the K_I values of a large number of competitive inhibitors[14] it was selected for use in this investigation. For comparison with the above Armour preparation a sample of α-chymotrypsin originally obtained as a twice recrystallized filter cake from the Worthington Biochemical Laboratories, which had been further recrystallized and then dialyzed in the cold, first against dilute aqueous hydrochloric acid of *p*H 3.5, then exhaustively against water, and finally lyophilized, was kindly placed at our disposal by Mr. E. F. Jansen of the Western Regional Research Laboratory. The experimental conditions and the analytical methods used in this investigation were identical with those employed previously.[3]

The results of the present study are summarized in Fig. 1 wherein eight determinations of the initial velocity at seven different initial substrate concentrations and a single enzyme concentration are expressed as a $[S]_0$ *versus* $[S]_0/v_0$ plot.[15] From the intercept of this plot, *i.e.*, $-K_S$, and the slope, *i.e.*, V, the K_S and k_3 values for nicotinyl-L-tryptophanamide were found to be 2.7×10^{-3} *M* and 1.5×10^{-3} mole/liter/min./mg. protein-nitrogen/ml., respectively.[16] These values are in excellent agreement with the previously determined K_S and k_3 values of 2.7×10^{-3} *M* and 1.6×10^{-3} mole/liter/min./mg. protein-nitrogen/ml., respectively.[3]

It can be concluded from the above results that the kinetic constants reported previously for systems containing bovine α-chymotrypsin[3-8,14] are those of systems containing a reproducible characteristic catalytic species of considerable stability. However, the agreement noted above adds little to what is already known about the accuracy of these values,[3] since an error that can still be present is the operational one involved in the determination of initial velocities and this has in a sense been standardized by using approximately the same procedure in all cases. An investigation is now in progress in which it is hoped that initial velocities can be estimated with much greater accuracy than has previously been possible.

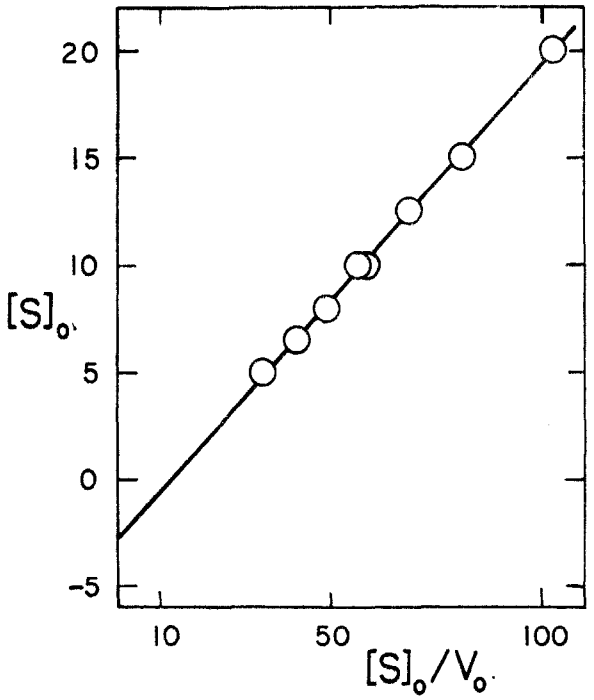


Fig. 1.—α-Chymotrypsin catalyzed hydrolysis of nicotinyl-L-tryptophanamide at 25° and *p*H 7.9; v_0 in units of 10^{-3} *M* per min., $[S]_0$ in units of 10^{-3} *M*, [E] equivalent to 0.144 mg. protein-nitrogen per ml., 0.02 *M* tris-(hydroxymethyl)-aminomethane–hydrochloric acid buffer.

(14) H. T. Huang and C. Niemann, THIS JOURNAL, **73**, 1555, 3223, 3228, 4039 (1951); **74**, 101 (1952).

(15) H. Lineweaver and D. Burk, *ibid.*, **56**, 658 (1934).

(16) An independent evaluation of these data by Dr. D. W. Thomas and based upon a least squares treatment gave $K_S = 2.8 \times 10^{-3}$ *M* and $k_3 = 1.5 \times 10^{-3}$ mole/liter/min./mg. protein-nitrogen/ml.

CONTRIBUTION NO. 1667 FROM THE
GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA 4, CALIFORNIA

Anion Exchange of Niobium in 7.0 Molar Hydrochloric Acid

BY E. H. HUFFMAN AND G. M. IDDINGS

RECEIVED MAY 15, 1952

It has recently[1] been reported that the elution of titanium from a cation exchange resin with citrate solution has resulted in broad elution bands with several peaks. This behavior was attributed to the probable partial separation of the isotopes of titanium. Work in this Laboratory on the elution of niobium with hydrochloric acid from an anion exchange resin, subsequent to that previously reported,[2] has shown a somewhat similar behavior, but under conditions which precluded any possible isotope separation.

When carrier-free Nb^{95}, prepared as described before,[2] was adsorbed from a 10.0 *M* hydrochloric acid solution on a Dowex 2 anion exchange resin column, 8.0 cm. long and 3.0 mm. in diameter, and then eluted with 7.0 *M* hydrochloric acid at the rate of about 2.4 ml. per hour, the elution curve shown in Fig. 1 was obtained. The possibility of any foreign activity in the purified Nb^{95} accounting for three peaks was eliminated by obtaining the decay rates of the samples taken at the top of each

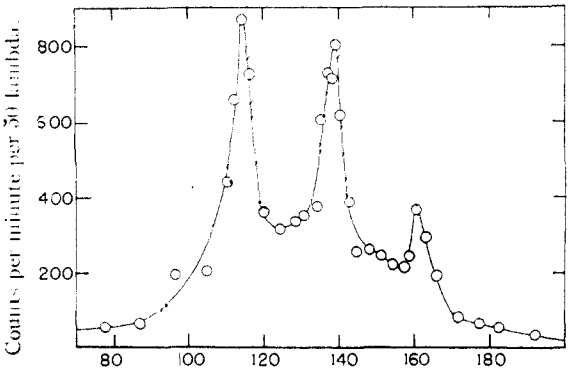


Fig. 1.

(1) William E. Brown and William Rieman, III, THIS JOURNAL, **74**, 1278 (1952).

(2) E. H. Huffman, G. M. Iddings and R. C. Lilly, *ibid.*, **73**, 4474 (1951).

peak. All three gave identical decay curves, corresponding to the disintegration rate of Nb^{95}. When this experiment was repeated a somewhat different curve was obtained. Again three peaks were found, but these were rounded, and the areas under the first and third were approximately equal and greater than that of the second. Brown and Rieman[1] also report that their elution bands were not exactly reproducible.

This departure from the expected type of elution band can probably be attributed to the slow establishment of equilibrium among various ionic species which are present. These ions would not necessarily have to have different charges, as in the case of the thiocyanate complexes of chromium,[3] but may contain different numbers of chloro-, oxy- and hydroxy-groups. Elution with 6.0 *M* hydrochloric acid gives the usual symmetrical curve.

This work was done under the auspices of the Atomic Energy Commission.

(3) E. L. King and E. B. Dismukes, *ibid.*, **74**, 1674 (1952).

RADIATION LABORATORY
UNIVERSITY OF CALIFORNIA
BERKELEY 4, CALIFORNIA

The State of Anthracene, *sym*-Trinitrobenzene and their 1 : 1 Complex in Liquid Sulfur Dioxide Solution

BY NORMAN N. LICHTIN, RALPH E. WESTON, JR., AND JUNE D. WHITE[1]

RECEIVED APRIL 3, 1952

Numerous investigations of molecular complexes between polynitroaromatic compounds and unsaturated hydrocarbons and their derivatives, both in the crystalline state and in solution, have led to varying interpretations as to the nature of the binding forces involved.[2] The investigation reported here was directed toward testing the proposal of Weiss[3] that such complexes are produced by complete transfer of an electron and are ionic in nature. The conductivity behavior and ultraviolet spectra of liquid sulfur dioxide solutions of *sym*-trinitrobenzene (TNB), anthracene and their 1:1 complex were accordingly investigated over a range of concentrations.

Experimental

Materials.—Reilly Tar and Chemical Corp. "Scintillation Grade" anthracene was employed, m.p. 215.4–215.5°,[4] strongly fluorescent. It was purified by sublimation at 120° and 1 mm. pressure to yield material melting sharply at 215.4°.[4] Eastman Kodak Co. "White Label" TNB, m.p. 122.2–122.4°,[4] was purified by sublimation at 100° and about 0.001 mm. pressure to yield slightly yellow material melting at 123.2–123.3°.[4] The complex was prepared from the vacuum sublimed components by the method of Briegleb and Schachowskoy.[5] The product consisted of long orange needles, m.p. 163.8–164.0°.[4] The purity of the sulfur dioxide employed in the conductivity measurements[6] and spectrophotometric work[7] is described elsewhere.

Measurements.—Conductivity measurements were carried out at 0.11 ± 0.03° using apparatus and procedures which are described elsewhere.[6] With anthracene and the complex the samples were pumped in the conductivity cell at about 0.001 mm. pressure and 0° for periods of at least 12 hours before sulfur dioxide was admitted. TNB was similarly pumped in only one run but this run did not differ significantly from others with this compound.

After some of the conductivity runs, the solute was recovered by pouring the solution into an evaporating dish and allowing the solvent to evaporate in air. Recovered anthracene melted at 215.2–216.8°.[4] Recovered TNB melted at 123°.[4] Recovered "complex" melted over the range 140–170°[4] even though it looked unchanged.

Spectrophotometric measurements were carried out at 1–2° using apparatus and procedures which are described elsewhere.[7]

Evaluation of Conductivity Measurements.—Solutions of the purified materials possess such low conductivities that, even though the specific conductivity of the solvent usually fell in the range 2.9×10^{-8} to 7.3×10^{-8}, this was normally more than 10% of the total specific conductivity of the most concentrated solutions (about 0.01 molar) and from 22 to 50% of the conductivity of the most dilute solutions (about 0.00005 molar). In this connection it must be emphasized that the measured conductivity of the solvent is highly sensitive to traces of electrolytes desorbed from the electrodes or the walls of the cell. This can be demonstrated by repeated redistillation of the solvent within the cell in the absence of added solute. Thus, in one case, six distillations reduced the solvent conductivity to one-fifth of its initial value. Correction of solution conductivities for solvent conductivity is therefore an approximate procedure. In the present case solute conductivities can be considered known to within a factor of two.

Data and Discussion

The molar conductances (Λ) of anthracene, TNB, and the complex were determined in the concentration range 4×10^{-4} *M* to 4×10^{-3} *M*. The Λ values ("corrected" for solvent conductivity) all fall in the range from 0.02 to 0.7 mho cm.^{2}/mole. The molar conductance of anthracene is somewhat lower than that of TNB at all concentrations. Within the reliability of the data, the conductance of the complex is equal to the sum of the conductances of its components.[8]

The spectral data are summarized in Fig. 1 where molar absorbancy index ($(1/bc)$ log (I_0/I), b in cm., c in moles per liter) is plotted logarithmically *vs.* wave length. It is apparent that the spectrum of the complex is within experimental error identical with the sum of the spectra of its components.

Solutions of the complex were found to obey Beer's law at 430 mμ (in the concentration range 4.85×10^{-4} to 5.16×10^{-5} *M*) with a molar absorbancy index of 1350. At this wave length, anthracene solutions were also found to obey Beer's law (in the concentration range 1.16×10^{-3} to 5.06×10^{-5} *M*) with a molar absorbancy index of 1450. The agreement of these two values is within experimental error.

It is notable that, although the spectrum of TNB in sulfur dioxide solution closely resembles that in carbon tetrachloride,[5] the spectrum of anthracene in sulfur dioxide lacks the fine structure observed in the latter solvent,[5] and extends much

(1) Taken in part from the A.M. Thesis submitted by June D. White to the Graduate School of Boston University.

(2) (a) G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 67–69; (b) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, London, 1949, pp. 184–185; (c) G. Briegleb, "Zwischenmolekulare Kräfte," G. Braun, Karlsruhe, 1949, pp. 12–15; (d) R. S. Mulliken, THIS JOURNAL, **74**, 811 (1952).

(3) J. Weiss, *J. Chem. Soc.*, 245 (1942).

(4) Capillary melting point, measured with Anschütz-type total immersion thermometer.

(5) G. Briegleb and T. Schachowskoy, *Z. physik. Chem.*, **19B**, 255 (1932).

(6) N. N. Lichtin and H. Glazer, THIS JOURNAL, **73**, 5537 (1951).

(7) P. D. Bartlett and R. E. Weston, Jr., *ibid.*, **74**, in press.

(8) The possibility that the observed conductivities are due to traces of electrolytic impurities cannot be ruled out. Presumably the impurities in the components would be carried into the complex.

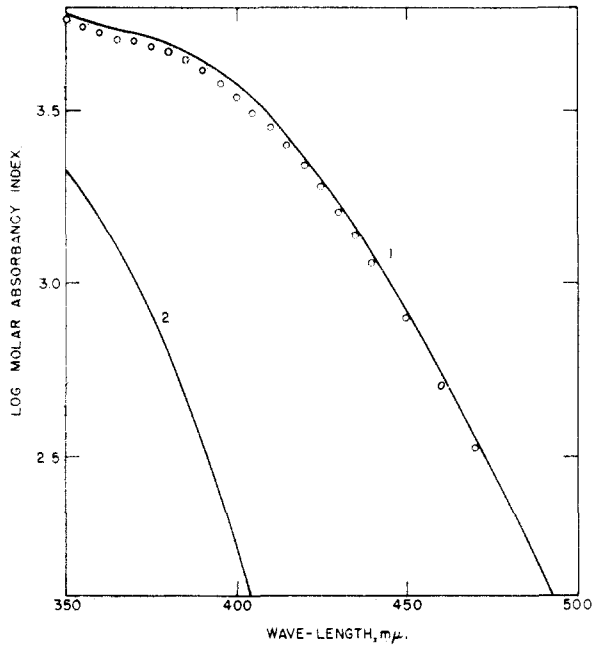


Fig. 1.—Ultraviolet absorption spectra in liquid sulfur dioxide at 1°: curve 1, anthracene; curve 2, s trinitrobenzene (1 + log molar absorbancy index); points O, anthracene–TNB complex.

further toward longer wave lengths. A specific interaction between anthracene and sulfur dioxide is indicated. This is in agreement with the known formation of complexes between benzene (and certain of its derivatives) and sulfur dioxide.[9]

It must be concluded that the conductivity data provide no evidence in support of the TNB–anthracene complex possessing an ionic nature. Furthermore, the spectrophotometric data provide no evidence for the existence of this complex in liquid sulfur dioxide solution. The spectral evidence for interaction of anthracene and sulfur dioxide suggests that molecules of the latter may effectively displace TNB from its complex with the hydrocarbon. The wide melting range of "complex" recovered from solution in sulfur dioxide supports this suggestion.

It must not be concluded, however, that no new information relevant to Weiss' theory[3] has been obtained. The data for anthracene and TNB lead to significant deductions. Anthracene is shown spectrophotometrically to interact strongly with sulfur dioxide, yet its conductance is no greater than that of TNB which shows no such interaction. The profound change in the anthracene spectrum suggests that all of the anthracene is involved in the interaction. This cannot be proven with the data at hand but a minimum value for the fraction of anthracene interacting can be determined. In inert media the molar absorbancy of anthracene at the sharp 375 mμ peak is at least 8000.[10] In sulfur dioxide at this wave length it is 5100. If one makes the extreme assumption that anthracene which is interacting with the solvent is completely transparent at this wave length, then it must be concluded that no more than 64% of the anthracene is free. Thus no less than 36% of the hydrocarbon is involved in the interaction. In view of the agreement of the spectral data for this compound with Beer's law, this holds at all concentrations. From these considerations it must be concluded that, contrary to the suggestion of Weiss,[11] the interaction between anthracene and sulfur dioxide cannot consist of complete electron transfer to yield the (radical) ion pair $(C_{14}H_{10})^+$ (SO_2^-). Such an ion pair would dissociate to about the same extent[12] as the pair triphenylcarbonium chloride which has been shown[7,12] to have a dissociation constant in sulfur dioxide no smaller than 10^{-3} at 0°. It would yield enormously greater conductances than those observed. To the extent that the anthracene–TNB and anthracene–sulfur dioxide interactions are similar,[2d] doubt is cast on Weiss' picture of the former as well.

Acknowledgment.—One of us (R. E. W.) gratefully acknowledges support of the spectrophotometric work by the Office of Naval Research (Contract No. N5ori-76 Task XX, with Harvard University). The conductivity study was made possible by a Frederick Gardner Cottrell Grant made to Boston University by the Research Corporation.

(9) L. J. Andrews and R. M. Keefer, THIS JOURNAL, **73**, 4169 (1951).

(10) (a) American Petroleum Institute Research Project 44 at the National Bureau of Standards. Catalog of Ultraviolet Spectrograms Serial No. 170, contributed by the Shell Development Co., Emeryville, Calif. (in isooctane); (b) ref. 5, p. 264 (in carbon tetrachloride); (c) W. V. Mayneord and E. P. M. Roe, *Proc. Roy. Soc. (London)*, **A152**, 299 (1935) (in ethanol); (d) K. Lauer and M. Horio, *Ber.*, **69**, 130 (1936) (in hexane).

(11) Reference 3, p. 250.

(12) N. N. Lichtin and P. D. Bartlett, THIS JOURNAL, **73**, 5530 (1951).

CHEMISTRY DEPARTMENT, BOSTON UNIVERSITY
BOSTON, MASSACHUSETTS, AND THE
CONVERSE MEMORIAL LABORATORY, HARVARD UNIVERSITY
CAMBRIDGE, MASSACHUSETTS

Observations Concerning Polymorphic Crystalline Modifications of the Phthalocyanines[1]

BY FRANCIS W. KARASEK AND J. C. DECIUS

RECEIVED JANUARY 14, 1952

Phthalocyanine and some of its metallic derivatives exist in two known polymorphic crystalline forms. The α-form is normally produced by dissolving the compound in concentrated sulfuric acid and precipitating it by dilution with ice-water. A micro crystal is formed whose structure is not known. The β-form may be produced by low pressure sublimation according to the technique of Barrett.[2] This procedure produces a well-defined monoclinic crystal whose complete structure has been determined by Robertson.[3]

In the course of obtaining the infrared absorption spectra of these compounds, it was found necessary to produce a sample with a very small particle size to avoid severe scattering losses at the shorter wave lengths. This was accomplished by subliming a film of the phthalocyanine directly onto a highly polished and relatively cool (below 200°) rock salt plate under a pressure of 10^{-5} mm. A

(1) Supported by a Frederick Cottrell Grant from the Research Corporation.

(2) P. A. Barrett, *et al.*, *J. Chem. Soc.*, 1719 (1938).

(3) J. M. Robertson, *ibid.*, 615 (1935).

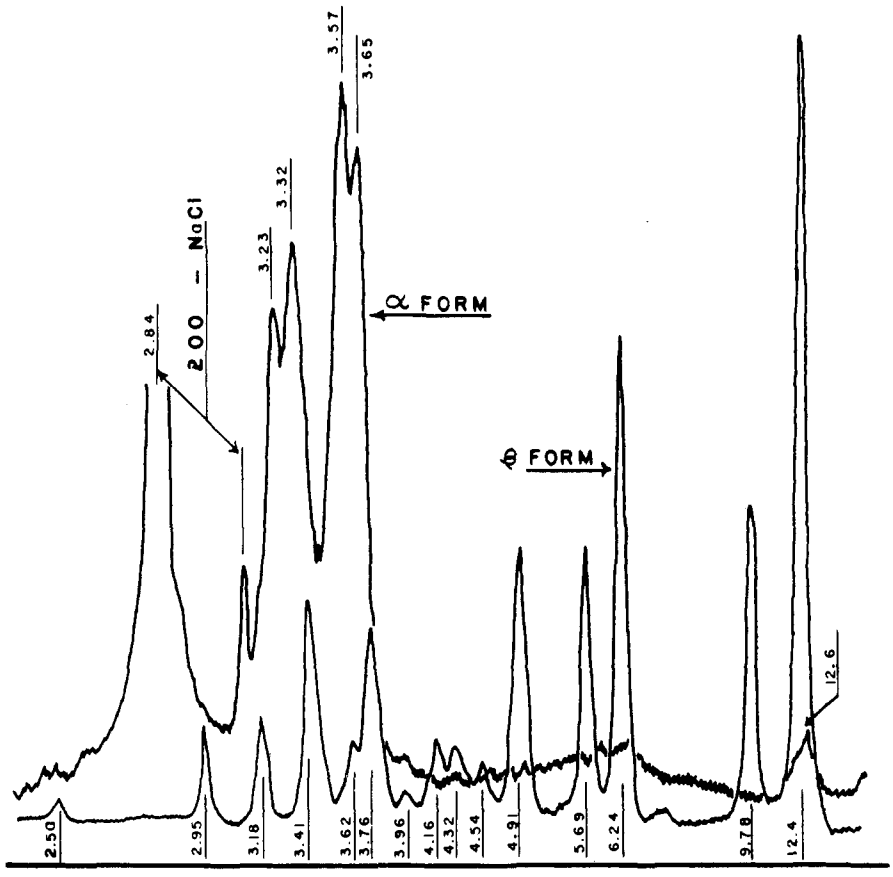


Fig. 1.—X-Ray diffraction patterns of metal-free phthalocyanine.

study of the infrared spectrum[4] and X-ray diffraction pattern of this material revealed that this technique produces the α-form of a phthalocyanine. The average particle size appears to be of the order of a few microns as evidenced by low scattering losses at wave lengths of 3 microns and above. Figure 1 illustrates the X-ray diffraction pattern of the β-form of metal-free phthalocyanine obtained as a powder, and superimposed on the same scale is that of the α-form deposited on a rock salt plate. The decrease in the relative intensity of the diffraction line at 12.6 Å. as compared with the results of Ebert and Gottlieb[5] may be attributed to partial orientation of the crystals produced by sublimation. The β-pattern agrees quite well with that calculated from the data of Robertson.

A preliminary investigation of the pressure dependence of the phase change indicated that the alpha form of metal-free phthalocyanine is produced at sublimation pressures up to 50 mm. The α-form of copper phthalocyanine is produced at pressures up to 0.1 mm.; above this pressure sublimation produces the β-form.

German scientists discovered that an α-β-phase transition occurs for the metal-free and copper phthalocyanine at temperatures above 200°.[6] Barrett's condensation temperature was 400°, which explains why the α-form of metal-free phthalocyanine was never produced by his procedure.

CORVALLIS, OREGON

(4) D. N. Kendall, 119th A.C.S. Meeting, April, 1951, Abstracts Division of Phys. and Inorg. Chem., 2p.

(5) A. A. Ebert, Jr., and H. B. Gottlieb, THIS JOURNAL, **74**, 2806 (1952).

(6) Fiat, Final Report 1313 Vol. III, U. S. Dept. of Commerce, Washington, D. C., 1948, pp. 345-439.

The Dissociation of Certain Benzohydryl Ethers

BY TI LI LOO

RECEIVED MARCH 20, 1952

The report by Kaye[1] and by Harms and Nauta[2] of the dissociation of certain benzohydryl ethers to afford *s*-tetraphenylethane finds support from work performed by the present author in 1947 in connection with other studies, first during preparation of the oxide of benzohydryl allyl ether, and again during the reaction of 1-benzohydryl ether of 3-chloro-1,2-propanediol with piperidine.

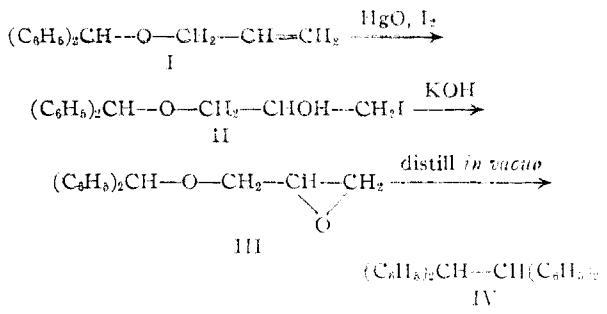
In the first instance, an unsuccessful attempt was made to prepare by the procedures of Brunel[3] and Bougault[4] the oxide (III) from benzohydryl allyl ether (I), through the iodohydrin (II) (not isolated). Upon distilling *in vacuo* an ethereal solution containing the supposed iodohydrin (II), a small amount of *s*-tetraphenylethane (IV) was obtained.

(1) I. A. Kaye, THIS JOURNAL, **73**, 5468 (1951); I. A. Kaye, I. C. Kogon and C. Parris, *ibid.*, **74**, 403 (1952).

(2) A. F. Harms and W. T. Nauta, *Rec. trav. chim.*, **71**, 431 (1952).

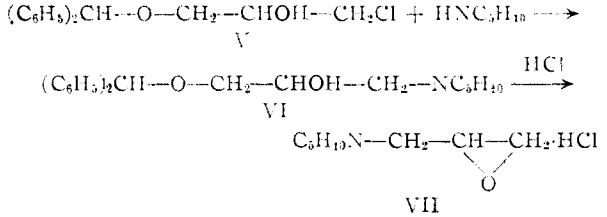
(3) L. Brunel, *Compt. rend.*, **135**, 1055 (1902).

(4) J. Bougault, *Bull. soc. chim.*, **25**, 444 (1901).



The decomposition was apparently catalyzed by iodine as in the case of isopropyl ether.[5]

The dissociation of benzohydryl ether was again observed in the second case in which the 1-benzohydryl ether of 3-chloro-1,2-propanediol (V) was allowed to react with piperidine.



Most unexpectedly, β-piperidopropylene oxide (VII) instead of the amine-ether (VI) was isolated. The fate of the rest of the molecule was not defined.

Experimental[6]

Benzohydryl Allyl Ether (I).—Diphenylchloromethane (16 g.) was carefully added to allyl alcohol (14 g.) in potassium hydroxide solution (5 g. dissolved in 15 ml. of water). When the reaction had subsided, the mixture was then refluxed on the steam-bath for five hours, cooled, diluted with water (100 ml.) and extracted three times with 50 ml. of ether. The ethereal extract was dried over calcium chloride and distilled under reduced pressure. The fraction distilling between 172–176° (18 mm.), weighed 16.5 g. (30.5% based on allyl alcohol).

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.2. Found: C, 85.0; H, 7.1.

Attempted Preparation of the Benzohydryl Ether of 1,2-Epoxypropanol (III).—To a solution of benzohydryl allyl ether (11.2 g.) in ether (110 ml.) was added yellow mercuric oxide (6 g.) and a little water (10 ml.). While the mixture was vigorously stirred, iodine (14 g.) was added in small portions. The stirring was continued for half an hour after the addition of all the iodine. The mixture was filtered and washed first with potassium iodide solution and then with a solution of sodium hyposulfite to remove the unreacted iodine. The clear ethereal solution was next shaken vigorously with 50 ml. of a 20% aqueous potassium hydroxide solution. The ethereal layer was dried over magnesium sulfate, then distilled *in vacuo*. It became dark red upon heating, with the visible liberation of iodine. The distillation was subsequently discontinued, and the solution again subjected to the treatment with sodium hyposulfite, extracted with ether, and the ethereal extract again shaken with concentrated potassium hydroxide. Upon redistilling the dried ethereal extract under reduced pressure, iodine was liberated as described before. When all volatile fractions, b.p. below 180° (18 mm.) (unidentified) were distilled off, an almost colorless crystalline residue remained, m.p. 211°, after recrystallizing from acetone. It was shown to be *s*-tetraphenylethane by elementary analyses and also by comparison with an authentic sample.

(5) J. V. S. Gluss and C. N. Hinshelwood, *J. Chem. Soc.*, 1815 (1928).

(6) All boiling points and melting points are not corrected. Microanalyses done by Dr. G. Weiler of Oxford, England.

1-Benzohydryl Ether of 3-Chloro-1,2-propanediol (V).[7]—Concentrated sulfuric acid (2 ml.) was very carefully dropped into an equimolecular mixture of benzohydrol (18.4 g.) and epichlorohydrin (9.3 g.). The mixture reacted very vigorously and soon turned dark. After six hours heating on the steam-bath, the solution was cooled, diluted with benzene (50 ml.), and carefully neutralized with barium carbonate (6 g.). It was filtered, dried over magnesium sulfate and fractionated *in vacuo*. The fraction boiling between 150–160° (20 mm.) was collected; it weighed 8 g. (27%).

Anal. Calcd. for $C_{16}H_{17}ClO_2$: Cl, 12.8. Found: Cl, 12.8.

The reaction of epichlorohydrin with the sodio-derivative of benzohydrol failed to give the expected ether.

Condensation of 1-Benzohydryl Ether of 3-Chloro-1,2-propanediol with Piperidine.—The 1-benzohydryl ether of 3-chloro-1,2-propanediol (8 g.) was mixed with piperidine (11.6 g.); evolution of heat was noted. The solution was warmed on the steam-bath for three hours, cooled, poured on ice, and carefully acidified with hydrochloric acid (6 *N*) until blue to congo red. It was extracted with about an equal volume of ether and the ethereal extract discarded. The acid solution was made strongly alkaline with potassium hydroxide solution, whereupon a light reddish, amine-smelling oil separated. This was extracted with benzene, and dried over anhydrous potassium carbonate. The benzene was distilled off leaving the free base as a residue. A colorless hydrochloride prepared from this base had an m.p. 245–247° (darkening at 238°), and weighed 4 g. Upon mixing the piperidine hydrochloride, a depression of 45° in m.p. was observed. The product analyzed correctly for the hydrochloride of β-piperidopropylene oxide (VII).

Anal. Calcd. for $C_8H_{15}NO\cdot HCl$: C, 54.1; H, 9.0; N, 7.9. Found: C, 53.5; H, 9.0; N, 8.1.

Acknowledgment.—This work was done in 1947 during the tenure of a research assistantship at the Department of Pharmacology, University of Oxford, England.

(7) E. Fourneau and I. Ribas, *Bull. soc. chim.*, **39**, 1584 (1926); **41**, 1046 (1927).

THE CHRIST HOSPITAL INSTITUTE OF MEDICAL RESEARCH
2139 AUBURN AVENUE
CINCINNATI 19, OHIO

The Separation of Catechol from Steam Distillates and Reaction Mixtures

BY W. WERNER ZORBACH AND J. ELLIOTT WEBER

RECEIVED APRIL 21, 1952

During experiments designed to determine yields in the conversion of *o*-aminophenol to catechol,[1] it was found that the product could easily be removed from the bulky steam distillate by precipitating as the barium salt,[2] thus rendering unnecessary tedious extraction procedures. Some difficulty, however, was encountered in attempts to regenerate the catechol in organic solvents by means of hydrogen chloride, but this was overcome by substituting lead for barium. In contradistinction, the lead salt[3] was readily decomposed in benzene with hydrogen chloride to yield catechol and lead chloride. Although this procedure proved quite satisfactory, the over-all yields from the reaction were found to be of a low order.

Applying further this property of catechol to form insoluble salts with heavy metals, a convenient and rapid method was found for the separation of this substance formed in the hydrogen peroxide

(1) Société Chimique des Usines du Rhone, D.R.P. 167,211 (1906).

(2) B. Elsner, *Monatsh.*, **40**, 361 (1919).

(3) C. Zwenger, *Ann.*, **37**, 332 (1841).

oxidation of salicylaldehyde,[4] particularly when small scale syntheses were undertaken. Due to interfering ions, lead acetate could not be used in the recovery. Instead, the catechol thus formed was precipitated directly from the reaction mixture with barium hydroxide and regenerated from the resulting salt with a small quantity of dilute, aqueous hydrochloric acid. Ether extraction gave yields comparable to those noted in the described synthesis. For excellent purity the crude product was vapor distilled with bromobenzene.[5]

Experimental

Catechol from *o*-Aminophenol.—To a solution of 35.6 g. (0.363 mole) of sulfuric acid in 50 ml. of water cooled to −10° was added with constant stirring 15.8 g. (0.145 mole) of *o*-aminophenol. The final solution was brought to about 10% by dilution with ice and then added at a moderate rate to a boiling solution of 50 g. (0.2 mole) of cupric sulfate pentahydrate in 50 ml. of water contained in a flask equipped for distillation. The catechol formed was steam distilled until the distillate gave only a faint test with alcoholic ferric chloride. To this distillate was added a 10% aqueous solution of normal lead acetate until precipitation was complete. The lead catecholate was then collected on a buchner funnel, washed thrice with cold water, then twice with small portions of acetone and finally sucked dry. The dry material was transferred to a 300-ml. round bottom flask, covered with 200 ml. of benzene and then treated with a rapid stream of dry hydrogen chloride. In 15 to 20 minutes the decomposition was complete, leaving a residue of lead chloride which was filtered off. The filtrate was then placed on a steam-bath and distilled at atmospheric pressure until the distillate appeared clear. The remainder of the benzene was evaporated *in vacuo*, leaving a brownish, crystalline residue of catechol which was transferred to a 50-ml. distilling flask, covered with 25 ml. of bromobenzene and vigorously distilled through an air condenser into a flask cooled to 0°. The separating product was filtered by suction and the filtrate returned to the distilling flask which contained undistilled catechol. This was likewise distilled, giving an additional amount of pure material in the distillate, and the process repeated until all the catechol was carried over. In this manner, 2.32 g. (9.7%) of colorless plates, m.p. 104°, was obtained.

Catechol from Salicylaldehyde.—Directions for this preparation, scaled down to 0.05 mole, were employed as noted above.[4] To the final reaction mixture, adjusted to a *p*H of approximately seven with acetic acid and warmed to 40°, was added a solution of 9.45 g. (0.03 mole) of barium hydroxide octahydrate in 30 ml. of water at 80°. Greenish-gold leaflets of barium catecholate separated and were immediately filtered by suction. The funnel and contents were transferred to a clean filter flask, washed with cold water until the washings appeared clear, then twice with acetone and allowed to dry by suction. To the first filtrate was added a solution of 6.30 g. (0.02 mole) of barium hydroxide octahydrate in 20 ml. of water, whereupon more material separated out. This was filtered and washed in a similar manner. The combined quantities of dry salt were crushed, placed in a 100-ml. round bottom flask and covered with 25 ml. of a hydrochloric acid solution containing 2.74 g. (0.075 mole) of hydrogen chloride. The mixture was then warmed on the steam-bath until complete solution was effected and the contents transferred quantitatively to a separatory funnel and extracted with two 100-ml. portions of ether. The ether extract in turn was washed with two 25-ml. portions of 5% potassium bicarbonate, dried for one-half hour over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*, leaving 3.91 g. (71%) of impure, crystalline catechol. Repeated distillation with bromobenzene, as described in the above experiment, gave 3.72 g. (68%) of colorless plates, m.p. 104°.

CHEMISTRY DEPARTMENT
BOWLING GREEN STATE UNIVERSITY
BOWLING GREEN, OHIO

(4) H. D. Dakin, "Organic Syntheses," Coll. Vol. I, 2d Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 149.

(5) N. Elliott, U. S. Patent 1,912,626 (1933).

Conductance of Aluminum Chloride in Sulfuryl Chloride on Adding Benzophenone or Sulfur Monochloride[1]

BY A. R. PRAY AND C. R. MCCROSKY

RECEIVED APRIL 28, 1952

Kraus, Van Dyke and their collaborators have recently reported studies on the complexes formed by some aluminum (or gallium) halides with other molecules in several non-aqueous solutions.[2] These solutes are of especial interest as their solutions are electrically conducting, the conductance changing in a marked way as the complexing agent is added.

We here report a somewhat similar study on aluminum chloride dissolved in sulfuryl chloride, using benzophenone and sulfur monochloride as complexing agents.

Experimental

Materials.—Sulfuryl chloride[3] was distilled immediately before use. The distilling apparatus, of ordinary kind with ground glass joints, was flushed out with a portion of the fraction boiling at 69° before collection of the portion to be used. The solvent so obtained had a specific conductance of 4×10^{-8} mho.

Aluminum chloride, anhydrous, of reagent grade, was purified by sublimation, the method resembling that given by Archibald[4] but simplified in detail.

Benzophenone was recrystallized three times from alcohol, dried in a current of warm air, and stored over barium oxide.

Sulfur monochloride was twice distilled from excess sulfur. The middle portion of the fraction boiling at 138° was used.

Apparatus and Procedure.—Conductance measurements were made on an assembled apparatus following the circuit of Jones and Josephs.[5] The conductance cell was immersed in an oil thermostat of 20-l. capacity maintained at 25 ± 0.05°. The conductance cell was a test-tube, 15 by 2.5 cm., fitted with a hard rubber cover. Through this cover two parallel glass tubes holding the electrodes passed. The electrodes were shiny platinum plates, about 1 cm. square and separated by about 1 mm. The glass tubes were separated by a glass spacer at the electrode end. The hard rubber cover was drilled to provide entry for a buret tip, by means of which the complexing agent was added. The buret was of 10-ml. volume, graduated in 0.05 ml. It was calibrated at each ml. It was found convenient to fit the top with a microcapillary to restrict air entry.

The addition of complexing agent to the aluminum chloride was carried out as follows. Twenty ml. of sulfuryl chloride was distilled into the conductance cell. From 0.3 to 1 g. of aluminum chloride was weighed out into the cell. The liquid was warmed slightly to hasten solution. The cell was closed with the cap holding the electrodes and immersed in the thermostat. About 10 g. of the complexing agent was weighed into a small (10–25 ml.) calibrated volumetric flask. The flask was made up nearly to the mark with sulfuryl chloride, allowed to stand in the thermostat, and finally adjusted to volume. The contents were then transferred to the buret. The initial conductance of the solution was then measured and discrete amounts of com-

(1) Presented at the 118th National Meeting of the American Chemical Society in Chicago, September 3–8, 1950.

(2) (a) Aluminum bromide with methyl ether in methyl bromide solution, W. J. Jacobet and C. A. Kraus, THIS JOURNAL, **71**, 2409 (1949); (b) Aluminum bromide with other molecules in nitrobenzene solution, R. E. Van Dyke and C. A. Kraus, *ibid.*, **71**, 2694 (1949), and R. E. Van Dyke, *ibid.*, **73**, 398 (1951); (c) gallium chloride with other molecules in nitrobenzene solutions, R. E. Van Dyke, *ibid.*, **72**, 2823 (1950); (d) aluminum bromide with other molecules in benzonitrile solution, R. E. Van Dyke and T. S. Harrison, *ibid.*, **73**, 402, 571 (1951); (e) aluminum chloride with other molecules in nitrobenzene solution, R. E. Van Dyke and H. E. Crawford, *ibid.*, **73**, 2018, 2022 (1951).

(3) Kindly furnished by the Hooker Electrochemical Co., Niagara Falls, New York.

(4) E. H. Archibald, "Preparation of Pure Inorganic Substances," John Wiley and Sons, Inc., New York, N. Y., 1932.

(5) G. Jones and R. J. Josephs, THIS JOURNAL, **50**, 1049 (1928).

plexing agent were added, in solution. The solution in the cell was agitated by gentle rotation of the hard rubber cover. After each addition a new reading was made until finally a large molar excess of complexing agent had been added. The cell constant was determined at the beginning and end of each set of observations.

Benzophenone.—The conductance of aluminum chloride in sulfuryl chloride, as benzophenone was added, was studied for three concentrations of aluminum chloride: 0.129, 0.323 and 0.564 molar. For the first of these, benzophenone solution of 0.632 molarity was added; for the second, of 0.711 molarity, and for the third, 1.034. Data

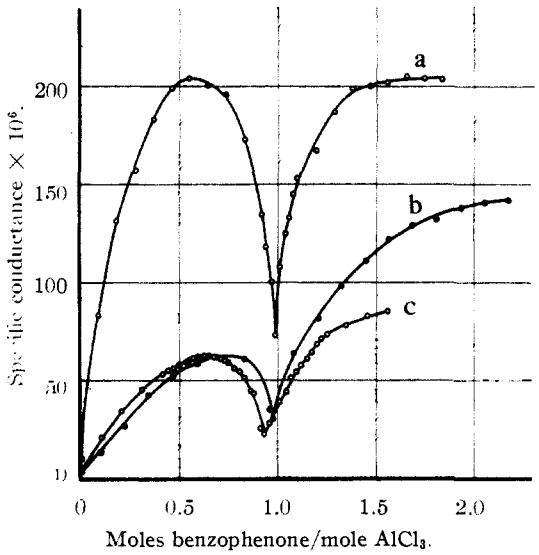


Fig. 1.—Conductance of aluminum chloride in sulfuryl chloride on addition of benzophenone at 25°: a, 11.25 millimoles $AlCl_3$, 1.035 molar benzophenone; b, 2.58 millimoles $AlCl_3$, 0.632 molar benzophenone; c, 6.86 millimoles $AlCl_3$, 0.711 molar benzophenone.

for these three additions are plotted in Fig. 1; a brief summary is given in Table I. It will be seen that the conductance of aluminum chloride is initially low and rises, as benzophenone is added, to a maximum at a molar ratio for benzophenone to aluminum chloride around 0.6–0.7; the conductance then falls markedly to a minimum for the molar ratio of (nearly) unity, and rises again thereafter.[6] This behavior is somewhat similar to that observed by Van Dyke and Harrison for the addition of pyridine to aluminum bromide in benzonitrile and in nitrobenzene[2d] as well as to that

TABLE I

THE CONDUCTANCE OF ALUMINUM CHLORIDE IN SULFURYL CHLORIDE ON THE ADDITION OF BENZOPHENONE

Curve a Ms. $AlCl_3$ = 0.01125 M. $C_{13}H_{10}O$ = 1.035		Curve b Ms. $AlCl_3$ = 0.00258 M. $C_{13}H_{10}O$ = 0.632		Curve c Ms. $AlCl_3$ = 0.00686 M. $C_{13}H_{10}O$ = 0.711	
$K \times 10^6$, mhos	Mole ratio $C_{13}H_{10}O/AlCl_3$	$K \times 10^6$, mhos	Mole ratio $C_{13}H_{10}O/AlCl_3$	$K \times 10^6$, mhos	Mole ratio $C_{13}H_{10}O/AlCl_3$
10.0	0.00	2.86	0.00	2.86	0.00
130.9	.184	41.7	.343	34.3	.207
203.6	.552	61.4	.710	53.3	.414
172.9	.828	34.6	.955	58.6	.493
117.5	.943	80.6	1.201	62.4	.673
72.9	.989	111.1	1.447	50.6	.829
125.1	1.035	128.7	1.690	22.48	.932
187.0	1.288	138.3	1.935	53.6	1.093
201.6	1.564	142.1	2.180	72.8	1.250
203.8	1.840	149.0	2.425	85.4	1.555

(6) Benzophenone is itself a conductor in sulfuryl chloride; the conductivity of a molar solution is about 3×10^{-4} mho, as compared to the pure solvent, ca. 4×10^{-6} mho.

observed by Van Dyke and Kraus for the addition of methyl ether to aluminum bromide in nitrobenzene,[7] and that observed by Jacober and Kraus for the addition of methyl ether to aluminum bromide, methyl aluminum bromide and dimethyl aluminum bromide in methyl bromide.[2a]

Sulfur Monochloride.—The conductance of aluminum chloride in sulfuryl chloride as sulfur monochloride was added was studied for two concentrations of aluminum chloride: 0.189 and 0.498 molar. The added sulfur monochloride had a molarity of 4.11. Data for these two additions are plotted in Fig. 2. It will be seen that the conductance

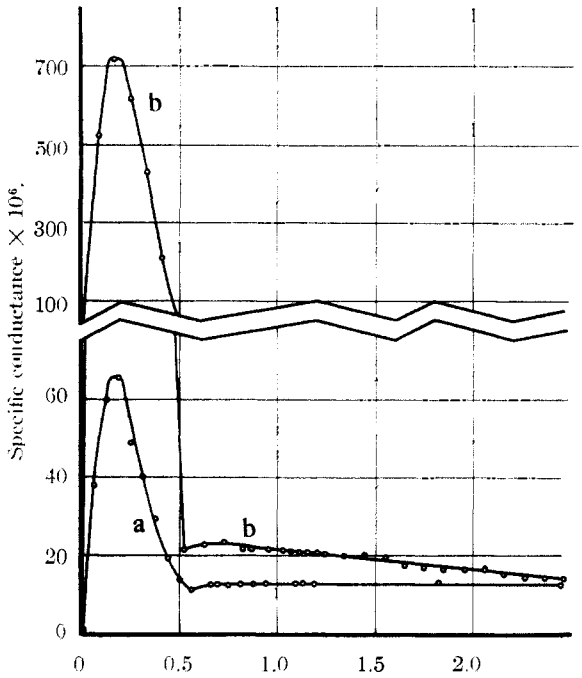


Fig. 2.—Conductance of aluminum chloride in sulfuryl chloride on addition of sulfur monochloride at 25°: a, 3.28 millimoles $AlCl_3$, 4.11 M S_2Cl_2; b, 9.96 millimoles $AlCl_3$, 4.11 molar S_2Cl_2.

of aluminum chloride in sulfuryl chloride is initially low and rises rapidly, as sulfur monochloride is added, to a maximum at a molar ratio for sulfur monochloride to aluminum chloride around 0.2; the conductance then falls rapidly to a minimum for the molar ratio of 0.5 ($S_2Cl_2/AlCl_3$), remaining constant thereafter.[8] As the addition of sulfur monochloride

TABLE II

THE CONDUCTANCE OF ALUMINUM CHLORIDE IN SULFURYL CHLORIDE ON THE ADDITION OF SULFUR MONOCHLORIDE

Curve a Ms. $AlCl_3$ = 0.00328 M. S_2Cl_2 = 4.11		Curve b Ms. $AlCl_3$ = 0.00996 M. S_2Cl_2 = 4.11	
$K \times 10^6$, mhos	Mole ratio $S_2Cl_2/AlCl_3$	$K \times 10^6$, mhos	Mole ratio $S_2Cl_2/AlCl_3$
1.03	0.00	8.35	0.00
37.8	.063	524	.0825
65.5	.188	719	.1649
40.3	.314	432	.330
19.3	.438	212	.412
11.28	.564	21.6	.515
12.72	.752	21.6	1.031
12.78	1.129	19.6	1.546
12.86	1.818	16.3	2.060
12.78	2.445	14.4	2.473

(7) R. E. Van Dyke and C. A. Kraus, THIS JOURNAL, 71, 2694 (1949).

(8) Sulfur monochloride is itself a non-conductor in sulfuryl chloride solution.

proceeds from the start, there precipitates out of the conductance vessel a white, crystalline solid with a composition corresponding to $Al_2Cl_6 \cdot S_2Cl_2$.[9] After the molar ratio ($S_2Cl_2/AlCl_3$) of 0.5 is reached, this compound ceases to precipitate and no further change in the solution is apparent. A brief summary of the data corresponding to Fig. 2 is given in Table II.

(9) Found for $Al_2Cl_6S_2Cl_2$: 13.3% Al, 70.4% Cl. Calcd.: 13.48% Al, 70.89% Cl.

SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA
MINNEAPOLIS, MINNESOTA, AND
DEPARTMENT OF CHEMISTRY, SYRACUSE UNIVERSITY
SYRACUSE, N. Y.

The Aluminum Chloride-Catalyzed Condensation of γ-Butyrolactone with Benzene

BY WILLIAM E. TRUCE AND CECIL E. OLSON

RECEIVED APRIL 14, 1952

The condensation of γ-butyrolactone with benzene in the presence of aluminum chloride has been reported by Christian.[1] We have independently studied this reaction and observed several differences. A higher yield of γ-phenylbutyric acid was realized and α-tetralone was obtained as a product. The relative amounts of the two products can be greatly altered by varying the amount of aluminum chloride as shown in Table I.

TABLE I

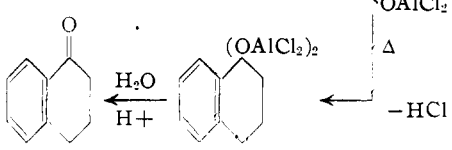
Molar ratio $AlCl_3$/lactone	Yield of α-tetralone, %	Yield of γ-phenylbutyric acid %
1.25	11	73
1.67	32	43
2.50	66	..

The formation of a ketone by the condensation of a lactone with benzene does not appear to have been reported previously. It is submitted as a convenient preparation of γ-tetralone and possibly it could be extended to the preparation of related cyclic ketones.

The following steps and intermediates for the reaction are suggested.

$$C_6H_6 + (CH_2)_3CO_2 + AlCl_3 \longrightarrow C_6H_5(CH_2)_3CO_2AlCl_2 + HCl$$

$$C_6H_5(CH_2)_3CO_2AlCl_2 + AlCl_3 \longrightarrow C_6H_5(CH_2)_3\overset{\oplus}{C}(OAlCl_3^{\ominus})(OAlCl_2)$$



Recent work by Birch and co-workers,[2] and later by Snyder and Werber,[3] in which γ-phenylbutyric acid was condensed to α-tetralone with various strong acids, lends support to the above proposal.

Experimental

The three reactions described below were carried out in a 500-ml., three-neck, round-bottom flask equipped with a reflux condenser (capped with a drying tube), mechanically-driven, sealed stirrer and a 125-ml. erlenmeyer flask connected to the reaction flask by flexible tubing.

Reaction No. 1.—To a well-stirred solution of benzene (200 ml., 176 g., dried over CaH_2) and γ-butyrolactone (20.8 g., 0.24 mole), C.P. anhydrous aluminum chloride (40.2 g., 0.3 mole) was added at a rate that kept the solution refluxing (about one hour). The solution was heated at reflux temperature until the evolution of hydrogen chloride had nearly ceased (about four hours).

The mixture was cooled to room temperature and poured over 200 g. of ice drenched in concentrated hydrochloric acid. The organic layer was separated and washed twice with water. The aqueous part was combined with the washings, washed twice with ether and discarded. The ether washings and the organic layer were combined, dried and distilled under reduced pressure. The first product was a colorless liquid, α-tetralone; b.p. 120–124° (10 mm.) (lit.[4] 128° (12 mm.)); $n^{30}D$ 1.5691, (lit.[3] 1.5688); semicarbazone, m.p. 214–216° (lit.[3] 216°), and yield 4.0 g. (11%). The second product was a waxy crystalline solid, γ-phenylbutyric acid, b.p. 148–155° (10 mm.) (lit.[1] 120–125° (1 mm.)), m.p. 47–48° (lit.[1] 48–49°), and yield 28.5 g. (73%).

Reaction No. 2.—The same amounts of benzene and γ-butyrolactone were used as in Reaction No. 1 with 53.6 g. (0.4 mole) of aluminum chloride and under the same conditions. The yield of α-tetralone was 11.1 g. (32%) and the yield of γ-phenylbutyric acid was 17.0 g. (43.3%).

Reaction No. 3.—Following the same procedure but using 80 g. (0.6 mole) of aluminum chloride, the yield of α-tetralone was 23.2 g. (66%). No phenylbutyric acid was isolated from the brown residue in the distilling flask.

Acknowledgment.—The authors are grateful to the Procter and Gamble Co. for financial support in this work.

(1) R. V. Christian, Jr., THIS JOURNAL, **74**, 1591 (1952).
(2) A. J. Birch, R. Jaeger and R. Robinson, *J. Chem. Soc.*, 582 (1945).
(3) H. R. Snyder and F. X. Werber, THIS JOURNAL, **72**, 2965 (1950).
(4) H. Luther and C. Wächter, *Chem. Ber.*, **82**, 161 (1949).

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

Ionophoresis in Non-aqueous Solvent Systems

BY M. H. PAUL AND E. L. DURRUM

RECEIVED MARCH 26, 1952

Recently there has been renewed interest in what Tiselius[1] has termed "Zone Electrophoresis." Electrophoresis on paper, particularly, has become a convenient and useful method for the separation of an ever increasing number of charged substances. Although considerable data had been amassed about the properties of non-aqueous solvent systems by Walden,[2] a search of the recent literature uncovered no references to electrophoretic separations in non-aqueous solvents with the exception of a paper[3] on the mobility of carbon black particles suspended in kerosene.

A preliminary study on the application of non-aqueous systems to filter paper ionophoresis was undertaken in an attempt to effect resolution of mixtures of certain biological compounds which are insoluble in aqueous electrolytes, such as cholesterol, higher fatty acids and steroid hormones.

The movement of dyes on filter paper was studied first because their migration is conveniently followed. Paper strips (30 × 1.5 cm.) cut from "Whatman 3 MM" filter paper were suspended in a glass and bakelite electrophoresis cell (apex height—13 cm.) similar to that previously described.[4]

(1) A. Tiselius, Abstracts, XII International Congress of Pure and Applied Chemistry, New York, N. Y., Sept., 1951, p. 67.
(2) P. Walden, "Electrochemie Nichtwässriger Lösungen," Barth, Leipzig, 1924.
(3) M. Hayek, *J. Phys. Colloid Chem.*, **55**, 1527 (1951).
(4) E. L. Durrum, THIS JOURNAL, **72**, 2943 (1950).

A small drop of the dye mixture (dissolved in the solvent system used) was placed at the apex of the strips and after the ascending solvent fronts had coalesced at the apex, a potential was applied across the strips by means of platinum electrodes immersed in the electrode vessels.

Figure 1 was prepared from a tracing of paper strips and illustrates the separation of an electropositive dye (crystal violet) and an electronegative dye (Oil Red O). In this separation a mixture of nitromethane (9 vol.) and glacial acetic acid (1 vol). was used. Similar separations have been effected in absolute ethyl alcohol, methanol and in pyridine–glacial acetic acid mixtures.[5] Included in Fig. 1 is an ascending chromatogram[6] in the same nitromethane–glacial acetic acid solvent where it will be noted no separation was achieved.

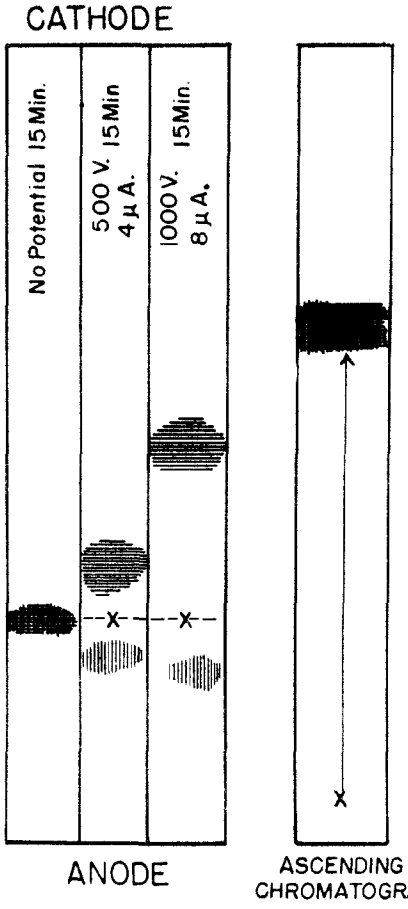


Fig. 1.—Separation of oil red O (vertical lines) and crystal violet (horizontal lines) in nitromethane–glacial acetic acid mixture.

In Fig. 2 the separation of a mixture of four dyes in absolute ethyl alcohol is illustrated.

Cholesterol, palmitic acid, 17-hydroxy-11-dehydrocorticosterone and testosterone were found to migrate toward the anode in the ethyl alcohol or nitromethane–glacial acetic acid systems; however, no separation of these mixtures of compounds

(5) The most highly purified commercially available solvents were employed; however, no effort was made to remove traces of moisture with which the solvents were in equilibrium, since the cell design did not completely exclude atmospheric moisture.

(6) R. J. Williams and H. Kirby, *Science*, **107**, 481 (1948).

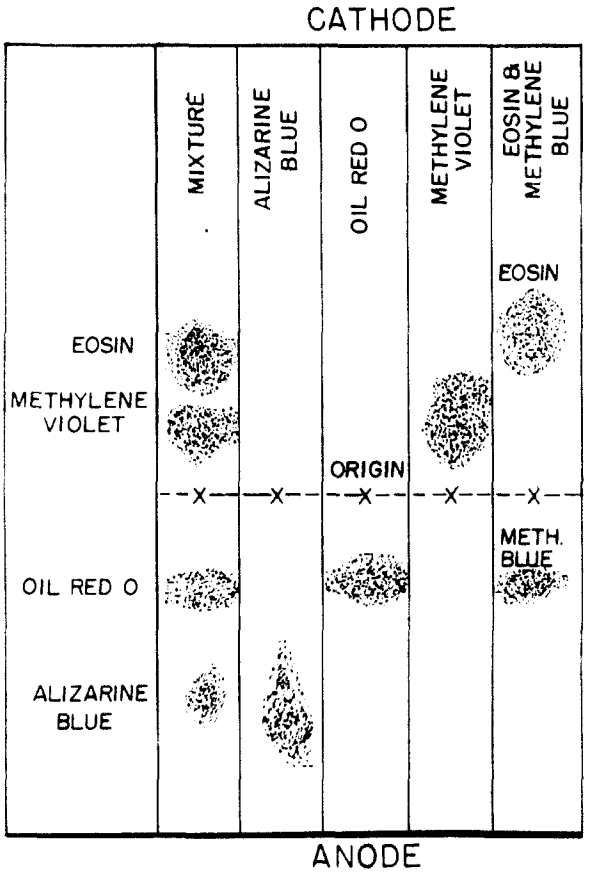


Fig. 2.—Separation of dye mixture in ethyl alcohol; 1000 volts 60 micraoamps, 50 min.

was apparent over the short distances traversed. It is perhaps significant that separations were achieved only with ions containing strongly polar groups (the dyes). The migration of the biological substances mentioned may be a passive electroendosmotic effect; however it is possible that these less polar materials could be separated in experiments of longer duration.

The separation of the dye mixtures on the filter paper establishes the feasibility of electrophoretic separations in non-aqueous solvent systems. It is possible that other solvent systems and experimental conditions may provide extension of this technique to a wider range of substances.

ARMY MEDICAL SERVICE GRADUATE SCHOOL
WALTER REED ARMY MEDICAL CENTER
WASHINGTON 12, D. C.

The Dissociation Energies of the First and Second Bond in H_2S and Some Comments on a Recent Paper by Franklin and Lumpkin

BY A. H. SEHON[1]

RECEIVED APRIL 21, 1952

Franklin and Lumpkin[2] have recently derived a value of 38.4(±5) kcal./mole for ΔH_f(SH) from relevant thermochemical data and their measurements of appearance potentials of carbonium ions

(1) Post-doctoral fellow, 1951–1952.

(2) J. L. Franklin and H. E. Lumpkin, THIS JOURNAL, **74**, 1023 (1952).

from various mercaptans. Their value agrees fairly well with the value of 32(±4) kcal./mole for ΔH_f(SH) determined in these laboratories,[3] especially if, as pointed out by them, the heats of formation of radicals obtained by the electron impact method tend to be rather high. Since

$$D(\text{H–SH}) = D_1 = \Delta H_f(\text{H}) + \Delta H_f(\text{SH}) - \Delta H_f(\text{H}_2\text{S}) \quad (1)$$

and the values for $\Delta H_f(\text{H}) = 52$ kcal./gram atom and for $\Delta H_f(\text{H}_2\text{S}) = -4.8$ kcal./mole are well established[4a,b] it is now possible to calculate in terms of the above values for ΔH_f(SH) the dissociation energy, D(H–SH), of the first bond in H_2S (denoted by D_1) at 95(±5) or 89(±4) kcal./mole, respectively.

Furthermore, the dissociation energy D(S–H) of the second bond in H_2S (denoted by D_2) can be calculated by the similar expression

$$D(\text{S–H}) = D_2 = \Delta H_f(\text{S}) + \Delta H_f(\text{H}) - \Delta H_f(\text{SH}) \quad (2)$$

Unfortunately, it is impossible at present to decide on one particular value for D_2 since in equation (2) ΔH_f(S) may have one of three values 53.5, 57 or 66.5 kcal./mole[5] depending on the choice of one of the three possible values of 76, 83 or 102.5 kcal./mole for D(S–S) in S_2.[6] Hence, D_2 can be 67, 70.5 or 80 kcal./mole on the basis of Franklin and Lumpkin's value for ΔH_f(SH) or 73.5, 77 or 86.5 kcal./mole on the basis of our value for ΔH_f(SH).

By adding equations (1) and (2) it follows that the sum of the two S–H dissociation energies in H_2S can vary between 162 and 175 kcal./mole depending on whether D(S–S) is taken as 76 or 102.5 kcal./mole. The uncertainty in choosing a particular value for D(S–S) is due to the difficulty of interpreting unambiguously the spectrum of S_2. However, Gaydon[6] after analyzing all relevant data is inclined to favor the highest value. From recent interpretations of the S–H spectrum Porter[7] and Ramsay[8] deduce values of 85 and 83 kcal./mole, respectively, for D_2. These, in conjunction with the values given above for D_1 support also the highest value for D(S–S).

Franklin and Lumpkin disagree with Porter's value for D_2 and suggest instead a value of 67 kcal./mole. Since the sum of their values for D_1 and D_2, respectively, 95 and 67 kcal./mole, is 162 kcal./mole it appears that they tacitly assumed the lowest value for D(S–S). Indeed, an analysis of their results indicates that they used this value throughout their calculations. They argue that if Porter's value of 85 kcal./mole for D_2 is correct then D_1 must be 77 kcal./mole, *i.e.*, D_1 would then be smaller than D_2, which is contrary to what one would expect by comparison with the corresponding bond strengths in H_2O. It seems, therefore, that their arbitrary choice of the lowest value for D(S–S) is the only reason for their disagreeing with Porter's value for D_2. Surprisingly, however, in spite of their method of calculation they suggest that on general chemical grounds the highest value for D(S–S) appears to be the correct one.

Thus if D(S–S) is, indeed, 102.5 kcal./mole then the sum of the two dissociation energies in H_2S is 175 kcal./mole, and since a value of ~90 kcal./mole for D_1 is supported by both electron impact and pyrolytic methods, D_2 will be ~85 kcal./mole, which is in reasonable agreement with Porter's and Ramsay's values obtained spectroscopically. A final settlement of this point can only be reached by an unambiguous determination of D(S–S) or ΔH_f(S).

Note: Franklin and Lumpkin give D(HS–SH) = 80.4 kcal./mole, a value, which was presumably obtained by them by using in their calculations $\Delta H_f(\text{H}_2\text{S}_2)_{\text{liq}} = -3.6$ kcal./mole instead of $\Delta H_f(\text{H}_2\text{S}_2)_g$, as required. Since the heat of vaporization of H_2S_2 is probably ~8 kcal./mole, it follows that D(HS–SH), based on their value for ΔH_f(SH), should have actually been 72.4 kcal./mole. On the other hand on the basis of our value for ΔH_f(SH) D(HS–SH) is 59.6 kcal./mole, a value which is comparable with D(HO–OH) of 54 kcal./mole.[9]

(3) This value has been calculated by using the data of our determination of $D(CH_3\text{–SH})$ by the "toluene-carrier" technique [A. H. Sehon and B. deB. Darwent, A. C. S. Meeting, Buffalo, March, 1952. A full account will be published shortly].

(4) (a) Selected Values of Chemical and Thermodynamic Properties, N. B. S., Washington, 1947; (b) K. K. Kelley, U. S. Dept. of Interior, Bureau of Mines, Bulletin 406 (1937).

(5) Since $[\Delta H_f(\text{S}) = (\Delta H_f(\text{S}_2)_g + D(\text{S–S})]/2$ where $\Delta H_f(\text{S}_2)_g = 30.80$ kcal./mole. [W. H. Evans and D. D. Wagman, Natl., Bur. Standards, Report No. 1037, Washington, 1951.]

(6) A. G. Gaydon, "Dissociation Energies and Spectra of Diatomic Molecules," Chapman and Hall, Ltd., London, 1947.

(7) G. Porter, *Discussion Faraday Soc.*, **81**, 60 (1950).

(8) D. A. Ramsay, *ibid.*, 80 (1950).

(9) M. Szwarc, *Chem. Revs.*, **47**, 75 (1950).

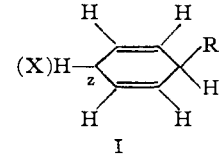
DIVISION OF CHEMISTRY
NATIONAL RESEARCH COUNCIL
OTTAWA, ONTARIO, CANADA

Quantum Mechanical Calculations of Orientation in Aromatic Substitution[1]

BY JOHN D. ROBERTS AND ANDREW STREITWIESER, JR.[2]

RECEIVED MARCH 11, 1952

Wheland[3] has shown definitely that the molecular orbital method makes possible a single unified treatment of electrophilic, free-radical and nucleophilic substitution reactions of aromatic molecules. His approach was based on calculations of the energies of activated complexes of type I where z is a unit positive charge, an unpaired electron or a unit negative charge depending on whether the attacking reagent (R) is an electrophilic, radical or nucleophilic species.



I

With various substituent groups (X) and reasonable assignments to appropriate parameters, he found that the pattern of aromatic substitution could be well reproduced.

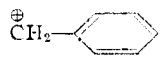
In the present work, the simple molecular orbital

(1) Supported by the research program of the U. S. Atomic Energy Commission under Contract AT(30-1)905.

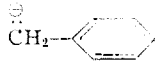
(2) U. S. Atomic Energy Commission Post-Doctoral Fellow, 1951–1952.

(3) G. W. Wheland, THIS JOURNAL, **64**, 900 (1942).

method[4,5] has been used to determine whether the pattern of some benzene substitutions could be obtained without adjustment of arbitrary parameters and, in fact, with avoidance of assumptions other than those used generally in the calculation of π-electron energies of unsaturated hydrocarbon molecules, radicals or ions. Such conditions are met if the energies are compared of the substitution activated complexes of benzene, the benzyl cation (II) and the benzyl anion (III). The $\overset{\oplus}{C}H_2-$ group of II may be considered as an analog of nitro, carbethoxyl



II



III

or comparable groups and by the usual qualitative considerations[6] should be expected to have similar directing powers. The $\overset{\ominus}{\underset{\cdot\cdot}{C}}H_2-$ group of III is analogous to the $:\overset{\ominus}{\underset{\cdot\cdot}{O}}-$, $\underset{\cdot\cdot}{N}H_2-$, etc., substituents and should similarly influence benzene substitution.

Our calculations may be illustrated by the following example. The total π-electron energy of benzene computed in the usual way[4] is $(6q + 8.00\beta)$[7] while that of I for the electrophilic substitution of benzene is $(4q + 5.46\beta)$. The net electrical work (Δw) for the formation of I is then $(2q + 2.54\beta)$ which may be compared with $\Delta w(2q + 2.86\beta)$ obtained as the difference in π-electron energies for the benzyl cation $(6q + 8.72\beta)$ and I (X = $\overset{\oplus}{C}H_2-$) for the para electrophilic substitution of the benzyl cation $(4q + 5.86\beta)$. It is thus seen that the para-substitution of II is calculated to be energetically less favorable than that of benzene by 0.32β[8] for electrophilic reagents. Values of Δw for various substitutions of benzene, II and III are given in Table I. To save space, the q-values have been omitted from Δw since these are constant for a given type of substitution; *i.e.*, $2q$ for electrophilic, q for radical and $0q$ for nucleophilic substitutions.

The calculated values of Δw are in reasonable agreement with qualitative expectations[3,6] for substitution reactions of II and III at the meta- and para-positions based on the behavior of analogous compounds. Thus, the reactivity of the various positions (neglecting statistical factors) is predicted to be: electrophilic substitution: III > benzene $\gtrsim$ meta-III $\sim$ meta-II > para-II; radical substitution: para-II $\sim$ para-III > benzene $\gtrsim$ meta II-$\sim$ meta-III; nucleophilic substitution: para-II > benzene $\gtrsim$ meta-II $\sim$ meta-III > para-III. The only discrepancies are in the predictions of (1) a general slightly too great reactivity for benzene and (2) equivalent reactivity of the meta-positions of II and III.

TABLE I

CALCULATED VALUES OF Δw FOR AROMATIC SUBSTITUTIONS

Reactant	Point of attack	Δw[a] Electrophilic	Radical	Nucleophilic
Benzene	...	2.54	2.54	2.54
Benzyl cation (II)	Ortho	2.62	2.18	1.73
	Meta	2.56	2.56	2.56
	Para	2.86	2.34	1.82
Benzyl anion (III)	Ortho	1.73	2.18	2.62
	Meta	2.56	2.56	2.56
	Para	1.82	2.34	2.86
Styrene (IV)	Ortho	3.07	3.07	3.07
	Meta	3.09	3.09	3.09
	Para	2.97	2.97	2.97
	β	2.25	2.25	2.25
Cinnamyl cation (V)	Ortho	2.56	2.21	1.87
	Meta	2.40	2.40	2.40
	Para	2.68	2.31	1.94

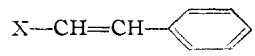
[a] In units of β, q values omitted.

The agreement for the ortho-positions is formally less satisfactory in that such positions in II or III are uniformly expected to be more reactive than the para-positions. In practice, such behavior appears to be encountered frequently only in nucleophilic substitutions.[9] It is interesting that the simple molecular orbital theory appears to predict that substitution at ortho-positions should be generally more facile than that at para-positions. The fact that facilitated ortho-substitution does not usually occur is explicable in terms of steric hindrance at these positions.

It is of considerable interest to see whether the method can be applied satisfactorily to other benzenoid systems and consequently we have investigated the substitution of styrene (IV) and the cinnamyl cation (V) (*cf.* Table I). Styrene is predicted to undergo nuclear substitution preferentially in the ortho and para-positions with all types of reagents[10] while, with V, meta-substitution is predicted with electrophilic reagents and ortho–para orientation with radical and nucleophilic species. In practice, the electrophilic substitution of substances like VI (with X = $-NO_2$, $-CO_2C_2H_5$, etc.) is well known to occur predominantly at the ortho-

IV

V



VI

(4) For refs., see J. D. Roberts, A. Streitweiser, Jr., and C. M. Regan, *ibid.*, **74**, 4579 (1952). It is important to note that our calculations (and others of similar character) may be rather seriously in error for any of the substitutions in which the initial molecules or the intermediate complexes of type I are charged since in such circumstances the π-electron charge distributions are not "self-consistent" and the values of q and β are probably different than for neutral entities.

(5) The treatment is different from that of Wheland[3] in that the non-orthogonality integrals S between adjacent atomic orbitals are neglected.

(6) *Cf.*, G. W. Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, Chap. 8.

(7) Notation of C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc.* (*London*), **A191**, 39 (1947).

(8) Equivalent to 5.5 kcal. if β is given the customary value of 17 kcal.

(9) Thus *o*-nitrobromobenzene reacts 100 times more rapidly with piperidine than *p*-nitrobromobenzene although the corresponding isomers of bromobenzonitrile react at comparable rates, W. C. Spitzer and G. W. Wheland, THIS JOURNAL, **82**, 2995 (1940). Recent studies by R. L. Dannley and E. C. Gregg, Abstracts of the Buffalo Meeting of the American Chemical Society, March, 1952, p. 1K, indicate preferential *ortho*-phenylation in the free-radical reactions of benzoyl peroxide with various substituted benzenes.

(10) Actually, non-nuclear substitution at the β-position of the double bond is predicted to yield the most stable activated complexes; *cf.* Table I.

and para-positions and it appears that V is not a good model for such compounds despite the fact that II seems to be a reasonable analog of nitrobenzene. The disparity can be resolved in the following way. The secular equation for II (and the corresponding activated complex I with X = $\overset{\oplus}{C}H_2$–) contains terms expressing the "resonance" integral β and the Coulombic integral q of the $\overset{\oplus}{C}H_2$–group. For a graded series of compounds ranging between II and benzene with various degrees of electronically deficient groups in place of $\overset{\oplus}{C}H_2$–, the q and β terms diminish to zero as one approaches benzene, but nonetheless, at all times, meta-substitution is predicted to be preferred. As a result, II is a good qualitative model for nitrobenzene or any similar substance where directing substituent exerts its influence by virtue of an electronically-deficient atom attached directly to the benzene ring.

On the other hand, in the transition between V and IV as β and q diminish, a changeover between prediction of meta- to ortho–para orientation must occur. Since the electronically-deficient atoms of the usual ortho-para substituting derivatives of VI (X = $-NO_2$, $-CO_2C_2H_5$, etc.) would be expected to have smaller q and β values than $\overset{\oplus}{C}H_2$–, it is possible that such groups on detailed analysis would be calculated to give different orientations from V. It will be interesting to determine whether electrophilic substitution of V or a suitable analog would actually occur in the meta-position as predicted.

Acknowledgment.—We are deeply indebted to Dr. W. G. McMillan, Jr., for advice on methods of calculation.

DEPARTMENT OF CHEMISTRY AND LABORATORY
FOR NUCLEAR SCIENCE AND ENGINEERING
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE 39, MASSACHUSETTS

Effects of Hydrogenation upon the Microbiological Activities of N^{10}-Methylpteroylglutamic Acid, Aminopterin and A-Methopterin

BY GLYNN P. WHEELER, MARGARET A. NEWTON, JEANENNE S. MORROW AND JOYCE E. HILL

RECEIVED MARCH 3, 1952

It has been found that hydrogenated folic acid has a growth-promoting activity for *Leuconostoc citrovorum 8081* which is intermediate between that of folic acid and that of leucovorin[1–3] and also intermediate between that of N^{10}-formylfolic acid and that of leucovorin.[3] Also, a commercial sample of aminopterin (4-aminopteroylglutamic acid), which inhibits the growth of *Leuconostoc citrovorum 8081*, was converted to a growth factor for this organism by hydrogenation under pressure.[4] It was later found that this growth-promoting activity was due to an impurity, but nevertheless the inhibitory action of pure aminopterin was decreased by hydrogenation.[5] These facts indicate that the state of oxidation of these compounds has important influence upon the microbiological activity.

Since hydrogenation at elevated temperature under pressure could conceivably cause degradation of the aminopterin molecule, it seemed worthwhile to carry out the hydrogenation under milder conditions and to extend the study to include N^{10}-methylpteroylglutamic acid and A-methopterin (N^{10}-methyl-4-aminopteroylglutamic acid). Accordingly, the compound (100 mg.) to be hydrogenated was suspended, without further purification, in water (25 ml.), and the *p*H was adjusted to 7.0–8.0 by adding a solution of sodium hydroxide, whereupon a homogeneous solution was obtained. Platinum oxide (50 mg.) was added, and hydrogenation was carried out at room temperature and atmospheric pressure. After approximately two moles of hydrogen had been taken up and hydrogenation appeared to be complete, the catalyst was removed by filtration through a bed of fullers earth on a sintered glass plate. The entire filtrate was subjected to freeze-drying, and this yielded a light-colored, fluffy, solid product which was stored under nitrogen. When compared with the spectra for pteroylglutamic acid and tetrahydropteroylglutamic acid,[6] spectra for the initial materials and the products of hydrogenation indicated that hydrogenation had been accomplished.

To determine the inhibitory activities of the initial materials and of the products of hydrogenation for *Streptococcus faecalis* R. the method of Mitchell and Snell[7] was used with slight modification, and folic acid was used as the growth factor. Constant levels of folic acid were used, and the quantity of test compound was varied. The final volume of medium per tube was 10 ml. Seventeen hours following inoculation the turbidity was determined by means of a Lumitron colorimeter with a 660 mμ filter. The resulting data are given in Table I. In all instances hydrogenation caused a considerable decrease in inhibitory activity.

TABLE I

EFFECT OF HYDROGENATION UPON THE INHIBITORY PROPERTIES OF CERTAIN FOLIC ACID ANTAGONISTS WITH *Streptococcus faecalis* R.

Compound[a]	Inhibition index[b] Folic acid (μg./10 ml.) 0.002	0.02	0.2	2.0
N^{10}-Methyl PGA	25	2.5	0.44	0.28
Hydrogenated N^{10}-methyl PGA	Less than 50% inhibition at all levels			
Aminopterin	26	2.8	1.5	0.34
Hydrogenated aminopterin	Less than 50% inhibition at all levels			
A-methopterin	25.5	2.5	0.25	0.04
Hydrogenated A-methopterin	45	70	26	11

[a] All compounds were used as the sodium salts. [b] Inhibition index = weight of agent required for half maximal inhibition/weight of folic acid.

(1) W. Shive, T. J. Bardos, T. J. Bond and L. L. Rogers, THIS JOURNAL, **72**, 2817 (1950).

(2) H. P. Broquist, M. J. Fahrenbach, J. A. Brockman, Jr., E. L. R. Stokstad and T. H. Jukes, *ibid.*, **73**, 3535 (1951).

(3) G. P. Wheeler, unpublished data.

(4) F. Weygand, A. Wacker, H.-J. Mann, E. Rowold and H. Lettré, *Z. Naturforschung*, **5b**, 413 (1950).

(5) F. Weygand, A. Wacker, H.-J. Mann and E. Rowold, *ibid.*, **6b**, 174 (1951).

(6) A. Pohland, E. H. Flynn, R. G. Jones and W. Shive, THIS JOURNAL, **73**, 3247 (1951).

(7) H. K. Mitchell and E. E. Snell, Univ. Texas Publ. 4137, 36 (1941).

TABLE II

GROWTH-PROMOTING ACTIVITIES OF HYDROGENATED COMPOUNDS

		Transmission, %		
	μg./10 ml.	Hydrogenated N^{10}-methyl PGA	Hydrogenated aminopterin	Hydrogenated A-methopterin
For *S. faecalis* R.	0.1	100	53	100
	1.0	100	36	100
	10.0	68	25	100
	100.0	66	26	100
For *L. citrovorum 8081*	0.1	90	91	91
	1.0	92	90	93
	10.0	90	77	94
	100.0	78	33	90

The hydrogenated materials were also tested as growth factors for *Streptococcus faecalis* R. and *Leuconostoc citrovorum 8081*. For the former organism, the same basal medium was used as was used for the inhibition studies but no folic acid was added. For the latter organism, the basal medium and technique of Sauberlich[8] were used with the exceptions that no supplementary glycine and alanine were used and a Lumitron colorimeter with a 660 mμ filter was employed. Turbidity was determined after 17 hours. Data are given in Table II. It is quite likely that the growth-promoting activity is due to an impurity in the original compound as suggested by Weygand.

Acknowledgment.—The authors wish to thank Lederle Laboratories for supplying the folic acid, N^{10}-methylpteroylglutamic acid, aminopterin and A-methopterin used in these experiments.

(8) H. E. Sauberlich, *J. Biol. Chem.*, **181**, 467 (1949).

SOUTHERN RESEARCH INSTITUTE
BIRMINGHAM, ALABAMA

COMMUNICATIONS TO THE EDITOR

A NEW METHOD FOR THE PREPARATION OF THIO ACIDS AND APPLICATION TO PEPTIDE CHEMISTRY

Sir:

Although Pawlewski[1] demonstrated that thio acids were very active acylating agents, the methods of preparation which have been available heretofore[2] have not been suitable for making the acylaminothio acids which could be useful in peptide synthesis. By passing hydrogen sulfide into a solution of the mixed anhydrides,[3,4,5] RCOO-$COOC_2H_6$, in methylene chloride with an equivalent of triethylamine at −20° and warming to room temperature, we have obtained the thio acids, RCOSH.

In this manner we have prepared, in addition to thioacetic and thiobenzoic acids, *p*-phenylthiobenzoic acid, 88% yield (from the carboxylic acid), m.p. 90–92° (*Anal.* Calcd. for $C_{13}H_{10}OS$: C, 72.89; H, 4.71; S, 14.94. Found: C, 72.86; H, 4.83; S, 15.09); thiohippuric acid, 70% yield, m.p. 98–100° (*Anal.* Calcd. for $C_9H_9NO_2S$: C, 55.39; H, 4.65; N, 7.18; S, 16.40. Found: C, 55.30; H, 4.69; N, 6.79; S, 15.99); phthaloylthioglycine, 45% yield, m.p. 114–116° (*Anal.* Calcd. for $C_{10}H_7NO_3S$: C, 54.30; H, 3.19; S, 14.47. Found: C, 54.52; H, 3.32; S, 14.21).

When thiohippuric acid was warmed to 90–110° in dimethylformamide with *d,l*-alanine in a nitrogen atmosphere, hydrogen sulfide was rapidly evolved and there was obtained a 70% yield of hippuryl-alanine, m.p. 200–201.5°[6] and giving the correct elemental analysis.

Upon treatment of thiohippuric acid with Raney nickel which had been deactivated over acetone[7] there was obtained in one experiment, a 30% yield of hippuraldehyde,[8] isolated as the 2,4-dinitrophenylhydrazone, m.p. 200–202° (*Anal.* Calcd. for $C_{15}H_{13}N_5O_5$: C, 52.48; H, 3.82; N, 20.40. Found: C, 52.63; H, 3.78; N, 20.18).

(1) Br. Pawlewski, *Ber.*, **31**, 661 (1898); **34**, 657 (1901); **35**, 110 (1902).

(2) R. Connor, "Organic Sulfur Compounds," p. 835 in Gilman's "Organic Chemistry," Vol. I, Second Edition, John Wiley and Sons, Inc., New York, N. Y., 1943; S. Sunner and T. Nilson, *Svensk. Kem. Tid.*, **54**, 163 (1942) [*C. A.*, **38**, 3249 (1944)]; B. Tchoubar and Letellier-Dupre, *Bull. soc. chim. France*, 792 (1947).

(3) R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951); J. R. Vaughan and R. L. Osato, THIS JOURNAL, **74**, 676 (1952).

(4) T. Wieland, W. Schäfer and E. Bokelmann, *Ann.*, **573**, 99 (1951), prepared $RCOSC_6H_5$ by addition of C_6H_5SH to the mixed anhydride.

(5) H. Adkins and Q. E. Thompson, THIS JOURNAL, **71**, 2242 (1949), prepared thiobenzoic acid by passing H_2S into dibenzoyl sulfide in pyridine.

(6) T. Curtius and E. Lambotte, *J. prakt. Chem.*, [2] **70**, 114 (1904).

(7) G. B. Spero, A. V. McIntosh and R. H. Levin, THIS JOURNAL, **70**, 1907 (19481.

(8) J. Bougault, E. Cattelain and P. Chabrier, *Bull. soc. chim.*, [5] **5**, 1699 (1938), have reported the conversion of thioacetic acid to acetaldehyde.

DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING
UNIVERSITY OF CALIFORNIA MARSHALL W. CRONYN
BERKELEY 4, CALIFORNIA JAMES JIU

RECEIVED JUNE 23, 1952

THE SYNTHESIS AND REACTIONS OF N-ACYL THIOL AMINO ACIDS

Sir:

Recent evidence that enzymatic acylations involve thiolacid derivatives as activated intermediates[1] has stimulated interest in similar thiol analogs of amino acids as possible participants in the physiological synthesis of peptides. By two

(1) For example, acetyl coenzyme A is considered to be a key intermediate in biological acetylations; F. Lynen, E. Reichert and L. Rueff, *Ann.*, **574**, 1 (1951); T. C. Chou and F. Lipmann, *J. Biol. Chem.*, **196**, 89 (1952).