NOTES

Studies in the Biphenyl Series. V. Bromination of 4-Methoxybiphenyl

By John Leo Abernethy and Henry Pollock

Other investigations in this sequence necessitated repetition of the work of Bell[1] on the bromination of 4-methoxybiphenyl. Our results on the bromination of this ether to mono- and dibrominated products are reported below.

Experimental Part

3-Bromo-4-methoxybiphenyl and 4-Methoxy-4'-bromobiphenyl.—To a solution of 20 g. of 4-methoxybiphenyl in 70 ml. of chloroform, 17.5 g. of bromine in 25 ml. of chloroform was added dropwise during a period of 45 minutes. During this period of time and for an additional 45 minutes the mixture was stirred and maintained at room temperature. Then the chloroform solution was washed with 75 ml. of 10% sodium thiosulfate solution and with 300 ml. of water and dried for 24 hours over anhydrous calcium chloride. The chloroform was removed by distillation and the oily residue was dissolved in ligroin (b.p. 65–110°). On cooling the solution, 21.3 g. of a crystalline mixture was obtained, m.p. 93–104°. Separation of the components of this mixture in a Soxhlet extractor with ligroin (b.p. 45–65°) yielded 6.3 g. (22.1% yield) of 4-methoxy-4'-bromobiphenyl as a residue, m.p. 143–144°,[1] and 3.2 g. (11.2% yield) of 3-bromo-4-methoxybiphenyl, m.p. 78–79°,[1] was obtained from the extract after recrystallization from ethanol.

3,4'-Dibromo-4-methoxybiphenyl.—At room temperature, a solution of bromine (35 g.) in chloroform (25 ml.) was added dropwise, during a period of one hour, to 20 g. of 4-methoxybiphenyl dissolved in 75 ml. of chloroform, to which had been added 0.3 g. of iron powder. In turn, the mixture was refluxed and stirred for 1.5 hours. It was cooled and washed with 75 ml. of 5% sodium thiosulfate solution and then with 300 ml. of water. The total yield of product, m.p. 132–134°,[1] obtained directly and subsequently by crystallization of fractions from ethanol, was 8.5 g. (23% yield). A mixture of equal amounts of the product and 3,4'-dibromo-4-methoxybiphenyl prepared from 3,4'-dibromo-4-hydroxybiphenyl[2] by methylation with methyl sulfate, melted at 133–134°.

Anal. Calcd. for $C_{13}H_{10}OBr_2$: Br, 46.8. Found: Br, 46.2, 46.6.

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[1] Bell, *J. Chem. Soc.*, 1075 (1930). In this article the yields attained in the bromination of 4-methoxybiphenyl were not reported.

[2] Hazlet and Hensley, This Journal, **69**, 708 (1947).

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Salts of Reinecke Acid with Certain Simple Amines

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The metathetical reaction of amine salts with "Reinecke salt" (ammonium reineckate, $NH_4[Cr(NH_3)_2(SCN)_4]$) in aqueous solution to produce insoluble amine reineckates has been used as a method of isolation of amines.[1] This procedure has been especially useful with certain amino acids and with a few high molecular weight water-soluble bases; *e.g.*, streptothricin. The reineckates are generally rather insoluble in water and recrystallize nicely from aqueous alcohol. Although many of these salts have been reported, in only a few cases have any constants other than analyses and solubilities been determined. The possibility that reineckates might possess melting or decomposition points satisfactory for characterization has led to the examination of a number of these compounds.

The reineckates were prepared by precipitation from aqueous solution and recrystallized from aqueous alcohol. Experimental data on nineteen reineckates are summarized in Table I. It may be seen from these results that the reineckates possess reasonably sharp decomposition ranges, generally between 130 and 230°. Accordingly, it is suggested that reineckates may be of use in the characterization of amines. Mention should be made of the fact that for best results these determinations were carried out in a bath with a heating rate of 6–8° per minute. In many cases, a momentary melting to a clear red liquid just previous to decomposition was noted. A "mixed melting point" using the reineckates of diethanolamine and triethanolamine showed no depression; accordingly, these derivatives are not recommended for such tests of identity. No reineckates could be obtained from the very weak bases piperine, urea and diphenylamine.

Table I

Amine Reineckates

Reineckate	Decomposition point, °C. (uncorrected)	Cr, % Calcd.	Found
Dimethylamine	272–273	14.25	14.42
Ethylamine	231–233	14.25	14.23
Diethylamine	259–261	13.24	13.20
Triethylamine	205–208	12.35	12.50
n-Butylamine	200–204	13.24	13.65
Di-*n*-butylamine	143–146	11.59	11.47
Tri-*n*-butylamine	131–133	10.30	10.33
n-Amylamine	156–158	12.78	13.05
Ethylenediamine	233–240	13.72 (mono) 14.87 (di)	14.01, 14.40
Diethanolamine	162–163	12.26	12.10
Triethanolamine	164–167	11.09	11.30
Creatinine	188–190	12.01	12.09
Glycine ethyl ester	175–178	12.29	12.38
Aniline	195–197	12.65	12.77
Methylaniline	151–152	12.19	12.50
Dimethylaniline	189–191	11.81	12.00
o-Toluidine	133–134	12.19	12.21
Quinaldine	195–198	11.24	11.32
p-Aminoazobenzene	219–220	10.06	10.29

Care must be taken to avoid heating reineckates above about 60° in aqueous or alcoholic solution. Decomposition becomes rapid at higher temperatures. The large temperature coefficient of solubility of all reineckates studied here prevented this limitation from being significant.

The extreme insolubility of reineckates at 0° is shown by experiments carried out upon dilute solu-

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[1] (a) Gmelin-Kraut, "Handbuch der anorganischen Chemie," Vol. III, pt. 1, Carl Winter, Heidelberg, 1912, p. 585; (b) Coupechoux, *J. pharm. chem.*, **30**, 118 (1939); (c) Dakin, *J. Biol. Chem.*, **99**, 531 (1933).

tions of two amines. The addition of ammonium reineckate solution saturated at 0° to 0.015% aniline hydrochloride or to 0.005% ethylammonium chloride at 0° resulted in the formation of a definite precipitate of the amine reineckate. It would thus appear that the use of ammonium reineckate for the isolation of many amines from very dilute aqueous solutions may be of practical value.

Experimental

Formation of Reineckates.—Hydrochloric acid was added to an aqueous solution or suspension of the amine until the mixture became acidic to congo red. The resulting solution was cooled to room temperature and a filtered, saturated (about 5%) solution of ammonium reineckate was added. Precipitation of the salt began immediately, but the solution was cooled in an ice-bath to improve the yield. The use of an excess (50–100%) of either reagent leads to a significant increase in yield.

Recrystallization.—The reineckates were recrystallized by warming in 70–80% ethyl alcohol to about 60°, filtering, and refrigerating. A few reineckates were sufficiently soluble to make it necessary to use more dilute alcohol. Drying was accomplished over phosphorus pentoxide at room temperature in a vacuum desiccator. Two or three recrystallizations were sufficient to give constant decomposition point and satisfactory analyses.

Analysis.—A weighed sample of the reineckate was heated carefully in a porcelain crucible until the initial vigorous decomposition was complete. The crucible was then ignited with a Meker burner until constant weight was achieved; the residue was weighed as Cr_2O_3. Analyses were run in duplicate and agreed well with theoretical (Table I).

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Alkyl-Substituted Chlorofluoroethanes[1]

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The Prins reaction has recently been extended to include the addition of polyhalo alkanes to polyfluoro alkenes.[2–5] This note describes the aluminum chloride catalyzed condensation of monochloroalkanes with chlorotrifluoroethylene and *unsym*-dichlorodifluoroethylene. The expected products were obtained with poor conversions, and in addition materials were obtained in which the aluminum chloride had substituted chlorine for fluorine in the original addition products.

The Reaction of Isopropyl Chloride and Polyfluoro Olefins.—A mixture of 127 g. of isopropyl chloride, 221 g. of chlorotrifluoroethylene and 25 g. of aluminum chloride was heated to 44° for 18 hours with mechanical shaking. The unreacted olefin was recovered and the residue was washed with water several times, dried over anhydrous sodium carbonate and distilled. Following the removal of the isopropyl chloride there was obtained 10 ml. of material boiling 26–26.2° at 30 mm. (112–113° at 750 mm.) and 2 ml. of material boiling 66–68° at 30 mm. There remained in the still-pot about 3 g. of residues.

The lower boiling material was found to have n^{25}_D 1.3870, d^{25}_4 1.3004. *Anal.* Calcd. for $C_5H_7Cl_2F_3$: C, 30.77; H, 3.59; Cl, 36.41; MR_D 35.3. Found: C, 30.24; H, 3.65; Cl, 36.68; MR_D 35.3.

The higher boiling material had n^{25}_D 1.4078. *Anal.* Calcd. for $C_5H_7Cl_3F_2$: C, 28.37; H, 3.31; Cl, 50.35. Found: C, 29.04; H, 3.55; Cl, 47.76.

A material identical with the higher boiling product was prepared by the aluminum chloride catalyzed condensation of isopropyl chloride with *unsym*-dichlorodifluoroethylene. Therefore it is proposed that the lower boiling material has the structure $(CH_3)_2CHCClFCClF_2$, and the higher boiling the structure $(CH_3)_2CHCCl_2CClF_2$.

Lower reaction temperatures and the use of the "tube" method of Schmerling[6] resulted in the production of a larger proportion of the lower boiling material and a smaller degree of conversion.

The Reaction of *t*-Butyl Chloride and Chlorotrifluoroethylene.—Under the conditions described for the isopropyl chloride reaction, *t*-butyl chloride and chlorotrifluoroethylene gave 5–10% yields of $(CH_3)_3CCClFCClF_2$, b.p. 55–57° at 50 mm., n^{25}_D 1.4020, and $(CH_3)_3CCCl_2CClF_2$, b.p. 77–80° at 25 mm., n^{25}_D 1.4405. *Anal.* Calcd. for $C_6H_9Cl_2F_3$: Cl, 33.93. Found: Cl, 34.10. Calcd. for $C_6H_9Cl_3F_2$: Cl, 47.17. Found: Cl, 46.68.

Other Prins Type Reactions Attempted.—Only a trace of reaction could be detected when *n*-butyl chloride was substituted for *t*-butyl chloride.

Allyl chloride could not be used as the alkyl halide because of immediate and extensive polymer formation in the presence of aluminum chloride.

When an attempt was made to use 1-chloro-1,1-difluoroethane as the alkyl halide with chlorotrifluoroethylene only methylchloroform was isolated as a reaction product.

1,2-Dichlorohexafluorocyclobutane and chlorotrifluoroethylene gave no product when heated together in the presence of aluminum chloride. This result was to be expected, since neither of these materials reacted separately with aluminum chloride.

Aluminum bromide could not be used as the catalyst in these reactions, because of its great tendency to substitute bromine for other halogens and because of extensive polymer formation by the alkyl halides in its presence. Stannic chloride and boron trifluoride–ethyl ether did not appear to have catalytic activity.

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RECEIVED JUNE 22, 1950

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[1] This document is based on work performed for the Atomic Energy Commission by Carbide and Carbon Chemicals Division, Union Carbide and Carbon Corporation, Oak Ridge, Tennessee.

[2] Harmon, U. S. Patent 2,404,706, issued July 1946.

[3] Imperial Chemical Industries, Ltd., British Patent 581,254, issued October 1946; *C. A.*, **41**, 2427 (1947).

[4] E. I. du Pont de Nemours and Company, British Patent 581,662, issued October 1946; *C. A.*, **41**, 2427 (1947).

[5] E. I. du Pont de Nemours and Company, British Patent 583,874, issued January 1947; *C. A.*, **41**, 5141 (1947).

[6] Schmerling, THIS JOURNAL, **68**, 1650 (1948).

Completely Halogenated Ethanes Containing Iodine[1]

BY JOHN T. BARR, J. DONALD GIBSON AND ROBERT H. LAFFERTY, JR.

The use of highly fluorinated materials in Grignard syntheses has been relatively unsuccessful, except to give the corresponding fluorohydrocarbon.[2,3] During the course of work here two completely halogenated ethanes containing iodine, 1,2-dichloro-1,1,2-trifluoro-2-iodoethane, and a material thought to be 1-chloro-1,2,2-trifluoro-1,2-diiodoethane, were prepared. Ethereal solutions of both compounds reacted readily with sodium or magnesium, but all attempts to perform a Grignard synthesis were unsuccessful. The Grignard reagent itself apparently was formed by the usual procedure, forming a lower layer in the reaction flask, although there was no evidence of reaction upon the addition of compounds such as benzaldehyde, methyl ethyl ketone or α-naphthyl isocyanate. These compounds al-

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[1] This document is based on work performed for the Atomic Energy Commission by Carbide and Carbon Chemicals Division, Union Carbide and Carbon Corporation, at Oak Ridge, Tennessee.

[2] J. J. Brice, W. H. Pearlson and J. H. Simons, THIS JOURNAL, **68**, 968 (1946).

[3] E. T. McBee and A. Truchan, *ibid.*, **70**, 2910 (1948).

ways were recovered unchanged. No olefins or condensation products of the haloethanes could be found, either in the reaction mixture, or as gaseous products of the reaction.

1,2-Dichloro-1,1,2-trifluoro-2-iodoethane.—Chlorotrifluoroethylene (88 g.) was bubbled through a mixture of 162 g. of iodine monochloride and 500 ml. of 1,1,2-trichloro-1,2,2-trifluoroethane (Freon-113) during the course of 5 hours. As the reaction proceeded the iodine chloride passed into solution, and the temperature of the reaction mixture rose to 35°. After the absorption of the olefin had ceased, the reaction mixture was washed with sodium thiosulfate solution, and then with sodium carbonate solution until colorless, and was dried over sodium carbonate. Fractional distillation of the solution gave 119 g., 57% of theory, of 1,2-dichloro-1,1,2-trifluoro-2-iodoethane boiling 43–44° at 100 mm., $n^{25}D$ 1.4474, d^{25}_{20} 2.1959. *Anal.* Calcd. for $C_2Cl_2F_3I$: C, 9.29; mol. wt., 279; *MR*D 34.3. Found: C, 8.87; mol. wt., 271, determined in n-C_7F_{16}; *MR*D 34.0. This material was stored in the dark at room temperature for several months without excessive decomposition. The above structure was assigned by analogy to other addition reactions with this olefin.[4]

A much less stable compound, thought to be 1-chloro-1,2,2-trifluoro-1,2-diiodoethane, was obtained in 30–35% yield by the distillation of a mixture of equal weights of chlorotrifluoroethylene and iodine which had stood at room temperature for several days sealed in a Pyrex reactor. This material, boiling 54–55° at 20 mm., with slight decomposition, and having a density of greater than 2.5, decomposed readily upon standing to yield crystals of iodine, but no other residue. A reliable analysis or refractive index could not be obtained because of this instability.

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[4] W. E. Hanford and G. W. Rigby, U. S. Patent 2,409,274, issued October, 1946; C. W. Huskins and P. Tarrant, "Preparation and Reactions of Certain Chlorofluoroethylenes," Report of Office of Naval Research under Contract N8onr503, June 15, 1946; J. A. Young and P. Tarrant, This Journal, **71**, 2432 (1949); K. E. Rapp, *et al.*, *ibid.*, **72**, 3642 (1950); R. L. Pruett, *et al.*, *ibid.*, **72**, 3646 (1950); J. T. Barr, *et al.*, *ibid.*, **72**, 4480 (1950).

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An Improved Synthesis of Mescaline

By Fred Benington and Richard D. Morin

In connection with certain studies of the synthesis of phenethylamines, we have had the occasion to prepare mescaline, β-(3,4,5-trimethoxyphenyl)-ethylamine, an alkaloid which occurs naturally in the cacti *Anhalonium*. The literature cites the synthesis of this alkaloid by two methods, neither of which gives a satisfactory yield.

Slotta and Heller[1] synthesized mescaline in four steps from 3,4,5-trimethoxybenzaldehyde in an over-all yield of 28%. A more direct method *via* the condensation of 3,4,5-trimethoxybenzaldehyde with nitromethane, followed by the reduction of the resulting nitrostyrene, was employed by Späth.[2] The nitrostyrene was first reduced to the corresponding aldoxime, which on further reduction gave mescaline. The two-stage reduction gave a 24.9% yield, and the over-all yield of mescaline from the aldehyde was only 20.8%.

An elegant method for reduction of β-nitrostyrenes to phenethylamines with lithium aluminum hydride has been reported.[3] Reduction of 3,4,5-trimethoxy-β-nitrostyrene by this method resulted in an 89% yield of mescaline hydrochloride. The over-all yield from 3,4,5-trimethoxybenzaldehyde has been increased to 65%.

Experimental[4]

3,4,5-Trimethoxybenzaldehyde.—Gallic acid was converted to trimethylgallic acid in 80% yield by methylation with methyl sulfate.[5] Trimethylgalloyl chloride was prepared in 81% yield by the action of phosphorus pentachloride on trimethylgallic acid.[1] The acid chloride was purified by distillation and redistillation under reduced pressure; b.p. 131–133° (2 mm.); m.p. 83–84°. Rosenmund reduction of 3,4,5-trimethoxybenzaldehyde was carried out as described[1] using 52 g. of 3% Pd–$BaSO_4$ catalyst per mole of acid chloride. Dry xylene was the solvent. The product was recovered by removal of the catalyst by filtration, stripping off the xylene and fractional distillation of the residue under reduced pressure. A forerun of pyrogallol trimethyl ether, b.p. 82–100° (0.1 mm.), was obtained, and 3,4,5-trimethoxybenzaldehyde was collected as the fraction boiling at 106–112° (0.1 mm.). After crystallization from alcohol the aldehyde melted at 73–74°; yield 59%.

3,4,5-Trimethoxy-β-nitrostyrene.—This compound was prepared by the procedure of Späth[2] in 82.7% yield; m.p. 121–122° after recrystallization from alcohol.

Mescaline Hydrochloride.—Reduction of 7.2 g. (0.03 mole) of 3,4,5-trimethoxy-β-nitrostyrene with 5.7 g. of lithium aluminum hydride was carried out as described[3a] for 4-hydroxy-3-methoxy-β-nitrostyrene. The yield of mescaline picrate, m.p. 210–212°, was 11.4 g. (86%). After recrystallization from alcohol, the picrate melted at 214–216°; reported[2] 216–218°. The mescaline picrate was converted to mescaline hydrochloride as described[3a] in 92% yield; m.p. 180–181° (after recrystallization from alcohol); reported[1] 181°.

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[1] K. H. Slotta and H. Heller, *Ber.*, **63**, 3029 (1930).

[2] E. Späth, *Monatsh.*, **40**, 144 (1919).

[3] (a) F. A. Ramirez and A. Burger, This Journal, **72**, 2781 (1950); (b) R. F. Nystrom and W. G. Brown, *ibid.*, **70**, 3738 (1948); (c) K. E. Hamlin and A. W. Weston, *ibid.*, **71**, 2210 (1949).

[4] All melting and boiling points uncorrected.

[5] H. Gilman and A. H. Blatt, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1941, Coll. Vol. I, 2nd Ed., p. 537.

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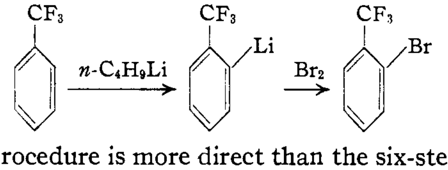
Preparation of *o*-Bromobenzotrifluoride

By Robert A. Benkeser and Roland G. Severson

In view of the recent interest in ortho and para derivatives of benzotrifluoride,[1,2] we are hereby reporting a two-step synthesis of *o*-bromobenzotrifluoride.

Metallation of benzotrifluoride with *n*-butyllithium has been shown to yield largely the ortho isomer.[3] Treatment of the metallated product with bromine vapor forms *o*-bromobenzotrifluoride in a 28% over-all yield.



This procedure is more direct than the six-step synthesis outlined by Jones[1] and the yield might conceivably be improved since the optimum reaction conditions were not investigated. As a proof of structure, *o*-bromobenzotrifluoride was found to undergo halogen–metal interconversion with *n*-butyllithium. The product upon carbonation was *o*-trifluoromethylbenzoic acid. It is of interest that

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[1] R. Jones, This Journal, **69**, 2346 (1947).

[2] M. Lilyquist, J. G. Wisler and P. Tarrant, Abstracts of 118th Meeting of the American Chemical Society, Chicago, Illinois, 1950.

[3] J. D. Roberts and D. Y. Curtin, This Journal, **68**, 1658 (1946).

o-bromobenzotrifluoride does not appear to react with lithium metal using the conventional procedure and yet it undergoes halogen–metal interconversion in high yields. This parallels the observations made on *m*-bromotrifluoromethylbenzene.[4]

Experimental

_o_-Bromobenzotrifluoride.—To a solution of *n*-butyllithium prepared from 278 g. (3 moles) of *n*-butyl chloride and 43 g. (6.2 g. atoms) of lithium in 1 l. of dry ether, was added 438 g. (3 moles) of trifluoromethylbenzene. This mixture was refluxed for 12 hours after the spontaneous evolution of butane had ceased. Bromine vapor was then carried into the reaction flask by a stream of nitrogen until approximately 400 g. had been added. The reaction mixture was poured into 1 l. of water with thorough mixing. The organic layer was washed with dilute sodium hydroxide, a sodium thiosulfate solution, and then with water. The resulting material was steam distilled to remove a rather large amount of tar. The organic layer from this operation was dried and fractionated giving 134 g. (30% recovery) of trifluoromethylbenzene, b.p. 100–101°, and after a relatively small intermediate fraction, 129 g. (28% yield) of *o*-bromobenzotrifluoride, b.p. 167–168°, $n^{25}\text{D}$ 1.4806.

To 6.75 g. (0.03 mole) of the *o*-bromotrifluoromethylbenzene thus prepared was added 66 ml. of an ether solution containing 0.03 mole of *n*-butyllithium at such a rate as to allow gentle reflux. The mixture was stirred for an additional 30 minutes and then carbonated with Dry Ice. Working up in the usual manner gave 4.73 g. (83%) of material, melting at 106–108°. Recrystallization from petroleum ether gave 4 g. (70%) of *o*-trifluoromethylbenzoic acid, m.p. 108–109.5°.

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(4) H. Gilman and L. Woods, THIS JOURNAL, **66**, 1981 (1944).

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Preparation of Pure Secondary Bromides

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It has long been realized that conversion of a secondary alcohol to the corresponding bromide is likely to be accompanied by rearrangement of the intermediate carbonium ion to yield an isomeric secondary bromide. In this connection, the *s*-amyl bromides have been studied carefully[1,2] for there are only two possible isomers. Lauer and Stodola[3] have made a careful study of the analysis of mixtures of the isomeric *s*-amyl bromides, and have concluded that analysis based on the index of refraction is quite unreliable but that the binary melting point diagram of the anilides may be used for reliable analysis of mixtures of the bromides. These investigators prepared 2-bromo- and 3-bromopentane by the methods judged to be most reliable for furnishing the pure bromides, but there has actually been no evidence that these "best" samples are entirely homogeneous isomers.

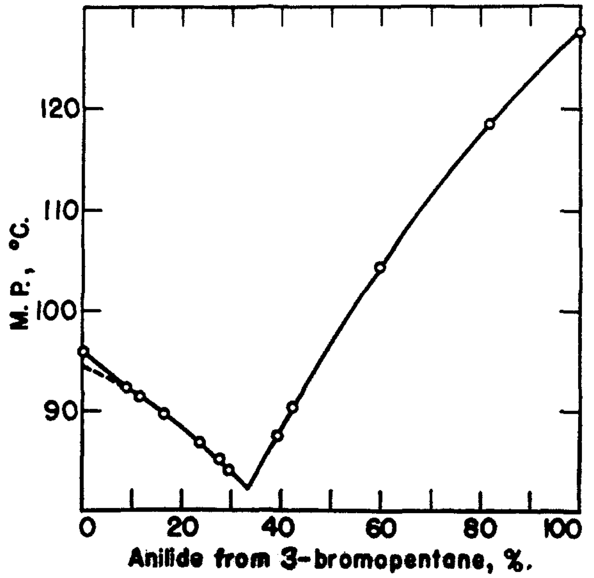

Fig. 1.—Binary melting point diagram of mixtures of the anilides prepared by reaction of 2-pentyl- and 3-pentylmagnesium bromide with phenyl isocyanate.

Evidence has been presented[4] that the reaction of bromine with the silver salt of a carboxylic acid, to give an alkyl halide, proceeds by way of a free radical mechanism. If this is the case, since free radicals are much less prone to rearrangement than carbonium ions, the reaction of bromine with the silver salt of an α-alkylalkanoic acid should lead to an isomerically pure *s*-alkyl halide. In the present investigation, this reaction has been carried out with silver 2-methylpentanoate and silver 2-ethylbutanoate to give, respectively, 2- and 3-bromopentane. The anilides obtained from these compounds proved to melt significantly higher than the best samples obtained by Stodola and Lauer,[3] who prepared the bromides from the alcohols with hydrogen bromide. Also, a direct comparison has been made with a sample of the bromide prepared by reaction of phosphorus tribromide with synthetic 2-pentanol, according to the procedure[5] considered best. The anilide from this bromide exhibited a melting point in agreement with the value reported by Stodola and Lauer, thus below the melting point of a sample prepared from bromide obtained *via* the silver salt reaction. It thus appears that a pure secondary bromide cannot be obtained from the corresponding alcohol in instances where isomeric secondary bromides are structurally possible.

Since analysis of mixtures of the *s*-amyl bromides is often desirable,[3] a binary melting point diagram has been constructed by use of mixtures of the pure anilides prepared from the *s*-amyl bromides obtained from the silver salt reactions. From this diagram (Fig. 1), it is indicated that the best sample of 2-bromopentane obtained previously[3] was of about 92% purity, and the best sample of 3-bromopentane was of about 87% purity. The right side of this curve (anilide from 3-bromopentane crystallizing) has a form normally characteristic of such diagrams, but the left side (anilide from 2-bromopentane crystallizing) does not. A characteristic curve (terminal portion dotted) may be drawn through all points except the upper one, and it is felt that the actual curve bends up at this point on account of association in the concentrated solution of a molecular compound of the *d*- and *l*-forms of the anilide. In another instance[6] in which the optical

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(1) Sherrill, Otto and Pickett, THIS JOURNAL, **51**, 3027 (1929).

(2) Sherrill, Baldwin and Hass, *ibid.*, **51**, 3036 (1929).

(3) Lauer and Stodola, *ibid.*, **56**, 1215 (1934).

(4) Arnold and Morgan, *ibid.*, **70**, 4248 (1948); Dauben and Tilles, *ibid.*, **72**, 3185 (1950); Smith and Hull, *ibid.*, **72**, 3309 (1950).

(5) Hsueh and Marvel, *ibid.*, **50**, 855 (1928).

(6) Cason and Winans, *J. Org. Chem.*, **15**, 157 (1950).

isomers were available, curves of this form were actually obtained. A similar behavior was first observed and discussed by Weitkamp.[7]

Experimental[8]

2-Methylpentanoic Acid.—Diethyl methyl-*n*-propylmalonate was prepared by alkylation, in the usual way,[9] of diethyl methylmalonate (prepared from ethyl oxalpropionate). The average yield was 83%, b.p. 108–112° (16 mm.), $n^{22}\mathrm{D}$ 1.4210. The diester was saponified with alcoholic potassium hydroxide, alcohol was distilled, and the acidified residue was extracted with ether. The crude malonic acid (m.p. 99–103°) was decarboxylated at 175°, to give 90% yield of 2-methylpentanoic acid, b.p. 95–96° (14 mm.), $n^{24}\mathrm{D}$ 1.4128. Hommelen[10] has reported b.p. 192–193.6°, $n^{20}\mathrm{D}$ 1.4136.

2-Ethylbutanoic acid, b.p. 113.4–113.6° (40 mm.), was obtained in a pure state by fractionation of the commercial acid through a three-foot packed column.

2-Bromopentane.—(A) The silver salt and bromine reaction was carried out as described for preparation of tridecyl bromide[11] except that acid was removed as the sodium salt rather than the barium salt. The carbon tetrachloride solvent was flash-distilled through a three-foot packed column, keeping the mole fraction of bromide in the pot below 0.2 until all solution had been added. After an intermediate fraction, the 2-bromopentane was collected in 55–65% yield at 117.0–117.8°, $n^{24}\mathrm{D}$ 1.4389. Stodola and Lauer[3] reported b.p. 116.4–117.4°, $n^{20}\mathrm{D}$ 1.4414.

This reaction was also carried out in methylene dichloride, in order to avoid the tedious separation from carbon tetrachloride, but this method proved even more troublesome on account of formation of small amounts of bromodichloromethane. From a 1-mole run there was obtained 2.4 g. of material of b.p. 90.4–92°, which after redistillation had $n^{20}\mathrm{D}$ 1.4911 (reported[12] for bromodichloromethane, b.p. 90.2°, $n^{20}\mathrm{D}$ 1.4985).

(B) Synthetic 2-pentanol[13] was converted to the bromide by the method of Hsueh and Marvel[5] except that the final heating period was omitted; yield 82%, b.p. 117–117.4°, $n^{20}\mathrm{D}$ 1.4413, $n^{24}\mathrm{D}$ 1.4392.

3-Bromopentane, prepared from silver 2-ethylbutanoate by the method described for the 2-isomer, was obtained in 76% yield, b.p. 118.1–118.9°, $n^{20}\mathrm{D}$ 1.4452. Lauer and Stodola[3] reported b.p. 117.4–118.4°, $n^{20}\mathrm{D}$ 1.4443.

Anilides from the bromopentanes were prepared by the method of Lauer and Stodola[3] except that the Grignard reaction with freshly distilled phenyl isocyanate was carried out in a three-necked test-tube fitted with mercury sealed stirrer, dropping funnel and reflux condenser. Crystallization of the anilides from aqueous methanol was as previously described except that the final addition of water was omitted.

The anilide from 2-bromopentane from the silver salt reaction, after a single crystallization, melted at 95.9–96.2°, and the best sample obtained (three crystallizations) melted at 96.0–96.4°.

The anilide from 2-bromopentane prepared from 2-pentanol, after a single crystallization, melted at 92.5–93.0°, and after three crystallizations, the m.p. was 94.7–95.6°. The best value previously reported[3] was 94.3°.

The anilide from 3-bromopentane, after a single crystallization, melted at 127.2–127.7° (best previous value[3] 125°). This anilide is polymorphic, for on removing the capillary from the m.p.-bath until crystallization sets in then immediately returning it to the bath, the substance rapidly remelts completely at temperatures down to 123.8°. Below this temperature, reversion to the original form occurred, with re-m.p. 127.4°. With the larger sample used for the binary melting point diagram, no difficulty with the lower-melting polymorph was encountered.

The binary melting point diagram was determined by the method described in detail by Cason and Winans.[6]

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[7] Weitkamp, THIS JOURNAL, **67**, 447 (1945).

[8] All melting points are corrected; all boiling points are uncorrected. All distillations, unless otherwise specified, were through a half-meter Vigreux type column with heated jacket and partial-reflux head.

[9] Adams and Kamm, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 250.

[10] Hommelen, *Bull. soc. chim. Belg.*, **42**, 243 (1933).

[11] Cason and Winans, *J. Org. Chem.*, **15**, 142 (1950).

[12] Timmermans and Martin, *J. chim. phys.*, **23**, 766 (1926).

[13] Cason and Coad, THIS JOURNAL, **72**, 4695 (1950).

Molecular Compounds of Aminoazo Dyes and Bile Acids I[1]

BY G. CILENTO

This paper describes the first results of an investigation of the coördinating affinity of aminoazo dyes for biologically important compounds. Related to this research was a recent note[2] in which the preparation of *p*-aminoazobenzenecholeic acid and of its N-dimethyl derivative was reported. Interest in this subject was induced by the present views on chemical carcinogenesis.

It is a well founded hypothesis that a common feature to carcinogenic molecules is the presence of at least one region which has a high electron density and an increased ability for addition reactions.[3] Actually there is an increasing amount of evidence which suggests that the carcinogen forms, in a first step—as it may be expected on the basis of its peculiar properties—an addition complex with some tissue constituent.[3] The results of the investigation, herein reported, of the coördinating ability of *p*-aminoazobenzene and *p*-dimethylaminoazobenzene, "butter yellow," for cholesterol, desoxycholic and cholic acids are in agreement with the views mentioned above.

p-Aminoazobenzene is a border line molecule with slight, if any, carcinogenic power, whereas the dimethyl derivative is very active when orally administered in inducing hepatomas in rats. Desoxycholic acid is known easily to form molecular compounds, the so-called choleic acids, with organic derivatives. This property, however, is rarely found in cholesterol or cholic acid.[4]

The research consisted of working out the solid–liquid equilibrium diagram between the azo dye and the sterid. Application was also made of ultraviolet and visible light spectrophotometry.

It has been found that neither of the two azo dyes form mixed crystals or molecular compounds with cholesterol. The eutectic point lies at 48% (by weight) *p*-aminoazobenzene, 108.5° in one case and at 60% (by weight) *p*-dimethylaminoazobenzene, 105.5° in the other case.

Figures 1 and 2 illustrate the phase diagrams involving desoxycholic acid. As it was expected, in both cases a maximum occurs in the liquid curve which indicates molecular addition. However, due to the flat shape of these maxima, it was impossible to decide if four or six molecules of the bile acid were associated with one molecule of the azo dye, nor could additional information be obtained from the

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[1] From a paper presented at the Second Meeting of the Sociedade Brasileira Para o Progresso da Ciência, Curitiba, November, 1950.

[2] G. Cilento, THIS JOURNAL, **72**, 4272 (1950).

[3] For a survey see P. Daudel and R. Daudel, *Biol. méd.* (*Paris*), **39**, 201 (1950).

[4] Harry Sobotka, "The Chemistry of the Sterids," The William and Wilkins Company, Baltimore, Md., 1938, p. 122.

solid curve.[5] A pentacoördination was ruled out on symmetry grounds.[6]

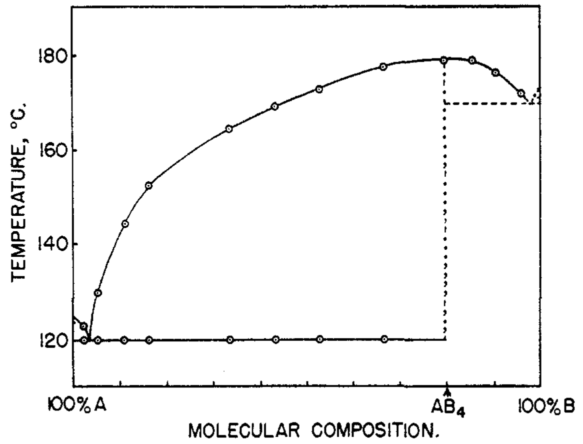

Fig. 1.—Binary system of *p*-aminoazobenzene (A) and desoxycholic acid (B).

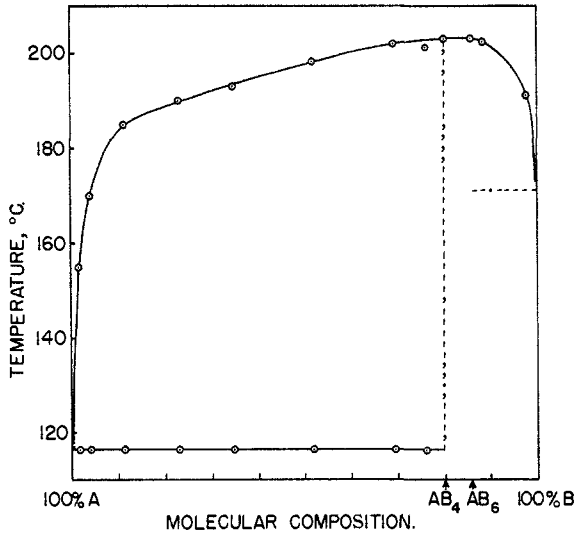

Fig. 2.—Binary system of *p*-dimethylaminoazobenzene (A) and desoxycholic acid (B).

Therefore the choleic acids were prepared and analyzed for their acholic content. It was found[2] that *p*-aminoazobenzene was associated with four molecules of the biliary acid. Unexpected results were obtained with its N-dimethyl derivative. Different samples showed a different content of the azo dye, which was always located between those expected for a tetra- and an hexacholeic, though in one case the expected percentage for an hexacholeic was obtained. It was also observed that recrystallization from ethyl alcohol raised the content of the acholic component. Therefore it was assumed that this azo dye can form both a tetra- and an hexacholeic.

Choleic acids of nitrogenous substances seem not to have been previously reported. It is interesting to note that while *p*-aminoazobenzene and its N-dimethyl derivative melt at 124.5° and 118°, respectively, their choleic acids melt at 183° and 204°. Among all the choleic acids hitherto reported only that of 1,2,5,6-dibenzanthracene melts higher (m.p. 223–224°)[7] than butter yellow choleic acid.

p-Aminoazobenzene choleic acid and its N-dimethyl derivative show, in alcoholic solution, the same spectrum as the pure azo dye. In alkaline solution the former showed a 10–12 mμ shift of the main bands toward shorter wave length making the shoulder representative of the N=N absorption more prominent. The faint shoulder at around 310 mμ disappeared. In the case of the N-dimethyl derivative no substantial shift nor disappearance of the 310 mμ shoulder was observed.

p-Aminoazobenzene and cholic acid display no ability for mutual addition at the temperatures investigated. The diagram shows a simple eutectic point (at 4.5 mole per cent. azo dye, 120°) and a very regular liquidus curve. However the observed data for the system involving the dimethyl derivative, shown in Fig. 3, indicate the existence of a molecular compound between one molecule of *p*-dimethylaminoazobenzene and two molecules of cholic acid.

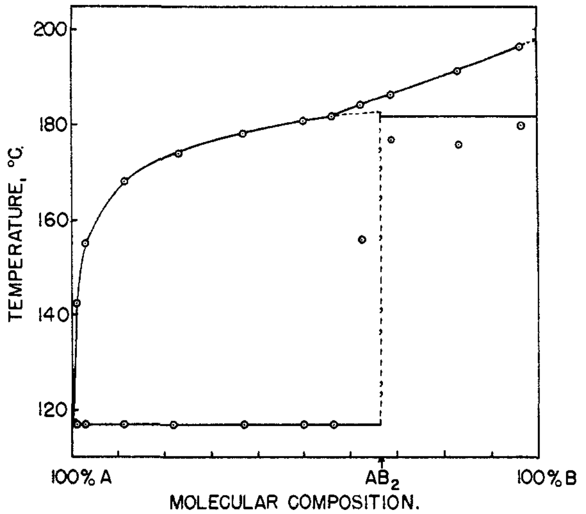

Fig. 3.—Binary system of *p*-dimethylaminoazobenzene (A) and cholic acid (B).

Owing to the existence of different polymorphic modifications of cholic acid, mixtures for the diagrams were prepared by close grinding of the components, without previous melting. Indeed, it was observed that if cholic acid (m.p. 200°) is previously melted and resolidified, it melts at around 135°, provided the sample is heated from low temperatures, otherwise it appears already melted even below 135°.

Some difficulties were found on ascertaining the solidus curve of the diagram depicted in Fig. 3. It was initially observed that all mixtures showed a thaw point coincident with the melting point of pure *p*-dimethylaminoazobenzene. Therefore the mixtures were partially melted between glass slides

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(5) Mixtures rich in desoxycholic acid started melting at relatively low temperature and apparently resolidified again, yet, it was impossible to determine their thaw point.

(6) H. Rheinboldt, *Ann.*, **451**, 256 (1927).

(7) L. F. Fieser and M. S. Newman, THIS JOURNAL, **57**, 1602 (1935).

and after resolidification, the slides rubbed against each other. It was observed that this procedure lowered the proportion of liquid phase to that of solid phase for mixtures containing less than 60 mole per cent. cholic acid and raised by some 40–60° the thaw point of mixtures richer in cholic acid. Thaw points for the latter mixtures shown in the diagram are averages of several determinations and are of rather poor accuracy.

p-Aminoazobenzene showed in sodium cholate solution practically the same spectrum as in sodium desoxycholate solution. With the N-dimethyl derivative in sodium cholate solution considerable changes, such as a shift toward longer wave length, were observed.[8]

Experimental

p-Dimethylaminoazobenzene, cholesterol and cholic acid were several times recrystallized from ethyl alcohol. The former two were dried in vacuum and showed m.p. 117–118° and m.p. 147.5–148.5°, respectively. Cholic acid was dried in Abderhalden drying apparatus at 94° until constant weight; m.p. 198–200°; desoxycholic acid (m.p. 171–173°). *p*-Aminoazobenzene (m.p. 123.5–124.5°) and its choleic acid (m.p. 180–183°) were described in a previous note.[2] Solid–liquid equilibrium diagrams were carried out according to Rheinboldt.[9] Thaw points were determined in a microscope equipped with a heating stage. *p*-Dimethylaminoazobenzene choleic acid was repeatedly prepared by the current method[2]; m.p. 201–204°. Analyses were carried out by the method previously described.[2] Percentages were computed from the optical densities D measured in 1.002 cm. silica cells at 410 mμ, which was, approximately, the wave length of the absorption maximum of *p*-dimethylaminoazobenzene. Alcoholic solutions of this azo compound showed, in average, $D/c = 0.1304$, c being the concentration in mg. per liter. Analyses of various samples are summarized in Table I. Calculated percentages of azo dye for a tetra-, penta- and hexacholeic acid were 12.5, 10.3 and 8.7, respectively.

TABLE I

ANALYSES OF VARIOUS SAMPLES OF *p*-DIMETHYLAMINOAZOBENZENE CHOLEIC ACID

	Choleic acid solution		
Sample	Mg./liter	D_{410}	Acholic in choleic, %
A[a]	103.1	1.219	9.0
B[a]	97.2	1.261	9.9
C[a,b]	50.9	0.722	10.8
	51.2	0.724	10.8
C[c]	49.8	0.728	11.2
	49.2	0.722	11.2
D[c]	68.4	0.951	10.6
	102.8	1.459	10.8
E[c]	118.5	1.620	10.5
	96.6	1.364	10.8

[a] Unrecrystallized. [b] Prepared from alcoholic solutions of butter yellow and desoxycholic acid in such concentrations that even if no choleic were formed on mixing them, there would not be precipitation of any reactant upon cooling. [c] Recrystallized.

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[8] All solutions were prepared in 0.1 *N* sodium hydroxide and had arbitrary concentrations of azo dye and bile acid.

[9] H. Rheinboldt, *et al.*, *J. prakt. Chem.*, [2] **111**, 242 (1925); **112**, 187, 199 (1926); **113**, 348 (1926); *Ber.*, **74**, 756 (1941).

Cleavage of Dimercaptols of Acetonylacetone by Mercuric Chloride

BY R. A. DINERSTEIN

When sugar mercaptals are treated with mercuric chloride in alcohol, the sulfur precipitates as the alkylmercapto mercuric chloride, RSHgCl, and the aldehyde is regenerated.[1] That this cleavage is general for mercaptals and mercaptols has been recognized in this Laboratory. To demonstrate the effect of treating dimercaptols with mercuric chloride, the dimercaptols of acetonylacetone were prepared from three different mercaptans according to the method of Rietz, Chapman and Fernandez[2] and then treated with mercuric chloride. The precipitates were analyzed for sulfur and compared by mixing melting point with the RSHgCl compound prepared directly from the mercaptan and mercuric chloride.[3] Mixed melting points (Table I) and sulfur analyses (Table II) demonstrated that the products are identical. Thus, cleavage takes place in the reaction of dimercaptols and mercuric chloride.

TABLE I

MELTING POINTS OF RSHgCl COMPOUNDS

R	From RSH and $HgCl_2$	From dimercaptol and $HgCl_2$	Mixed	Reported by Rietz[4] for "addition product"
n-Amyl	183–184	181–182	182–183	184–185
n-Decyl	155–156	154–155	154–155	155–156
n-Dodecyl	153–154	152–153	152–153	153–154

TABLE II

SULFUR CONTENTS (% S) OF RSHgCl COMPOUNDS

R	Obsd. from RSH and $HgCl_2$	Obsd. from dimercaptol and $HgCl_2$	Calcd. for RSHgCl	Calcd. for "addition product"
n-Amyl	9.4	9.7	9.5	6.9
n-Decyl	7.7	7.6	7.8	6.9
n-Dodecyl	7.1	7.2	7.3	6.5

This conclusion differs from that of Rietz, *et al.*,[4] regarding the same reaction. In a study of the dimercaptols of acetonylacetone prepared from mercaptans containing one to twelve carbons, these authors described the "mercuric chloride addition products" derived from each member of the series. Carbon and hydrogen analyses led the authors to assume that four to eight mercuric chloride molecules were attached to each dimercaptol molecule, the exact number being a function of chain length; two cases in which this number was 4.5 were considered "anomalous."

Identification of the reaction products as the RSHgCl compounds permits a simpler explanation. Confirmation is provided by the sulfur analyses (Table II). Furthermore, the calculated carbon and hydrogen contents of the RSHgCl compounds

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[1] H. Gilman, "Organic Chemistry," second edition, John Wiley and Sons, Inc., New York, N. Y., 1943, Vol. II, pp. 1562, 1575.

[2] E. G. Rietz, R. D. Chapman and J. B. Fernandez, THIS JOURNAL, **70**, 3486 (1948).

[3] S. Blackburn and F. Challenger, *J. Chem. Soc.*, 1872 (1938).

[4] E. G. Rietz, J. B. Fernandez, L. T. Snider and T. K. Todsen, THIS JOURNAL, **71**, 3433 (1949).

are in agreement with the observed data reported by Rietz.[4]

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RECEIVED OCTOBER 19, 1950

Investigations on Lignin and Lignification. V. Lignin of Cork[1]

BY ROBERT M. DEBAUN AND F. F. NORD

Two procedures have been successfully applied to the isolation of authentic native lignin preparations from wood.[2,3a,b,4] Although several lignins have been isolated by chemical means from cork and bark,[5–11] no native product has been obtained from these sources. We wish to report on the isolation and fractionation of the native lignin of cork.

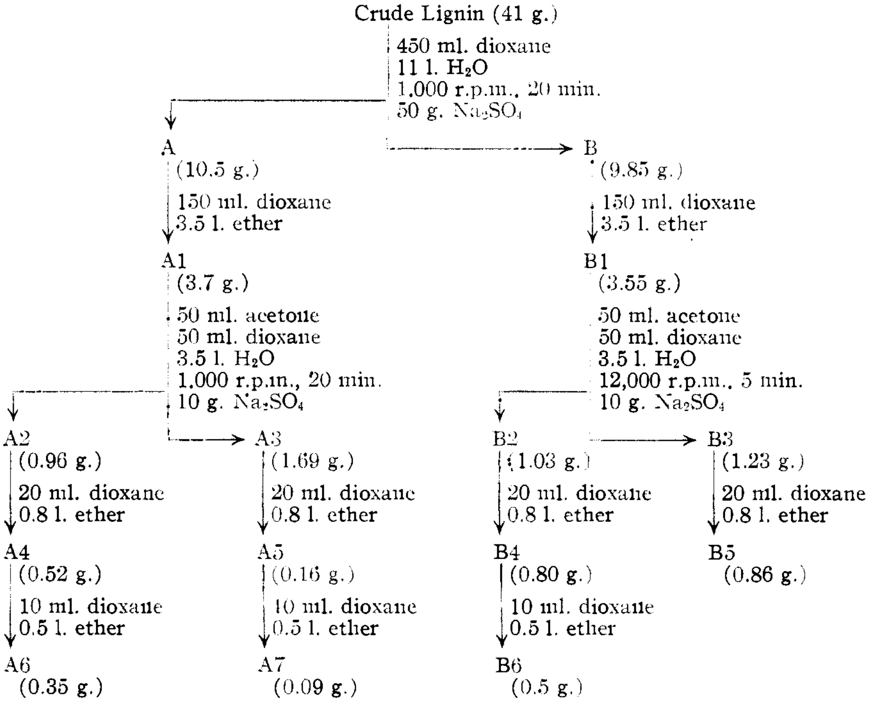

Fig. 1.—Fractionation of the cork native lignin.

This material was fractionated according to the scheme summarized in Fig. 1, and the various fractions were studied with regard to their composition, ultraviolet and infrared absorption spectra, their reaction with the "phenol" reagent,[12,13] and with the phloroglucinol-HCl test.[14,15,16]

An alkali lignin of cork was also prepared.

The dissimilarity of the composition of our native lignin from the alkali lignin, and from the other cork lignins[10,11] suggested to us that our product might be admixed with phenolic extractive materials such as tannin and/or phlobaphene. This supposition was verified by paper chromatography.

Experimental

Native Lignin.—One and one-half kilograms of "männlicher Kork",[10] the bark of *Quercus suber*, ground to 40–60 mesh, was extracted with alcohol in a percolator-type extractor[17] until the extract no longer gave the phloroglucinol-HCl test. The solution was evaporated to dryness *in vacuo* at 40°. The residue (120 g.) was washed with ether several times, and again with water by centrifugation and resuspension with fresh solvent until the supernatant became opalescent. The residual material (41 g.) was then treated as outlined in Fig. 1. Solutions in purified dioxane[18] were added to the ice-cold non-solvents, slowly with stirring. Anhydrous sodium sulfate was used as the salting agent throughout.

Alkali Lignin.—Ether- and then methanol-preextracted cork was autoclaved for 8 hours at 23 pounds pressure in the presence of ten times its amount of 3% sodium hydroxide. The filtered hot mixture was acidified with hydrochloric acid, and the resulting precipitate was redissolved in base and reprecipitated with acid. It was then reprecipitated from acetone solution with ether until a constant methoxyl value (12.40%) was obtained.

Spectra.—The ultraviolet absorption spectra were obtained with a Beckman model DU quartz ultraviolet spectrophotometer, absolute ethanol being used as the solvent. The infrared absorption spectra were determined in an experimental model of the Baird double beam recording spectrophotometer. The wave length accuracy of the instrument was 0.04 μ. The samples were run as mulls in mineral oil.

Colorimetry.—The colorimetric readings were taken in an Evelyn Photoelectric Colorimeter. A 550 mμ filter was used in the phloroglucinol-HCl test. Isolated native white Scots pine lignin was used as the standard, and the reaction is accurate to $\pm 3\ \gamma$ in the range 20–120 γ/ml. The production of color is reported to be due to the presence of coniferyl aldehyde groups.[16,19a,b,c] The cork native lignin on contact with phloroglucinol and HCl gives a color similar in spectrum to that obtained with the softwood lignin. The results of the phloroglucinol-HCl test are expressed as per cent. of lignin, the white Scots pine native lignin being taken as 100%. A 600 mμ filter was used for the study with the Mehta reaction. The cork alkali lignin was applied as the standard, and the reaction could be conducted with an accuracy of $\pm 5\ \gamma$ in the range 50–200 γ/ml. Addition of 15% Na_2CO_3 is necessary for full development of the color.

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(1) Presented before the Cellulose Division of the A. C. S. at the autumn meeting, Chicago, Ill., 1950.

(2) Brauns, *Fortschr. Chem. Org. Naturstoffe*, **5**, 175 (1948).

(3) (a) Schubert and Nord, THIS JOURNAL, **72**, 977 (1950); (b) Schubert and Nord, *ibid.*, **72**, 3735 (1950).

(4) Kudzin and Nord, *ibid.*, **73**, 690 (1951).

(5) v. Wacek and Schön, *Holz als Roh und Werkstoff*, 4, 18 (1941).

(6) Hilpert and Knackstedt, *Ber.*, **72**, 1582 (1939).

(7) Clothofski, Weikert and Nick, *ibid.*, **74B**, 299 (1941).

(8) Clothofski and Junge, *ibid.*, **74B**, 1415 (1941).

(9) Cram, Eastwood, King and Schwartz, "Chemical Composition of Red Cedar Bark," Dominion Forest Service Circular No. 62.

(10) Stockar, Dissertation, Technische Hochschule, Zürich, 1948.

(11) Fierz-David and Ulrich, *Experientia*, **1**, 160 (1945).

(12) Folin and Denis, *J. Biol. Chem.*, **12**, 239 (1912).

(13) Mehta, *Biochem. J.*, **19**, 958 (1925).

(14) Wiesner, *Sitzber. Akad. Wiss., Wien, Math. Naturw. Kl.*, **77**, 60 (1878).

(15) Kalb, in Klein's "Handbuch der Pflanzenanalyse," Wien, J. Springer, 1932, III, 179.

(16) DeBaun and Nord, *Tappi*, **34**, No. 2 (1951).

(17) Nord and Schubert, *Holzforschung*, **5**, 1 (1951).

(18) Hess and Frahm, *Ber.*, **71**, 2627 (1938).

(19) Adler, *et al.*, (a) *Acta Chem. Scand.*, **2**, 93 (1948); (b) **2**, 839 (1948); (c) **3**, 85 (1949).

The results with the phenol reagent are expressed in terms of optical density after 3 minutes × 1,000 divided by the γ of lignin taken.

Paper Chromatography.—Fractions A6, A7 and B6 were chromatographed on Schleicher and Schuell Paper No. 696, with water as the developing solvent. If the paper were sprayed with phloroglucinol–HCl, pink spots were obtained on the original base line. If an identical strip were sprayed with phenol reagent, and then with 15% Na_2CO_3, blue spots appeared, both on the original base line and at the liquid front. The intensities of the blue spots were of the same order of magnitude.

TABLE I

COMPOSITION OF CORK LIGNIN FRACTIONS

Fraction	C. %	H. %	OMe. %	Lignin. %	Phenol reagent
A1	58.86	5.66	5.15	15, 17.5	33.8, 34.1
A2[a]	59.6	5.14	3.7	21	38.5
A3	58.62	4.94	3.5	12	18.7
A4[b]	59.8	5.8	4.8	14	58.6
A5	58.61	5.86	5.4	12	24.2
A6	59.2	5.5	4.6	..	..
A7[c]	57.2	5.7	5.1	..	..
B1[d]	59.13	5.1	5.34	13	24.8
B2	58.77	4.93	4.26	..	..
B3[e]	58.3	5.2	4.21	6	34.4
B4[f]	58.18	5.29	4.75	14	12.1
B5[g]	...	..	4.68	..	..
Alkali lignin	...	..	12.40	..	58.6, 59.5

Corrected for: [a] 1.5% ash; [b] 2.3% ash; [c] 1.0% ash; [d] 1.8% ash; [e] 11.97% ash; [f] 2.1% ash; [g] 10.22% ash.

Discussion

Our lignin appears to be contaminated with other extractable material such as tannin and/or phlobaphene. This is shown by its low methoxyl content. Although low methoxyl lignins have been obtained from barks,[5,6] it is not certain whether they were free of non-lignin matter. Also, phlobaphene has been obtained, admixed with native lignin,[20,21] and lignin of redwood bark was reported[22] to be contaminated with low methoxyl containing components.

While it appears that our fractions possess varying total composition, as evidenced by their spectra (Figs. 2, 3), the fact that the lignin content does not rise upon successive reprecipitation indicates that a pure lignin cannot be obtained from this mixture by the Brauns method for isolating and purifying native lignin.

Although the ultraviolet spectra are generally similar, the infrared spectra differ, particularly in the regions of 865 and 722 cm.$^{-1}$. Their incomplete resolution, as compared to those spectra of wood lignins previously obtained,[3b,4,23] suggest the complexity and inhomogeneity of our lignins. The complexity of bark over wood[24] is thus borne out by these experiments.

Acknowledgments.—We wish to thank the Armstrong Cork Company, Lancaster, Pa., for generous samples of virgin and refugo cork and Drs. J. D. Hardy and Carl C. Clark of Cornell University Medical College for obtaining the infrared spectra for us. The microanalyses were done by Mr. A. A. Sirotenko of this department. This work was carried out under the auspices of the Office of Naval Research.

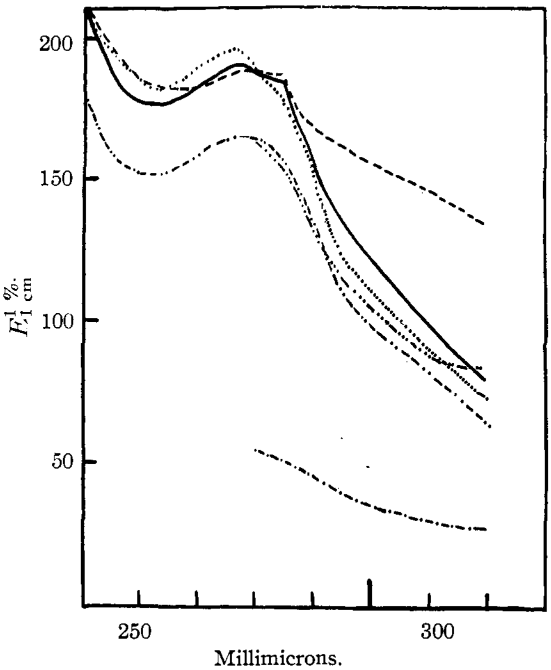

Fig. 2.—Ultraviolet spectra of cork lignin fractions: native cork lignin A6, ——————; A7, ...; B6, —··—··—··—··; A1, —·—·—·—·—·—; B1, —···—···—···; cork alkali lignin, - - - - - - - - -.

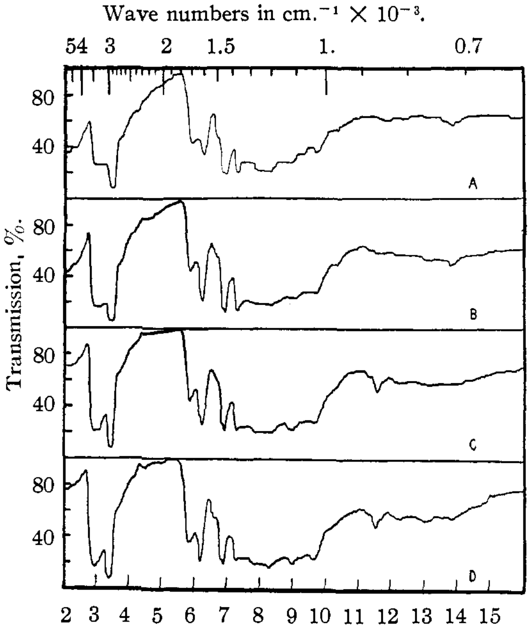

Fig. 3.—Infrared spectra of cork lignin fractions: Cork alkali lignin, A; cork native lignin: A6, B; A7, C; B6, D.

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(20) Buchanan, Lewis and Kurth, *Ind. Eng. Chem.*, **36**, 907 (1944).

(21) Graham and Kurth, *ibid.*, **41**, 409 (1949).

(22) Lewis, Brauns, Buchanan and Kurth, *ibid.*, **36**, 759 (1944).

(23) Jones, *Tappi*, **32**, 167 (1949).

(24) Kurth, *Chem. Revs.*, **40**, 33 (1947).

A New Preparation of Potassium Dinitromethane and its Conversion to 2,2-Dinitro-1,3-propanediol[1,2]

BY H. FEUER, G. B. BACHMAN AND J. P. KISPERSKY[3]

Dinitromethane or its potassium salt has been prepared by a number of previous investigators.[4]

The yield of potassium dinitromethane by earlier procedures is low and a shorter and more convenient synthesis has been developed utilizing nitromethane as a starting material. The following equations show the two-step synthesis which gives the desired product in a yield of 25% based on chloronitromethane.

$$\mathrm{CH_3NO_2} \xrightarrow[\mathrm{NaOH}]{\mathrm{Cl_2}} \mathrm{CH_2Cl(NO_2)} \qquad (1)$$

$$\mathrm{CH_2ClNO_2} \xrightarrow[\mathrm{KNO_2}]{\mathrm{OH^-}} \mathrm{K^+CH^-(NO_2)_2} \qquad (2)$$

The second step of the synthesis was carried out by the dropwise addition of the base to a cold (−5 to 0°) aqueous methanol solution of chloronitromethane and potassium nitrite. The crude potassium dinitromethane crystallized from the reaction mixture as it was formed.

When aqueous ethylene glycol was substituted for aqueous methanol the crude salt obtained was of higher purity. It was also found possible to prepare potassium dinitromethane under anhydrous conditions in methanol; however, the procedure is not recommended. In one such experiment a finely divided dark red powder was obtained which "fumed-off" with a flash when touched with a metal spatula.

The reaction is fairly rapid and most of the product is obtained in the first 30 minutes after the addition of the base. It is best carried out in the temperature range of −5 to 0°.

The amount of water present in the solvent has less influence on the yield of product than the reaction time or reaction temperature. It was found that the most consistent yields were obtained when the solvent contained 15 to 30 weight per cent. of water. Attempts to increase the yield by using twice the theoretical amount of potassium nitrite were unsuccessful. Substitution of bromonitromethane for chloronitromethane, did not influence the yield.

The crude product was purified by washing and recrystallization. It was identified: (1) by its explosion point, (2) by nitrogen analysis, (3) by conversion to potassium dinitroethanol,[5] which also analyzed satisfactorily for nitrogen. Further confirmation of the identity of the salt was obtained by converting it to the known ether-soluble dinitromethane. The salt was reformed by treatment with a methanol solution of potassium methoxide.

Potassium dinitromethane was converted, in one step, to 2,2-dinitro-1,3-propanediol by acidifying an aqueous mixture of the salt and formaldehyde, using a 10% excess of the latter. It does not give a positive test for the hydroxyl groups when tested with ceric nitrate reagent. On treatment with an equimolar amount of base the diol is decomposed to potassium dinitroethanol and formaldehyde. When the diol is heated with an excess of aqueous alkali the corresponding salt of dinitromethane is obtained. The alcohol is quite stable in acidic solution and even prolonged heating with fuming nitric acid at 60–70° has no effect. It yielded a distillable diacetate on treatment with acetyl chloride.

Experimental

Preparation of Potassium Dinitromethane.—To 96 g. (1.0 mole) of chloronitromethane[6] in 250 ml. of methanol at −5°, was added 100 g. (1.0 mole of 87% assay) of potassium nitrite dissolved in 133 ml. of water; then a solution of 66 g. (1.0 mole of 86% assay) of potassium hydroxide in 250 ml. of methanol was added dropwise, with stirring. The addition required 2 hours and the mixture was stirred for an additional 9 hours at −5°. The slurry was filtered and 151 g. of moist, crude salt was obtained. It was purified by mixing it with 200 ml. of water to dissolve the potassium chloride and potassium nitrite which were present as contaminants. After filtration and recrystallization from hot water 36.1 g. (25% yield) of potassium dinitromethane was obtained which exploded at 208°; literature values[4] 205 and 207°. The salt was converted to potassium dinitroethanol according to the directions of Duden.[5]

Anal. Calcd. for $\mathrm{C_2H_3N_2O_5K}$: N, 16.0. Found: N, 15.6.

Preparation of 2,2-Dinitro-1,3-propanediol and Its Diacetate.—To 50 ml. of water and 34 ml. of 40% formalin solution (0.45 mole of formaldehyde) was added 28.8 g. (0.20 mole) of potassium dinitromethane. The flask was cooled in an ice–water mixture, and 12 g. of acetic acid dissolved in 15 ml. of water was added dropwise, with stirring. After the addition, the mixture was stirred for 90 minutes without cooling. The solution was extracted with three 50-ml. portions of ether and the combined extracts were evaporated leaving a straw-colored oil which crystallized. Recrystallization from benzene gave 21.9 g. (66%) of long, white needles of 2,2-dinitro-1,3-propanediol, m.p. 142°. The diol was soluble in the common organic solvents such as acetone, ether, dioxane, alcohols and nitromethane as well as in water.

Anal. Calcd. for $\mathrm{C_3H_6N_2O_6}$: C, 21.8; H, 3.61; N, 16.86. Found: C, 22.3; H, 3.77; N, 16.92.

The diacetate ester was prepared by treating the diol with acetyl chloride at 10–15° for 2 hours. The ester was obtained as a clear liquid, b.p. 113–115° (1 mm.).

Anal. Calcd. for $\mathrm{C_7H_{10}N_2O_8}$: C, 33.6; N, 11.2; H, 4.0. Found: C, 33.55; N, 10.84; H, 4.02.

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(1) Abstracted from a thesis submitted to the Faculty of the Graduate School of Purdue University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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

(3) Aerojet Engineering Corporation, Azusa, Calif.

(4) G. Chancel, *Compt. rend.*, **86**, 1405 (1878); P. Duden, *Ber.*, **26**, 3003 (1893); R. A. Gotts and L. Hunter, *J. Chem. Soc.*, **125**, 445 (1924); P. Lipp, *Ann.*, **449**, 23 (1926); S. M. Losanitch, *Ber.*, **16**, 51 (1883); R. Scholl and A. Schmidt, *Ber.*, **35**, 4291 (1902); W. Wislicenus, *Ann.*, **460**, 282 (1928).

(5) P. Duden and G. Ponndorf, *Ber.*, **38**, 203 (1905).

(6) J. B. Tindall, U. S. Patent 2,309,806, February 2, 1943.

LAFAYETTE, IND. RECEIVED NOVEMBER 22, 1950

Heat Capacity of Crystalline Dextrose between 25 and 95°

BY THOMAS B. DOUGLAS, ANNE F. BALL AND JOHN L. TORGESEN[1]

As part of a project sponsored at the National Bureau of Standards by the Corn Industries Research Foundation for the determination of the physical properties of raw materials, industrial products and pure substances of importance in the

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(1) Research Associate, Corn Industries Research Foundation.

corn milling industry, the relative enthalpy of pure crystalline α-dextrose was measured over a temperature range, 25 to 95°, in which this sugar was expected to be completely stable. The heat capacity was calculated from the enthalpy data.

Experimental

The dextrose used was Standard Sample material[2] issued by this Bureau. It had been recrystallized twice from water, the last recrystallization being carried out at 55° to yield the anhydrous form. In order to reduce the moisture content to a minimum, it was dried for 6 hours in a vacuum oven between 60 and 70° and at 2 mm. pressure and then stored in a vacuum desiccator. It is believed that this treatment yielded a sample whose ash and moisture content did not exceed 0.003 and 0.01%, respectively.

The apparatus and method for measuring enthalpy have been described in detail elsewhere.[3] Briefly, a sample that had been heated in a furnace to a temperature measured by a platinum resistance thermometer was dropped into an electrically calibrated ice calorimeter. This measured the heat delivered in cooling the sample to 0°. The enthalpy change of the container itself was accounted for by "blank" experiments. Using a metal container that had been sealed by a gold gasket after the air had been replaced by helium, 42 determinations were made with the empty container and 25 with the sample, with the furnace temperature varied in approximately 10° steps from 25 to 95°.[4] At a given temperature the probable error of the mean value of the enthalpy of dextrose computed from these observed heats was ±0.02 cal./g. on the average. These probable errors at the respective temperatures evidenced no definite trend with temperature.

The mean observed values of the enthalpy of dextrose, in excess of that at 0°, were: (25°) 6.953, (35°) 9.918, (45°) 12.947, (55°) 16.136, (65°) 19.328, (75°) 22.656, (85°) 26.048 and (95°) 29.684 cal./g.[5] By the method of least squares there were fitted to the mean observed enthalpy values at these temperatures quadratic equations for the empty container and container with sample, with an average deviation of 0.1%. The difference between these two equations led to the following equation for the heat capacity of dextrose, in cal./g.-deg. at $t°$

$$C_p = 0.2665 + 0.000955t \ (t = 25 \text{ to } 95°) \qquad (1)$$

One check on the general accuracy of the method was obtained by making several measurements, using the same apparatus, of the enthalpy change of water between 0 and 25°. The mean value obtained, which itself had a probable error of ±0.12%, was 0.05% lower than a more precise value obtained with an adiabatic calorimeter.[6]

Slightly higher values than those given by equation (1) for dextrose were obtained by Parks and Thomas,[7] who reported

$$C_p = 0.270 + 0.00092t \ (t = -10 \text{ to } +60°) \qquad (2)$$

Nelson and Newton,[8] using a calorimeter with an isothermal jacket at 60°, gave the following equation

$$C_p = 0.265 + 0.000975t \ (t = 0 \text{ to } 60°) \qquad (3)$$

This equation gives heat capacities at 47.5, 25 and 10° that are lower by 0.2, 0.3 and 0.5%, respectively, than those given by equation (1). They checked the accuracy of their procedure by making measurements at these temperatures on water, obtaining average heat capacities that were lower by 0.2, 0.5 and 0.6% at these respective temperatures than the values of the precise work[6] referred to above. If their results for dextrose are corrected by these latter figures to account for what may be supposed to be a systematic error in their method, their values become higher by 0.0, 0.2 and 0.1%, respectively, than those of equation (1).

Huffman and Fox[9] have accurately determined the heat of combustion of dextrose. After the recalculation of their values with the use of more recent values for the heat of combustion of benzoic acid and the heats of formation of water and of carbon dioxide,[10] their data gave for the standard heat and free energy of formation (ΔH_f^0 and ΔF_f^0) of dextrose at 25° the values −304.37 and −217.34 kcal., respectively. The available heat capacity data reliably determine the variation of these quantities between 25 and 95°. Using the above values, equation (1) for dextrose, and equations accurately fitting in this temperature range the heat capacities of carbon (graphite), hydrogen and oxygen as recently tabulated[11] at this Bureau, the following equations were derived in kcal./mole at T, °K.

$$\Delta H_f^0 = -288.60 - 0.06825T + 6.840(10^{-5})T^2 - 448/T \qquad (T = 298 \text{ to } 368°\text{K.})$$

$$\Delta F_f^0 = -288.60 + 0.15715T \log_{10}T - 6.840(10^{-5})T^2 - 224/T - 0.12695T \qquad (T = 298 \text{ to } 368°\text{K.})$$

The authors wish to thank Dr. D. C. Ginnings for his help and advice in this work.

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(2) F. J. Bates and Associates, "Polarimetry, Saccharimetry and the Sugars," N. B. S. Circular C440, U. S. Government Printing Office, Washington, D. C., 1942; R. F. Jackson, *Bull. Bur. Standards*, **13**, 633 (1916).

(3) D. C. Ginnings, T. B. Douglas and A. F. Ball, *J. Research Natl. Bur. Standards*, **45**, 23 (1950).

(4) According to previous reports, no appreciable decomposition of the dextrose is to be expected in this temperature range. See, *e.g.*, G. S. Parks, H. M. Huffman and F. R. Cattoir, *J. Phys. Chem.*, **32**, 1366 (1928).

(5) 1 cal. = 4.1840 absolute joules.

(6) N. S. Osborne, H. F. Stimson and D. C. Ginnings, *J. Research Natl. Bur. Standards*, **23**, 197 (1939).

(7) G. S. Parks and S. B. Thomas, THIS JOURNAL, **56**, 1423 (1934).

(8) E. W. Nelson and S. B. Newton, *ibid.*, **63**, 2178 (1941).

(9) H. M. Huffman and S. W. Fox, *ibid.*, **60**, 1400 (1938).

(10) R. S. Jessup, *J. Research Natl. Bur. Standards*, **36**, 421 (1946); D. D. Wagman, J. E. Kilpatrick, W. J. Taylor, K. S. Pitzer and F. D. Rossini, *ibid.*, **34**, 143 (1945); E. J. Prosen, R. S. Jessup and F. D. Rossini, *ibid.*, **33**, 447 (1944).

(11) F. G. Brickwedde, M. Moskow and J. G. Aston, *ibid.*, **37**, 263 (1946); H. W. Woolley, R. B. Scott and F. G. Brickwedde, *ibid.*, **41**, 379 (1948); H. W. Woolley, *ibid.*, **40**, 163 (1948); "Thermal Properties of Gases," NBS-NACA Tables 7.10 and 9.10, U. S. Government Printing Office, Washington, D. C., 1949.

NATIONAL BUREAU OF STANDARDS
WASHINGTON, D. C.
RECEIVED NOVEMBER 10, 1950

A Synthesis of ϵ-Bromocaproic Acid

BY HAROLD W. HEINE AND HOWARD JONES

The methods, recently described by Westerfeld[1] for the oxidation of cyclopentanone to δ-valerolactone and by Fling, Minard and Fox[2] for the transformation of the intermediate alkaline oxidation mixture to δ-bromovaleric acid, have been extended to the preparation of ϵ-bromocaproic acid.

Cyclohexanone was oxidized with hydrogen peroxide and the reaction mixture subsequently

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(1) Westerfeld, *J. Biol. Chem.*, **143**, 177 (1942).

(2) Fling, Minard and Fox, THIS JOURNAL, **69**, 2466 (1947).

treated with hydrobromic acid. An over-all yield of 19% was obtained for the bromo-acid. A considerable amount of a high boiling fraction which solidified upon cooling was also isolated. This material was identified as adipic acid by its melting point and neutral equivalent. Marvel and co-workers[3] prepared ε-bromocaproic acid in an over-all yield of approximately 40% by the treatment of δ-phenoxybutyl bromide with ethyl malonate and subsequent decomposition of the diethylphenoxybutyl malonate with hydrobromic acid.

Several unsuccessful attempts were made to isolate the ε-caprolactone from the oxidation step. The excess peroxide was destroyed by the addition of sodium bisulfite and the solution extracted with ether. The ether was evaporated and the residue subjected to vacuum distillation. A violent explosion occurred. This behavior did not parallel the results of Westerfeld who was able to isolate δ-valerolactone. Two subsequent experiments only served to confirm the original observation.

Experimental

To a solution of 600 ml. of 2 *N* NaOH was added alternately with continuous stirring, 114 g. of redistilled cyclohexanone with 300 ml. of 30% hydrogen peroxide (Merck Superoxol). The temperature of the oxidation mixture was held at 45°. Water was distilled from the reaction mixture under diminished pressure until a white pasty residue was formed.

The crude reaction product was treated with 100 ml. of 48% hydrobromic acid solution followed by the slow addition of 100 ml. of concd. sulfuric acid. After gentle refluxing for 3 hours the reaction mixture was diluted with one liter of water and extracted 5 times with ether. Upon evaporation of this ethereal extract 43.6 g. of ε-bromocaproic acid was obtained. It distilled completely at 142-143° (11 mm), m.p. 32.5°. The acid was recrystallized from petroleum ether. *Anal.* Calcd. for $C_6H_{11}O_2Br$: Br. 40.9. Found: Br, 40.3.

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(3) Marvel, *et al.*, This Journal, **46**, 2841 (1924); **49**, 1831 (1927).

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Positive Halogens from Trifluoroacetyl Hypohalites[1]

By Albert L. Henne and William F. Zimmer

CF_3COOBr and CF_3COOI are a source of positive bromine and iodine, respectively, as shown by the fact that they halogenate toluene in the ring in marked preference to or even to the exclusion of the side chain. They are conveniently made by adding the stoichiometric amount of bromine or iodine to a solution of silver trifluoroacetate in an organic solvent: (1) $CF_3CO_2Ag + X_2 \rightarrow AgX\downarrow + CF_3CO_2X$ and (2) $CF_3CO_2X + CH_3C_6H_5 \rightarrow CF_3CO_2H + CH_3C_6H_4X$. Discoloration is a convenient measure of the reaction progress. Trifluoroacetic acid is recoverable.

The positive character of the halogen in these hypohalites is similar to that of the bromine in perfluorinated N-bromosuccinimide $\overline{\mathrm{CO}(\mathrm{CF}_2)_n\mathrm{CON}}\mathrm{Br}$.[2] In both cases, the positive halogen "hangs" from a polarizable atom attached to one or two strongly electronegative perfluoroacetyl groups.

Other acyl hypohalites should, and do show a similar property, but to a smaller extent (CH_3CO_2Br) or in a less convenient form (CCl_3CO_2Br). The solubility of silver trifluoroacetate in organic solvent is of great practical help, and the resistance of the CF_3CO_2 ion to decarboxylation[3] minimizes the importance of the so called Hunsdiecker or Simonini reactions, with formation of CF_3X. Specifically,[4] the reaction $CF_3CO_2Ag + I_2 \rightarrow CO_2 + CF_3I + AgI$ does not occur appreciably below 100°.

A private communication[5] reports that "CF_3CO_2X halogenates benzenic derivatives such as phenol, aniline and benzoic acid in the expected positions." These experiments confirm the ability of X to act in a positive form, yet have no opportunity to show that it does so in preference to acting in atomic form.

Experimental

Iodination of Toluene.—CF_3CO_2Ag[4] (55 g. or 0.25 mole) dissolved in toluene (120 g.) was added dropwise to a slurry of iodine (63.5 g. or 0.25 mole) in toluene (125 g.). Reaction with heat evolution, silver iodide precipitation and formation of CF_3CO_2H fumes was instant. AgI was decanted. Trifluoroacetic acid and the excess of toluene were distilled off. Tolyl iodide (46 g. or 0.21 mole) $n^{20}D$ 1.6005 was then collected about 210°; this is an 84% yield. A small amount was oxidized with chromic acid to give iodobenzoic acid, which after one crystallization from benzene melted at 269–270°, correct for *p*-iodobenzoic acid.

Bromination of Toluene.—A solution of bromine (80 g. or 0.36 mole) in carbon tetrachloride was added to CF_3CO_2Ag (80 g. or 0.36 mole) and toluene (33.1 g. or 0.36 mole) in carbon tetrachloride. Stirring and cooling were maintained throughout the reaction. Working up was as above. Distillation gave tolyl bromide (45 g. or 73%) at 179–181°. A small amount of this was converted to its Grignard derivative and the latter carbonated to methylbenzoic acid; after one crystallization from water, a m.p of 176-178° was observed which denoted *p*-methylbenzoic acid.

Bromination of Methylnaphthalene.—Bromine (32 g. or 0.20 mole) was added in 90 minutes to an ether solution of β-methylnaphthalene (28.5 g. or 0.20 mole) and CF_3CO_2Ag (44.2 g. or 0.20 mole) with constant stirring and cooling in a water-bath. After filtration of AgBr, the filtrate was brown and could not be bleached by a bisulfite wash. Distillation at reduced pressure gave: β-methylnaphthalene, 4.8 g., b. 116–120° (16 mm.), intermediate, 1.3 g., b. 120–140° (16 mm.); α-bromo-β-methylnaphthalene, 26.7 g., b. 107–115° (1.0 to 1.5 mm.); higher boiling fraction, 1.3 g., b. 115–140° (1.0 to 1.5 mm.); residue, 5.4 g. The third fraction (26.7 g. or 0.121 mole) is a 60.5% conversion, or a 77.1% net yield when fraction 1 is taken into count. A small amount of this was converted to its Grignard derivative and carbonated; after one crystallization from benzene, the reaction product melted at 126–127°, denoting β-methyl-α-naphthoic acid.

Testing of Acetyl Hypoiodite.—Silver acetate was mechanically dispersed in an excess of toluene containing an equimolecular amount of iodine; the reaction was slow and required gentle heating to proceed to completion. During the working up, extensive decomposition was observed, with liberation of iodine. The yield of tolyl iodide was only 47.5%, mostly the para-isomer as shown by oxidation to low grade *p*-iodobenzoic acid.

Testing of Trichloroacetyl Hypoiodite.—Preparation of silver trichloroacetate proved inconvenient, light sensitive and beset with silver chloride formation. The reaction was then tried by placing CCl_3CO_2H in an excess of toluene, stirring with silver oxide until neutralized and adding an

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(1) A. L. Henne, Am. Chem. Soc., Chicago Meeting, Sept., 1950, *Abstracts* p. 10L.

(2) A. L. Henne and W. F. Zimmer, *ibid.*, p. 11L; and This Journal, **73**, 1103 (1951).

(3) I. Auerbach, F. Verhoek and A. Henne, *ibid*, **72**, 299 (1950).

(4) A. L. Henne and W. G. Finnegan, *ibid.*, **72**, 3806 (1950).

(5) R. N. Haszeldine, The University, Cambridge, England.

equivalent solution of iodine in toluene. No more than half the expected amount of iodine reacted; the silver precipitate was heavier than computed, and contained silver chloride. Decomposition with iodine evolution occurred during distillation; no tolyl iodide was obtained; a small, charred iodine colored residue remained.

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RECEIVED OCTOBER 17, 1950

Heat Capacity of the Furfuryl Alcohol–Aniline System[1]

BY E. W. HOUGH,[2] D. M. MASON AND B. H. SAGE

The isobaric heat capacities of furfuryl alcohol–aniline mixtures in the liquid phase at compositions from 0.0 to 1.0 weight fraction furfuryl alcohol were determined at bubble-point pressure in a stainless steel bomb calorimeter. Six sets of heat capacity measurements were made for compositions of approximately 0.0, 0.2, 0.4, 0.6, 0.8 and 1.0 weight fraction furfuryl alcohol in the temperature ranges 50 to 175, 30 to 115, 25 to 100, 30 to 95, 30 to 95, and 30 to 65°, respectively. The density of these mixtures was determined for atmospheric pressure at 5, 40, and 70°. The refractive index of these mixtures was determined at 25°.

TABLE I

SMOOTHED VALUES OF ISOBARIC HEAT CAPACITY OF FURFURYL ALCOHOL-ANILINE SYSTEM AT BUBBLE POINT

Composition, weight fraction furfuryl alcohol	Isobaric heat capacity, cal./g., °C. 40°	60°	80°	100°	120°	140°	160°	180°
0.00	0.503	0.511	0.520	0.528	0.536	0.544	0.552	0.561
.10	.502	.511	.520	.529	.537	...	...	...
.20	.501	.511	.521	.530	.539	...	...	...
.30	.501	.512	.522	.531	.541^a	...	...	...
.40	.501	.512	.523	.533	.544^a	...	...	...
.50	.501	.512	.524	.536	.547^a	...	...	...
.60	.501	.513	.526	.538	.551^a	...	...	...
.70	.501	.514	.528	.542	.555^a	...	...	...
.80	.501	.516	.531	.547	.561^a	...	...	...
.90	.501	.517	.535^a	.552^a	.568^a	...	...	...
1.00	.501	.519	.538^a	.557^a	.576^a	...	...	...

^{a} These values are extrapolated.

TABLE II

SMOOTHED VALUES OF DENSITY OF FURFURYL ALCOHOL–ANILINE SYSTEM AT BUBBLE POINT

Composition, weight fraction furfuryl alcohol	Density, g./ml. 10°C.	20°C.	30°C.	40°C.	50°C.	60°C.	70°C.	80°C.	90°C.
0.00	1.033^a	1.023^a	1.014^a	1.006	0.9966	0.9874	0.9785	0.9692	0.9602
.10	1.043	1.034	1.025	1.016	1.007	0.9976	0.9885	0.9794	0.9704
.20	1.054	1.045	1.036	1.027	1.017	1.007	0.9989	0.9898	0.9808
.30	1.065	1.056	1.046	1.038	1.028	1.019	1.009	1.000	0.9909
.40	1.076	1.066	1.057	1.048	1.038	1.029	1.020	1.010	1.001
.50	1.086	1.077	1.068	1.059	1.049	1.039	1.030	1.020	1.011
.60	1.097	1.088	1.078	1.069	1.060	1.050	1.040	1.031	1.021
.70	1.108	1.099	1.090	1.080	1.071	1.061	1.051	1.042	1.038
.80	1.120	1.110	1.101	1.091	1.082	1.072	1.062	1.053	1.044
.90	1.131	1.122	1.112	1.102	1.093	1.084	1.074	1.064	1.055
1.00	1.143^a	1.133^a	1.124	1.114	1.105	1.095	1.086^a	1.076^a	1.067^a

^{a} These values are extrapolated.

Experimental.—A description of the equipment and techniques employed is available.[3,4,5] A stainless steel bomb calorimeter with a volume of approximately 1 liter was suspended by small wires within a vacuum jacket. An electrical heater was used to raise the temperature of the calorimeter and contents. The temperature was established within 0.002° by means of a platinum resistance thermometer. The liquid sample within the calorimeter was agitated by a small centrifugal impeller. (The energy measurements were made in watt-seconds and were converted to gram calories by the relation: 1 thermochemical calorie = 4.1840 abs. joules.)

The apparatus was calibrated[6] by measurements with water for which accurate thermodynamic data are available. The volume of the gas phase was less than 2.5% of the total volume of the calorimeter, and therefore simplifying assumptions in the calculations of the heat capacity from the thermal data are justified at temperatures below 100°.[3]

The furfuryl alcohol and aniline were purified by fractional distillation at reduced pressure in an Oldershaw column. The mixtures were prepared by weighing the constituents and mixing them before introduction into the calorimeter.

Results.—Smoothed values of the isobaric heat capacity of the furfuryl alcohol–aniline system are shown in Table I for compositions from 0.0 to 1.0 weight fraction in the temperature range from 40 to 180°. In Fig. 1 the data are presented graphically and, for comparison, literature

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(1) This paper presents the results of one phase of research carried out for the Jet Propulsion Laboratory, California Institute of Technology, under Contract No. W-04-200-ORD-1482 sponsored by the U. S. Army Ordnance Department.

(2) Stanolind Oil and Gas Company, Tulsa, Oklahoma.

(3) B. H. Sage and E. W. Hough, *Anal. Chem.*, **22**, 1304 (1950).

(4) W. P. White, "The Modern Calorimeter," The Chemical Catalog Co., New York, N. Y., 1928.

(5) N. S. Osborne, H. F. Stimson and E. F. Fiock, *Nat. Bur. Standards, J. Res.*, **5**, 411 (1930).

(6) B. H. Sage and W. N. Lacey, *Trans. Am. Inst. Min. and Met. Engrs.*, **136**, 136 (1940).

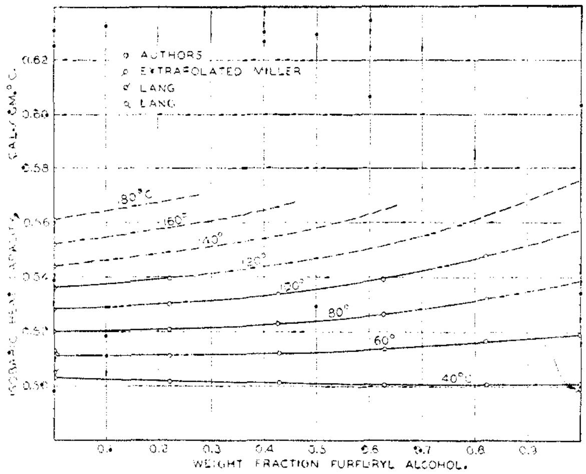

Fig. 1.—Isobaric heat capacity of the furfuryl alcohol–aniline system.

values for pure furfuryl alcohol[7] and aniline[8] are included. The maximum error of these data is estimated to be 1.0%. Density measurements were made with a pycnometer for a number of mixtures at compositions between 0.0 and 1.0 weight fraction furfuryl alcohol at temperatures between 5 and 90°, and the smoothed data are presented in Table II. In Table III is presented the refractive index for several mixtures at compositions between 0.0 and 1.0 weight fraction furfuryl alcohol at 25°. For comparison, data reported in the literature for pure furfuryl alcohol[9] and pure aniline[10] are included.

TABLE III

REFRACTIVE INDEX OF FURFURYL ALCOHOL–ANILINE SYSTEM AT 25°

Composition, weight fraction furfuryl alcohol	Refractive index, λ = 5893 Å.	
	Measured	Literature[9,10]
0.0000	1.5832	1.5863(20°)
.2184	1.5631	....
.4247	1.5433	....
.6248	1.5219	....
.8213	1.5023	....
1.0000	1.4835	1.4843–5

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(7) P. Miller, *Iowa State Coll. J. of Sci.*, **10**, 91 (1936).

(8) H. R. Lang, *Proc. Roy. Soc. (London)*, **A118**, 138 (1928).

(9) Dunlop and Peters, *Ind. Eng. Chem.*, **34**, 814 (1942).

(10) Brühl, *Z. physik. Chem.*, **16**, 193 (1895).

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The Chemistry of Scandium. III[1,2]

BY MORTON J. KLEIN AND PETER M. BERNAYS

The exact nature of the precipitate obtained when a scandium-containing solution is treated with oxalic acid has been the subject of much disagreement in the literature.

Based upon the complete analysis of the salt, Nilson[3] assigned to it the formula $Sc_2(C_2O_4)_3 \cdot 6H_2O$. However, Crookes,[4] who did not determine the scandium oxide, refers varyingly to a mono-, di-, tri- and pentahydrate. Meyer and Winter[5] prepared an oxalate salt whose analysis corresponds closely to that of a tetrahydrate. By precipitating scandium out of acid solution, using oxalic acid or ammonium oxalate, Meyer and Wassjuchnow[6] prepared the pentahydrate. These authors reported no analyses. By far the most careful work was done by Sterba-Böhm. He precipitated the salt from a slightly acid solution at 60° and allowed the crystals to dry in air, excluding all ammonia vapors.[7] The analyses he reports strongly indicate the hexahydrate. The method described below produces pure scandium oxalate hexahydrate.

Experimental

A dilute solution of $ScCl_3$ was heated to 60° and treated with an excess of dilute oxalic acid solution. After 20 minutes, shiny white crystals appeared. Two days drying in air, protected from ammonia vapors, did not yield a homogeneous material. A second batch of crystals were prepared as described above, and dried in a desiccator over anhydrous calcium chloride. After 2 days the material fell apart into a fine powder.

In order to determine the composition of the product, weighed samples were heated in a closed system through which dried nitrogen was passed. The moisture evolved was collected in a phosphorus pentoxide drying tower. Oxalate was determined by the permanganate method, and scandium by the basic tartrate procedure.[8] Typical results are

Preparation no.	Sc, %	$C_2O_4^{=}$, %	H_2O, %
1	19.39	57.10	23.25
2	19.93	57.02	23.77
3	19.60	57.23	23.46
Calcd. for $Sc_2(C_2O_4)_3 \cdot 6H_2O$	19.51	57.11	23.38

All analyses are the average of two or more determinations.

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(1) Paper II, submitted to *Analytical Chemistry*.

(2) Aided by a Frederick Gardner Cottrell grant from the Research Corporation.

(3) L. F. Nilson, *Ber.*, **13**, 1448 (1880).

(4) (a) W. Crookes, *Chem. News*, **98**, 295, 307 (1908); (b) W. Crookes, *Z. anorg. Chem.*, **61**, 368 (1909).

(5) R. J. Meyer and H. Winter, *ibid.*, **67**, 409 (1910).

(6) R. J. Meyer and A. Wassjuchnow, *ibid.*, **86**, 9 (1914).

(7) J. S. Sterba-Böhm, *Coll. Czechoslov. Chem. Comm.*, **1**, 1 (1929).

(8) R. Fresenius and G. Janeler, "Handbuch der Analytischen Chemie," Springer, Berlin, 1942, Part III, p. 734.

DEPARTMENT OF CHEMISTRY
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RECEIVED SEPTEMBER 23, 1950

The Carbonation of Grignard Reagent Solutions

BY ALLEN S. HUSSEY

A convenient technique for the carbonation of Grignard reagents to give high yields of carboxylic acids involves the addition of the Grignard solution to a well-stirred slurry of powdered Dry Ice and dry ether. This procedure[1] permits rapid carbonation at a low temperature, conditions which minimize the secondary reactions which form ketones and tertiary alcohols,[2–5] but has the advantage over the use of powdered Dry Ice[6] in that the reaction mixture can be easily stirred, thus immediately exposing all of the organometallic compound to the action of carbon dioxide.

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(1) The use of an ether–Dry Ice slush in the carbonation of organolithium compounds has been reported by Gilman and Beel, THIS JOURNAL, **71**, 2328 (1949).

(2) F. Bodroux, *Compt. rend.*, **137**, 710 (1903).

(3) D. Iwanov, *Bull. soc. chim.*, **37**, 287 (1925).

(4) H. Gilman and N. St. John, *Rec. trav. chim.*, **49**, 1172 (1930).

(5) The marked effect of these secondary products on the yield of carboxylic acid has been pointed out by C. R. Kinney and M. L. Mayhue, THIS JOURNAL, **53**, 190 (1931).

(6) J. F. Spencer and E. M. Stokes, *J. Chem. Soc.*, **93**, 68 (1908); L. F. Fieser, H. L. Holmes and M. S. Newman, *ibid.*, **58**, 1055 (1936).

Carbonation by this procedure requires about 1.5 kg. of Dry Ice and 600–700 cc. of dry ether per mole of Grignard reagent.[7] Special precautions to exclude moisture when pulverizing the Dry Ice are not necessary. In one experiment, a 65% yield of benzoic acid was obtained when phenylmagnesium bromide was carbonated using wet ether containing enough water to hydrolyze two-thirds of the organometallic compound. The solution can be added rapidly (about 15 minutes per mole) and the reaction mixture can be conveniently hydrolyzed as soon as the excess Dry Ice has evaporated.

Using this procedure, benzoic acid, *p*-methoxybenzoic acid and α-naphthoic acid were obtained in 88–92% of the theoretical.[8] Most of the remainder of the organic halide used could be accounted for as Wurtz coupling product. Cyclopentanecarboxylic acid was prepared in 86% yield. A very small amount of dicyclopentyl ketone apparently was formed, but no aromatic ketones could be detected in the neutral products.

Experimental[9]

An ether solution of phenylmagnesium bromide was prepared from 157 g. of bromobenzene in 400 cc. of anhydrous ether by reaction with 24.5 g. of magnesium turnings in an atmosphere of dry, oxygen-free nitrogen. The solution was blown through a filter-tube extending to the bottom of the flask into a dropping funnel and the flask was rinsed with a little dry ether. This solution was then added over 15 minutes to a well-stirred slurry of 1.5 kg. of powdered Dry Ice[7] and 600 cc. of dry ether in a 3-l. three-neck flask protected from moisture. After the excess Dry Ice had evaporated (about 1 hour), the reaction mixture was carefully acidified with 400 cc. of cold 6 *M* hydrochloric acid. Isolation of the benzoic acid by extraction with dilute ammonia followed by acidification gave 111 g. (91%) of benzoic acid, m.p. 119.3–120.6°, neut. equiv., 120.8.

From the ether solution there was obtained 5.8 g. of crystalline material from which no benzophenone 2,4-dinitrophenylhydrazone could be prepared. Recrystallization from ethyl alcohol gave 4.5 g. (6%) of biphenyl, m.p. 68.1–69.0°.

By the same procedure, *p*-bromoanisole gave 92% of *p*-methoxybenzoic acid, m.p. 183.2–184.5°,[10] and 5% of 4,4′-dimethoxybiphenyl, m.p. 172.0–173.6°.[11] 1-Bromonaphthalene in ether and benzene gave 89% of 1-naphthoic acid, m.p. 159.5–161.0°,[12] 2% of naphthalene (by sublimation from the neutral product), m.p. 79–80°, and 5% binaphthyl, m.p. 156.5–158.1°[13] (from Skellysolve C). Bromocyclopentane gave 86% of cyclopentanecarboxylic acid, b.p. 101–104° at 9 mm., n^{20}_{D} 1.4533,[14] and a small amount of pleasant-smelling lower-boiling material, presumably dicyclopentyl ketone.

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(7) Less Dry Ice is required if the carbonation flask is insulated with asbestos floc or similar material.

(8) Compare H. Gilman and H. H. Parker, *Org. Syntheses*, **5**, 75 (1925); H. Gilman, N. St. John and F. Schulze, *ibid.*, **11**, 80 (1931).

(9) All m.p's. corrected.

(10) A. Oppenheim and S. Pfaff, *Ber.*, **8**, 893 (1875).

(11) A. Gillmeister, *ibid.*, **30**, 2849 (1897).

(12) S. F. Acree, *ibid.*, **37**, 627 (1904).

(13) C. Willgerodt and P. Schlosser, *ibid.*, **33**, 698 (1900).

(14) N. Zelinsky, *ibid.*, **41**, 2627 (1908).

CHEMICAL LABORATORIES
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RECEIVED AUGUST 31, 1950

Refractive Indices for the Methyl Esters of the C_{12}–C_{28} Saturated *n*-Aliphatic Acids

BY CHARLES F. KREWSON

In connection with a recent investigation on the composition of buckwheat leaf meal fat,[1] refractive index values were required for the methyl esters of the even-number saturated fatty acids up to methyl octacosanoate. No data for these compounds above C_{18} were available in the literature. To obtain comparative data, methyl esters of C_{18}-C_{28}[2] acids were prepared by direct esterification of the respective *n*-fatty acids with an excess of absolute methanol, using sulfuric acid as a catalyst. The esters were recrystallized once from ethanol and then from acetone until constant values for refractive indices were obtained. The refractive indices were determined on an Abbe refractometer equipped with a constant-temperature bath and a variable-speed circulating pump. Each recorded value in Table I represents an average of ten readings. The values obtained at 45° for the 12, 14, 16 and 18 carbon atom esters agreed to within 1 or 2 figures in the fourth decimal place of those already reported by Althouse, *et al.*[2] Melting points were taken on a calibrated microscope hot stage.

The identities of these methyl esters were confirmed[3] by comparing the X-ray diffraction patterns with those of Francis and Piper.[4]

TABLE I

MELTING POINTS AND REFRACTIVE INDICES OF METHYL ESTERS OF SATURATED *n*-ALIPHATIC ACIDS

Carbon content of acid	M.p., °C. (cor.) Found	M.p., °C. (cor.) Lit.[4]	Index of refraction 50° Found	Index of refraction 80° Found
12			1.4199	1.4078
14			1.4249	1.4131
16	30.4	30.55	1.4294	1.4173
18	39.0	39.1	1.4328	1.4213
20	46.5	46.6	1.4352	1.4238
22	53.2	53.3		1.4262
24	59.2	58.4		1.4283
26	63.8	63.45		1.4301
28	68.5	67.5		1.4320

EASTERN REGIONAL RESEARCH LABORATORY[5]
PHILADELPHIA 18, PENNA.
RECEIVED SEPTEMBER 28, 1950

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(1) Manuscript in preparation.

(2) P. M. Althouse, G. W. Hunter and H. O. Triebold, *J. Am. Oil Chem. Soc.*, **24**, 257 (1947).

(3) The author wishes to thank E. F. Jordan of this Laboratory for samples of methyl esters of C_{12} and C_{14} *n*-acids; K. S. Markley of the Southern Regional Research Laboratory for samples of *n*-acids, C_{20}–C_{28}; and L. P. Witnauer of this Laboratory for the X-ray examination.

(4) F. Francis and S. H. Piper, THIS JOURNAL, **61**, 577 (1939).

(5) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, U. S. Department of Agriculture. Article not copyrighted.

γ-Chlorobutyraldehyde and its Diethyl Acetal

BY ROBERT BERNER LOFTFIELD[1]

We find that γ-chlorobutyryl chloride is reduced to the aldehyde in very satisfactory yield under usual Rosenmund conditions[2] but not as well by the modified method of Weygand and Meusel.[3] Previously one other haloacid chloride has been reduced by the Rosenmund method, English and

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(1) Chemistry Department, Harvard University, and Medical Laboratories of the Collis P. Huntington Memorial Hospital, Massachusetts General Hospital, Boston, Massachusetts. This is publication No. 728 of the Cancer Commission of Harvard University.

(2) E. B. Hershberg and J. Cason, *Org. Syntheses*, **21**, 84 (1941).

(3) C. Weygand and W. Meusel, *Ber.*, **76**, 502 (1943).

Velick[4] having prepared undecyne-10-al-1 ethyl acetal by reduction of 10,11-dibromoundecanoyl chloride and elimination of hydrogen bromide in 25% over-all yield.

Kharasch[5] has reported that sulfuryl chloride chlorination of butyric acid gives approximately 45% of γ-chlorobutyryl chloride and 45% of the β-chloro isomer. Using essentially his conditions, we obtained the desired γ-chloro compound in 31% yield (based on sulfuryl chloride), but the β-isomer was found only to the extent of 3%. Instead we isolated as much as 21% of α-chlorobutyryl chloride.

This work was supported by an Institutional Grant from the American Cancer Society, Inc., to the Massachusetts General Hospital.

Experimental

A mixture of 600 cc. of carbon tetrachloride, 665 cc. (7.28 moles) of technical butyric acid, 486 cc. (6 moles) of sulfuryl chloride and 10 g. of benzoyl peroxide was refluxed in the dark two hours. The mixture was cooled and 600 cc. (8.3 moles) of thionyl chloride was cautiously added. After eight more hours of refluxing, everything boiling below 100° (40 mm.) was removed by distillation. Redistillation through an 18-plate column gave the following fractions: 174 g. of **butyryl chloride**, b.p. 46–47.5° (100 mm.); 170 g. of **α-chlorobutyryl chloride**, b.p. 44–49° (40 mm.); 28 g. of **β-chlorobutyryl chloride**, b.p. 64–68° (40 mm.); and 263 g. of **γ-chlorobutyryl chloride**, b.p. 83–90° (40 mm.).

γ-Chlorobutyraldehyde.—A mixture of 168 g. (1.19 moles) of γ-chlorobutyryl chloride, 900 cc. of toluene, 16 g. of palladium–barium sulfate catalyst[2] and 1.66 cc. of poison[2] was refluxed and vigorously stirred in a two-liter, 3-neck flask. Hydrogen was passed through and the effluent gas bubbled through water. After nine hours the evolution of hydrogen chloride ceased at 94% of the theoretical. The toluene was washed with water, twice with sodium bicarbonate solution and twice more with water. Distillation through a Vigreux column at 35 mm. gave 58 g. (46%) of **γ-chlorobutyraldehyde**, b.p. 69–70° (35 mm.), $n^{20}\text{D}$ 1.4480. The dinitrophenylhydrazone recrystallized from alcohol had m.p. 130–131°.[6]

Anal. Calcd. for $C_{10}H_{11}O_4N_4Cl$: C, 41.89; H, 3.87. Found: C, 42.20; H, 3.65.

γ-Chlorobutyraldehyde Diethyl Acetal.—The aldehyde could be converted to the diethyl acetal in 63% yield by reaction with five parts of ethanol and calcium chloride. Better over-all yields were obtained if the aldehyde was not isolated. Thus, 250 cc. of absolute ethanol and 50 g. of calcium chloride were added to the cold Rosenmund reduction mixture and stirring was continued 16 hours. The mixture was filtered, the phases separated and the upper layer washed twice with sodium bicarbonate solution and once with water. Water was removed by brief boiling. Distillation yielded 118 g. (55% based on the acid chloride) of γ-chlorobutyraldehyde diethylacetal, b.p. 89–92° (14 mm.).

Anal. Calcd. for $C_8H_{17}O_2Cl$: C, 53.19; H, 9.49. Found: C, 53.76; H, 9.49.

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(4) J. English and S. F. Velick, THIS JOURNAL, **67**, 1413 (1945).

(5) M. Kharasch and H. Brown, *ibid.*, **62**, 925 (1940).

(6) R. Paul and S. Tchelitcheff (*Bull. soc. chim.*, [5] **15**, 197 (1948)) report a melting point of 135° for this dinitrophenyl hydrazone.

MASS. GEN. HOSP.
BOSTON, MASS.
RECEIVED OCTOBER 23, 1950

Pentafluorobenzoic Acid

BY E. T. MCBEE AND EDWARD RAPKIN

Pentafluorobenzoic acid has been synthesized in low yield by sulfuric acid hydrolysis of perfluorotoluene according to the method of LeFave.[1] The slow rate of hydrolysis and the low yield obtained may be attributed to the relatively low boiling point (103°) of the fluorocarbon as well as to its lack of solubility in sulfuric acid. Even with rapid stirring two layers were still apparent and neither the reaction rate nor the yield were appreciably increased.

Reduction of pentafluorobenzoic acid with lithium aluminum hydride gave pentafluorobenzyl alcohol in good yield. The alcohol was not isolated but was converted to the corresponding *p*-nitrobenzoate and isolated as such.

Experimental[2]

Pentafluorobenzoic Acid.—A mixture of 10 g. (0.042 mole) of perfluorotoluene[3] and 30 g. of concd. sulfuric acid was stirred vigorously at reflux temperature for one week. During this period the lower acid layer became black while the unreacted fluorocarbon layer remained colorless. Hydrogen fluoride evolution was extremely slow.

When the fluorocarbon layer had completely disappeared the black acid solution was poured on ice, diluted with water to a volume of 250 ml., and boiled with Norite for several minutes. After filtration, the resulting colorless solution was ether extracted and the extract dried with Drierite. Evaporation of the ether gave white crystals of pentafluorobenzoic acid. While the material can be recrystallized from water, a mixture of petroleum ether (90–100°) diluted with some toluene proved more satisfactory. From this solvent pair 2.2 g. (25% yield) of large square plates of pentafluorobenzoic acid, m.p. 106–107°, was obtained.

Anal. Calcd. for $C_7HF_5O_2$: C, 39.6; H, 0.47. Found: C, 39.4; H, 0.47.

Pentafluorobenzyl *p*-Nitrobenzoate.—Pentafluorobenzoic acid (0.5 g.) was added to a refluxing mixture of lithium aluminum hydride (0.5 g.) and 10 ml. of ether. The mixture was hydrolyzed with excess dilute hydrochloric acid and the ether layer removed and dried. Evaporation of the ether left a colorless, pleasant-smelling oil. This oil was converted to the *p*-nitrobenzoate (0.63 g.) which was alternately recrystallized four times from alcohol and petroleum ether (90–100°). The colorless crystals sintered at 108° and melted at 110–112°.

Anal. Calcd. for $C_{14}H_6F_5NO_4$: C, 48.4; H, 1.73; N, 4.03. Found: C, 48.6; H, 1.85; N, 4.11.

Acknowledgment.—The authors are indebted to the Moorman Manufacturing Co., Quincy, Ill., for financial support which made this work possible.

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(1) G. M. LeFave, THIS JOURNAL, **71**, 4148 (1949).

(2) Microanalyses by Dr. H. Galbraith.

(3) E. T. McBee, V. V. Lindgren and W. B. Ligett, *Ind. Eng. Chem.* **39**, 378 (1947).

PURDUE RESEARCH FOUNDATION AND
DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
W. LAFAYETTE, IND.
RECEIVED OCTOBER 21, 1950

Some Azoproteins and Their Isoelectric Points[1]

BY R. L. MCGEACHIN AND B. D. ASHLEY

Haurowitz[2] found that the introduction into proteins of azophenyl radicals containing acidic groups gave azoproteins whose isoelectric points were lower than those of the original proteins. We have coupled casein, ovalbumin, pumpkin seed globulin and beef serum protein with excess diazotized *p*-arsanilic acid and determined the isoelectric points of these azoproteins. In all cases, the isoelectric point of the azoprotein was lower than that of the original protein, confirming Haurowitz's findings on

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(1) Taken from the M. S. thesis of B. D. Ashley.

(2) F. Haurowitz, *Kolloid Z.*, **74**, 208 (1936).

other proteins. The greatest change in isoelectric point (from 4.6 to 3.2) was found in the azocasein, the product containing the most arsenic. This is to be expected since the isoelectric point of a protein is at least partially determined by the numbers of free acidic and basic groups.

Our results on the coupling of casein seem to agree with those of Kapeller-Adler and Boxer[3] who found an arsenic content of 8.20% (8.10, 8.19, 8.33), when an excess of diazotized *p*-arsanilic acid was used. Our product contained an average of 8.32% arsenic (8.10, 8.55).

Experimental

4-Arsonophenylazoproteins.—Casein, ovalbumin, pumpkin seed globulin and beef serum protein were coupled with *excess* diazotized *p*-arsanilic acid following the method of Landsteiner and van der Scheer.[4]

Anal.[5] Azocasein, Found: As, 8.10, 8.55. Azovalbumin, Found: As, 3.62, 3.43. Azopumpkin seed globulin, Found: As, 6.22. Azobeef serum protein, Found: As, 3.56.

Isoelectric point determinations on both the original proteins and the azoproteins were carried out using the method of Hawk, Oser and Summerson.[6]

ISOELECTRIC POINTS

	Original protein	Azoprotein
Casein	4.6	3.2
Ovalbumin	5.2	4.3
Pumpkin seed globulin	5.3	4.6
Beef serum protein	>6.2	<6.2

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(3) R. Kapeller-Adler and G. Boxer, *Biochem. Z.*, **285**, 55 (1936).

(4) K. Landsteiner and J. van der Scheer, *J. Exp. Med.*, **45**, 1045 (1927).

(5) A modification of the method of F. E. Cislak and C. S. Hamilton, THIS JOURNAL, **52**, 638 (1930), was used in the arsenic analyses.

(6) P. B. Hawk, B. L. Oser and W. H. Summerson, "Practical Physiological Chemistry," Twelfth Edition, The Blakiston Company, Philadelphia, Pa., 1947, p. 160.

DEPARTMENT OF BIOCHEMISTRY
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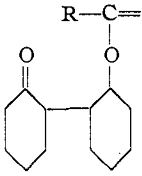
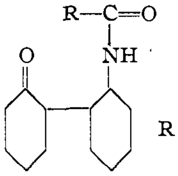
LOUISVILLE, KY.
RECEIVED SEPTEMBER 18, 1950

Acid-catalyzed Reactions of Nitriles. IV. Condensation of Cyclohexanone with Nitriles

BY EUGENE E. MAGAT

In a recent communication, Bruson, Riener and Riener[1a] have shown that cyclohexanone condenses with nitriles, in the presence of aluminum chloride, to yield compounds whose properties have suggested that they are imino-ethers of the aldol of cyclohexanone having the general formula (I). It is the purpose of this paper to report evidence which indicates that the products are in reality the isomeric amides of 1-(2-oxocyclohexyl)-cyclohexylamine (II).[1b]


(I)


(II)

R = CH_3

The following properties of the reaction product contradict the assignment of structure (I).

(1) Tertiary alcohols do not form imino-ethers as do primary and secondary alcohols; the tertiary alcohols rather lose water to form unsaturated compounds.[2] (2) Imino-ethers are usually unstable at high temperatures and gradually decompose to the original nitrile and alcohol,[3] whereas the condensation product can be distilled at 175–225° at 0.5–1 mm. without decomposition. (3) Imino-ethers are basic compounds which form stable salts with acids. If the condensation product were an imino-ether it should be necessary to neutralize the hydrochloric acid salt, which would form in the presence of aluminum chloride, before isolating the free imino-ether. However, no neutralization step is necessary in the isolation of (I). (4) The infrared absorption spectrum of the condensation product shows bands at 3.03, 3.25, 6.00 and 6.45 microns characteristic of the peptide linkage –CO–NH–.[4] These bands are sufficiently intense to show a high concentration of –CO–NH– groups. The infrared spectrum is shown in Fig. 1.

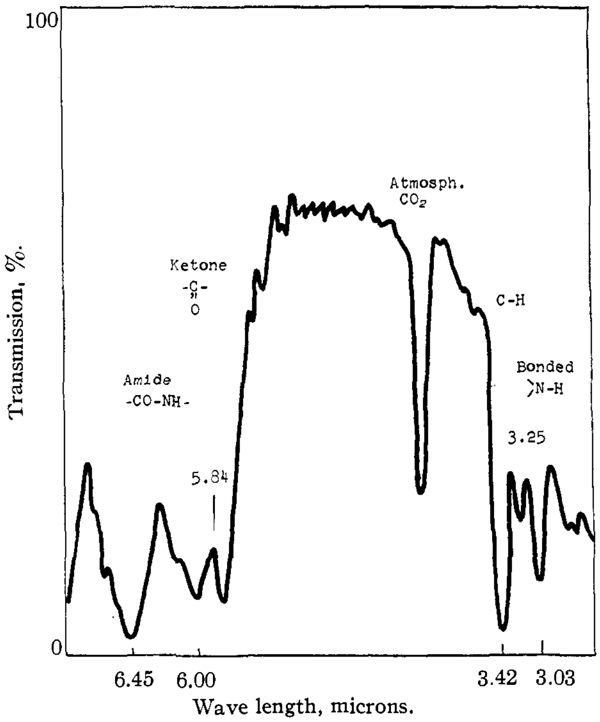


Fig. 1.—Infrared spectrum of reaction product of acetonitrile and cyclohexanone, 0.001 inch thick. Tracings of spectra recorded on Perkin-Elmer Infrared Spectrometer Model 12C with rock-salt prism in accordance with instruction manual.

These properties are in accord with structure (II). In addition, the following properties of the reaction product are also in accord with structure (II): (a) Ketone derivatives are formed. (b) Amides are, in general, soluble in concentrated hydrochloric acid and are reprecipitated unchanged

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(1) (a) Bruson, Riener and Riener, THIS JOURNAL, **70**, 483 (1948); (b) A similar formulation has been suggested by Mowry and Ringwald, *ibid.*, **72**, 4439 (1950).

(2) Migrdichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold Publishing Corp., New York, N. Y., 1947, p. 86.

(3) *Ibid.*, p. 84.

(4) Richards and Thompson, *J. Chem. Soc.*, 1248 (1947).

upon dilution with water. (c) Amides of primary amines where the amino group is attached to a tertiary carbon atom yield an olefin, an acid and ammonia upon steam distillation with 10% sulfuric acid.[5]

Cyclohexanone probably goes to cyclohexenylcyclohexanone in the presence of aluminum chloride and the condensation of cyclohexenylcyclohexanone and a nitrile is similar to the reaction of cyclohexene with hydrogen cyanide in the presence of aluminum chloride to give a 30% yield of N-formylcyclohexylamine[6] and to the reaction of nitriles and tertiary olefins to give N-tertiary alkyl amides.[5]

Acknowledgment.—The assistance of Dr. J. R. Downing of the Chemical Department, E. I. du Pont de Nemours and Company, Inc., is gratefully acknowledged for the interpretation of the infrared data.

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(5) Ritter and Minieri, THIS JOURNAL, **70**, 4045 (1948).

(6) Wieland and Dorrer, *Ber.*, **63**, 404 (1930).

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WILMINGTON, DELAWARE
RECEIVED OCTOBER 11, 1950

Methyl *n*-Propyl Ketone and its Conversion to *n*-Propylpyridine

BY RAYMOND P. MARIELLA AND ROGER STANSFIELD

In agreement with earlier workers,[1-4] ethyl formate was found to condense with the methyl group of methyl *n*-propyl ketone in the presence of sodium. This was established by converting the product (I) into the pyridone (II) and subsequent degradation to *n*-propylpyridine.

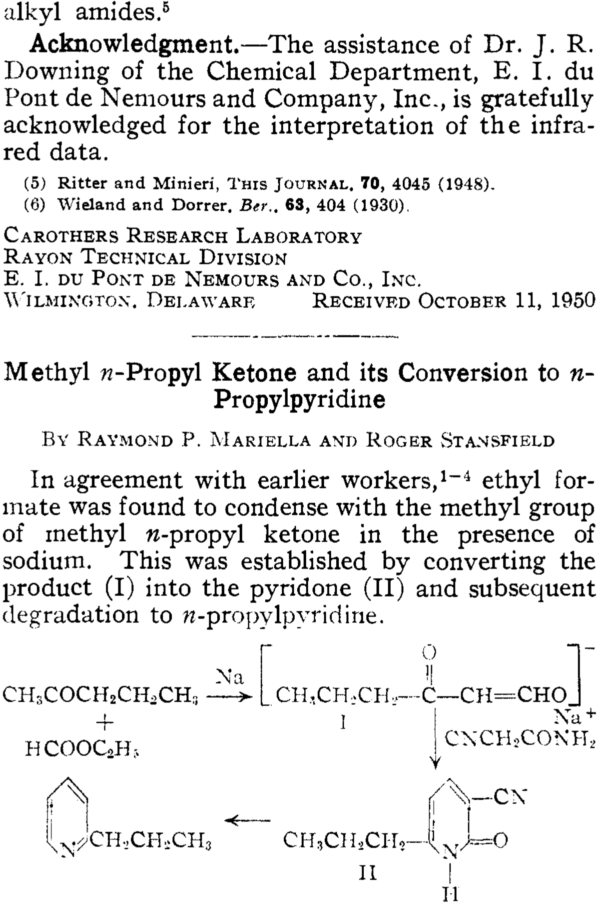

Fig. 1.

However, the condensation might have occurred partly at the methylene group, since the pyridone (II) could not be isolated in better than a 37% yield. The condensation product (I) was obtained in a 74% yield. These results are interesting because the previous workers had indicated that the methyl group was the only site of condensation. It was possible to isolate the free hydroxymethylene ketone as a colorless liquid, but in a poor yield (13%), as it decomposed rapidly.

Experimental[5]

Since the experimental details parallel those published before,[6] only the essential features will be mentioned.

3-Cyano-6-*n*-propyl-2(1)-pyridone (II).—From 46 g. of sodium metal ribbon in 1.5 l. of dry ether, by the addition of 172 g. of methyl *n*-propyl ketone (b.p. 101.3° at 752 mm.) and 148 g. of ethyl formate, there was obtained 200 g. (74% yield) of crude sodium salts as a yellow powder.

A solution of 136 g. of the above sodium salt and 90 g. of cyanoacetamide in 500 ml. of water, containing piperidine acetate catalyst, after refluxing for 3 hours, gave 100 g. of crude brown product.

A sample was recrystallized several times from absolute alcohol and resulted in white needles, m.p. 153°.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.24; H, 6.18; N, 17.2. Found: C, 66.23; H, 6.41; N, 16.9.

The 100 g. obtained above represented very crude material since the m.p. was over a wide range, 120–145°. One recrystallization and treatment with Norit gave 60 g. (37% yield) of yellow prisms, m.p. 142–148°. An investigation of the mother liquor showed the presence of a dark-brown solid, softening in the range 50–110°, which appeared to be a complex mixture. Many attempts at purification using alcohol, acetone or glacial acetic acid as crystallizing solvents did not improve the melting point.

The Free Hydroxymethylene Ketone.—Fifteen grams of sodium salt was treated with excess sulfuric acid and shaken with ether. The ether was dried and removed *in vacuo*, leaving a dark-red liquid. Distillation gave 1.7 g. (13% yield) of colorless liquid, b.p. 51° at 16 mm., n^{24}_{D} 1.4190 and d^{24}_{4} 1.009. This liquid rapidly darkened.

6-*n*-Propyl-2(1)-pyridone-3-carboxylic Acid.—A solution of 50 g. of recrystallized cyanopyridone (II) in 500 ml. of concentrated hydrochloric acid was refluxed for 6 hours and gave 49 g. (88%) of the acid. A sample was recrystallized several times from water, colorless powder, m.p. 160°.

Anal. Calcd. for $C_9H_{11}NO_3$: N, 7.7. Found: N, 7.8.

6-*n*-Propyl-2-pyridol.—From 31 g. of pyridone acid, by heating at 335° for 15 minutes, there was obtained 21.5 g. (92%) of colorless long needles. Sublimation produced short needles, m.p. 88–89°.

Anal. Calcd. for $C_8H_{11}NO$: N, 10.2. Found: N, 10.4.

6-Chloro-2-*n*-propylpyridine.—From a solution of 20 g. of pyridol and 33 g. of phosphorus pentachloride in 25 ml. of phosphorus oxychloride, there was obtained 7 g. (33%) of a colorless liquid, b.p. 81.0–81.2° at 6 mm., n^{20}_{D} 1.5164, n^{25}_{D} 1.5135 and d^{25}_{25} 1.073.

Anal. Calcd. for $C_8H_{10}ClN$: N, 9.0. Found: N, 8.6.

2-*n*-Propylpyridine.—From 6.5 g. of the chloropyridine, using palladium-on-charcoal in acid solution, there was obtained 6.0 g. (92%) of colorless needles of 2-*n*-propylpyridine hydrochloride. The free base had the following physical constants: b.p. 166–167° at 750 mm., d^{25}_{25} 0.912, and n^{20}_{D} 1.4925. The derivatives had the following melting points: picrate 74°, chloroplatinate 161–162° and chloroaurate, 77–80°, and did not depress the m.p. of authentic samples.[7]

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(1) L. Claisen and N. Stylos, *Ber.*, **21**, 1148 (1888).

(2) E. Benary, H. Meyer and K. Charisius, *ibid.*, **59**, 110 (1926).

(3) E. Benary, *ibid.*, **59**, 600 (1926).

(4) W. Gruber and H. Schlogl, *Monatsh.*, **81**, 83 (1950).

(5) Analyses by Misses Virginia Hobbs and Margaret Hines.

(6) R. P. Mariella, THIS JOURNAL, **69**, 2670 (1947).

(7) R. P. Mariella, L. Peterson and R. Ferris, *ibid.*, **70**, 1494 (1948).

CHEMICAL LABORATORY
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RECEIVED OCTOBER 26, 1950

Quinoxaline Studies. II. The Preparation of 2-Hydroxy-3,6-dimethylquinoxaline and 2-Hydroxy-3,7-dimethylquinoxaline

BY BURTON MARKS[1] AND HARRY P. SCHULTZ

The condensation of 3,4-diaminotoluene with pyruvic acid was reported by Hinsberg[2] to produce a quinoxaline of undetermined structure melting at 220°. A low yield of another quinoxaline, m.p. 238°, presumably 2-hydroxy-3,7-dimethylquinoxa-

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(1) Abstracted in part from a thesis by Burton Marks, presented to the Graduate Faculty of the University of Miami, in partial fulfillment of the requirements for the degree of Master of Science in chemistry, August, 1950.

(2) O. Hinsberg, *Ann.*, **237**, 351 (1887).

line, resulted from the condensation of 3,4-diaminotoluene with ethyl α-bromopropionate.[3]

We have prepared by unequivocal means both 2-hydroxy-3,6-dimethylquinoxaline and 2-hydroxy-3,7-dimethylquinoxaline. The former melts at 254–255°, and the latter at 243–244° (reported[4] 237°).

The material melting at 220° described by Hinsberg[2] appears to be an eutectic of the above two isomers. A melting point diagram of these two substances is given in Fig. 1.

2-Hydroxy-3,6-dimethylquinoxaline was prepared from 3-nitro-4-acetamidotoluene. 3-Amino-4-acetamidotoluene was prepared by reduction of 3-nitro-4-acetamidotoluene over palladium-charcoal. Poor yields of the isolated 3-amino-4-acetamidotoluene resulted, due to cyclization of the amine to 2,6-dimethylbenzimidazole when the reduction solvent was removed. Hence, except for preliminary investigations, the reduced product was not isolated.

3-Amino-4-acetamidotoluene was condensed with ethyl α-bromopropionate to give the ethyl ester of N-(2-acetamido-5-methylphenyl)-*dl*-α-alanine. Hydrolysis and cyclization of this ester were completed in acid solution. The intermediate dihydroquinoxaline was oxidized in basic solution with hydrogen peroxide to 2-hydroxy-3,6-dimethylquinoxaline.

The synthesis of 2-hydroxy-3,7-dimethylquinoxaline was effected by a shorter procedure than that employed by Hinsberg.[4] The condensation of 3-nitro-4-aminotoluene with α-bromopropionic acid gave N-(2-nitro-4-methylphenyl)-*dl*-α-alanine. This product was reduced over palladium-charcoal to 2-hydroxy-3,7-dimethyldihydroquinoxaline. The dihydro compound was not isolated, but was air-oxidized to 2-hydroxy-3,7-dimethylquinoxaline.

A preparation was carried out using Hinsberg's procedure[2] wherein 3,4-diaminotoluene was treated with pyruvic acid. The Hinsberg product obtained in this Laboratory was a mixture of 2-hydroxy-3,6-dimethylquinoxaline and 2-hydroxy-3,7-dimethylquinoxaline melting at 214–215°. Eight recrystallizations of this product from ethanol gave a small yield of the slightly less soluble 2-hydroxy-3,7-dimethylquinoxaline.

Hinsberg's condensation[3] of 3,4-diaminotoluene with ethyl α-bromopropionate was repeated, but his numerous recrystallizations of the impure condensation product were avoided by utilizing methods of purification which restricted recrystallizations from organic solvents. Obvious enrichment of the mixed isomers mentioned in the preceding paragraph was thereby circumvented. The melting point (222–228°) and mixed melting points of this reaction product with each of the pure isomers indicated a mixture in which there was more 2-hydroxy-3,7-dimethylquinoxaline than 2-hydroxy-3,6-dimethylquinoxaline.

Experimental Procedures

Ethyl Ester of N-(2-Acetamido-5-methylphenyl)-*dl*-α-alanine.—Into 75 ml. of ethanol was placed 19.4 g. (0.1 mole) of 3-nitro-4-acetamidotoluene[5] and 1 g. of 5% palladium chloride on charcoal.[6] The theoretical quantity of hydrogen was absorbed at 30° and four atmospheres in 1 hour. The reduction solution containing 3-amino-4-acetamidotoluene[7] was filtered and 120 ml. of water and 9.23 g. (0.051 mole) of ethyl α-bromopropionate[8] were added. The reaction mixture was heated on a steam-bath for 5 hours, then poured into 500 ml. of water. After 12 hours at 5° a precipitate of 8.42 g. (63% yield) of gray powder was obtained, m.p. 124–126°. The material was recrystallized from ethanol-water with negligible loss to give the ethyl ester of N-(2-acetamido-5-methylphenyl)-*dl*-α-alanine, m.p. 126.8–127.1°.

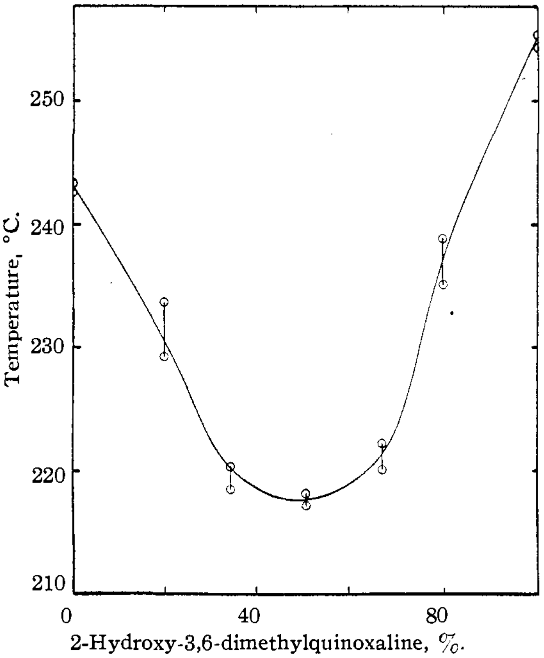

Fig. 1.—Melting point–composition curve of 2-hydroxy-3,6-dimethylquinoxaline and 2-hydroxy-3,7-dimethylquinoxaline; melting point range of each mixture indicated by O—O.

Anal. Calcd. for $C_{14}H_{20}O_3N_2$: N, 10.6. Found: N, 10.5.

3-Amino-4-acetamidotoluene could be isolated in only 10% yield from the reduction solution of 3-nitro-4-acetamidotoluene; 2,6-dimethylbenzimidazole was obtained in great quantity. When the isolated amine was condensed with ethyl α-bromopropionate, a 74% yield of the ethyl ester of N-(2-acetamido-5-methylphenyl)-*dl*-α-alanine melting at 126.8–127.1° was obtained. Analysis and mixed melting point proved the identity of the material prepared by the two different procedures.

2-Hydroxy-3,6-dimethylquinoxaline.—A mixture of 8.42 g. (0.032 mole) of the ethyl ester of N-(2-acetamido-5-methylphenyl)-*dl*-α-alanine, 50 ml. of water and 50 ml. of concd. sulfuric acid was stirred on a steam-bath for 4 hours. After cooling and neutralizing the solution, the precipitate was filtered and heated on a steam-bath for 2 hours in a solution of 15 ml. of 8% sodium hydroxide mixed with 15 ml. of 3% hydrogen peroxide solution. Again the solution was cooled and brought to *p*H 4 to give 0.9 g. of yellow crystals, m.p. 245–249°. For analysis the material was sublimed at 150° (1 mm.), then recrystallized from ethanol-water to give 0.5 g. (9% yield) of white crystals, m.p. 254–255°. (All melting points of these quinoxalines were obtained by placing the capillary melting point tube in an aluminum block 5 to 7° below the melting point to avoid extensive sublimation of the material.)

Anal. Calcd. for $C_{10}H_{10}ON_2$: N, 16.1. Found: N, 16.0.

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[3] O. Hinsberg, *Ann.*, **248**, 77 (1888).

[4] O. Hinsberg, *Ber.*, **25**, 2419 (1892).

[5] A. McGookin and S. R. Swift, *J. Soc. Chem. Ind.*, **58**, 152 (1939).

[6] R. Mozingo, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1946, p. 78.

[7] G. T. Morgan and F. M. G. Micklethwait, *J. Chem. Soc.*, **103**, 1397 (1913).

[8] N. Zelinsky, *Ber.*, **20**, 2026 (1887).

N-(2-Nitro-4-methylphenyl)-*dl*-α-alanine.—A mixture of 7.6 g. (0.05 mole) of 3-nitro-4-aminotoluene[5] and 3.83 g. (0.021 mole) of α-bromopropionic acid[9] was heated for 8 hours on a steam-bath. The cooled melt was extracted with 20 ml. of 15% ammonium hydroxide. The ammonium hydroxide solution was treated with charcoal, then acidified with 10% hydrochloric acid to give 2.1 g. of red crystals, m.p. 142–144°. Repetition of the above purification gave 1.8 g. (38% yield) of N-(2-nitro-4-methylphenyl)-*dl*-α-alanine, m.p. 149.5–150°. Hinsberg[4] prepared this compound by a different process, reporting a melting point of 148°.

2-Hydroxy-3,7-dimethylquinoxaline.—A solution of 2.65 g. (0.012 mole) of N-(2-nitro-4-methylphenyl)-*dl*-α-alanine in 40 ml. of ethanol was reduced over palladium–charcoal at 30° and two atmospheres of hydrogen until the theoretical quantity of hydrogen had been absorbed. Catalyst and solvent were removed, and the tan residue was dissolved in 35 ml. of 10% sodium hydroxide solution and oxidized by drawing air through the solution for 18 hours at 70–80°. The solution was cooled and clarified by filtration; the filtrate was brought to *p*H 4 with acetic acid, precipitating 2-hydroxy-3,7-dimethylquinoxaline. The precipitate was sublimed at 150° (1 mm.) to give 0.9 g. (43% yield) of white sublimate, m.p. 240–241°. The material was crystallized from ethanol–water to constant melting point with no appreciable loss of product, m.p. 243–244°. The melting point previously reported[4] was 237°.

Anal. Calcd. for $C_{12}H_{10}N_2O$: N, 16.1. Found: N, 16.1.

Absorption Spectra.—The ultraviolet absorption spectra in Fig. 2 were obtained on a Beckman model DU quartz spectrophotometer. All curves were run on analytical material at concentrations of 10 mg./l. of solvent; width of quartz sample cell was 1.003 cm.

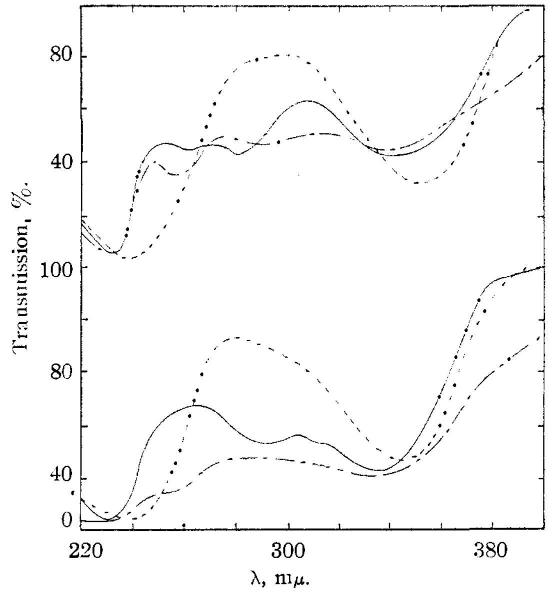

Fig. 2.—Ultraviolet absorption spectra of 2-hydroxy-3,6-dimethylquinoxaline, upper: 2-hydroxy-3,7-dimethylquinoxaline, lower; —, 95% ethanol; ------, 0.1 *N* sodium hydroxide; -·-·-·- 0.1 *N* hydrochloric acid.

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(9) Eastman Kodak Company White Label material.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MIAMI
CORAL GABLES, FLORIDA

RECEIVED SEPTEMBER 19, 1950

The Preparation of N-Alkylethylenediamines

BY RUSSELL C. O'GEE AND HENRY M. WOODBURN[1]

N-Alkylethylenediamines are desirable intermediates for certain types of organic synthesis but their preparation has been unsatisfactory because of poor yields, complicated procedures, or methods limited to a specific type of substituent.

The situation has been reviewed by Aspinall[2] and by Coleman and Callen[3] both of whom proposed methods of their own. The first requires preliminary preparation of monoacetylethylenediamine and its N-benzenesulfonyl derivative and gives over-all yields of 10–33%. The second employs the catalytic addition of primary and secondary amines to ethylenimine, the reaction being favored by elevated temperatures. Actually, the only primary amines described are aniline and benzylamine.

The recent offering of 2-bromoethylamine hydrobromide in commercial quantities[4] suggested investigation of the reaction

$$RNH_2 + BrCH_2CH_2NH_2{\cdot}HBr \longrightarrow RNHCH_2CH_2NH_2 + 2HBr$$

as a source of N-alkylethylenediamines. The reaction proved to be straightforward and easily carried out. Yields from both normal and branched-chain aliphatic primary amines are quite acceptable and the reaction has the double advantage of simplicity and the use of easily available reagents. Results of the investigation are summarized in Table I.

TABLE I

N-ALKYLETHYLENEDIAMINES ($RNHCH_2CH_2NH_2$)

					Derivatives			
		B.p.,[a] observed			Dihydrochloride m.p., °C.		Dipicrate m.p., °C.	
R	Yield, %	°C.	Mm.	Ref.	Obsd.	Ref.	Obsd.	Ref.
CH_3	41	113–115	748	(2)	131	(5)	222–223	(5)
C_2H_5	40	125–127	743	(2)	168		193–194	(2)
n-C_3H_7	38	153–154	749	(6)	204–205		167–168[b]	(6)
i-C_3H_7	35	137–138	752	(7)	122–123		192–193	
n-C_4H_9	52	76–78	25	(6)	230	(5)	177	

[a] B.p.'s and m.p.'s uncorrected. [b] King and McMillan[6] report 224°. Our figure is supported by the following analysis: Calcd. for $C_5H_{14}N_2{\cdot}2C_6H_3N_3O_7$: C, 36.4; H, 3.6. Found: C, 36.6; H, 3.7.

Experimental

A solution of 102.5 g. (0.5 mole) of 2-bromoethylamine hydrobromide in 100 ml. of water was added to a 25% aqueous solution containing 2.5 moles of alkylamine. The resulting mixture was refluxed gently for 12 hours. It was then cooled and treated with solid sodium hydroxide until the base no longer dissolved. The solution separated into two layers as it became alkaline. The upper layer was taken off and the lower layer extracted with ether. The combined upper layer and extracts were dried over anhydrous potassium carbonate and fractionated through a 12″ column packed with glass helices.

The dihydrochlorides and dipicrates were made as an additional check on the identity of the diamines. The hydrochlorides not previously reported were analyzed for chlorine by the Mohr method. New picrates were analyzed for carbon and hydrogen by semi-micro carbon combustion technique.

N-Ethylethylenediamine dihydrochloride: Calcd. for $C_4H_{12}N_2{\cdot}2HCl$: Cl, 44.1. Found: Cl, 44.3.

N-Propylethylenediamine dihydrochloride: Calcd. for $C_5H_{14}N_2{\cdot}2HCl$: Cl, 40.6. Found: Cl, 40.7.

N-Isopropylethylenediamine dihydrochloride: Calcd. for $C_5H_{14}N_2{\cdot}2HCl$: Cl, 40.6. Found: Cl, 40.6.

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

(2) Aspinall, THIS JOURNAL, **63**, 852 (1941).

(3) Coleman and Callen, *ibid.*, **68**, 2006 (1946).

(4) Dow Chemical Co., Midland, Michigan.

(5) Johnson and Bailey, THIS JOURNAL, **38**, 2135 (1916).

(6) King and McMillan, *ibid.*, **68**, 1774 (1946).

(7) Pearson, Jones and Cope, *ibid.*, **68**, 1225 (1946).

N-Isopropylethylenediamine dipicrate: Calcd. for $C_6H_{14}N_2 \cdot 2C_6H_3N_3O_7$: C, 36.4; H, 3.6. Found: C, 36.7; H, 4.1.

N-Butylethylenediamine dipicrate: Calcd. for $C_6H_{16}N_2 \cdot 2C_6H_3N_3O_7$: C, 37.6; H, 3.8. Found: C, 37.3; H, 4.0.

Grateful acknowledgment is made to the Dow Chemical Co. which furnished a sample of 2-bromoethylamine hydrobromide, and to Sharples Chemicals, Inc., which furnished the *n*-propylamine.

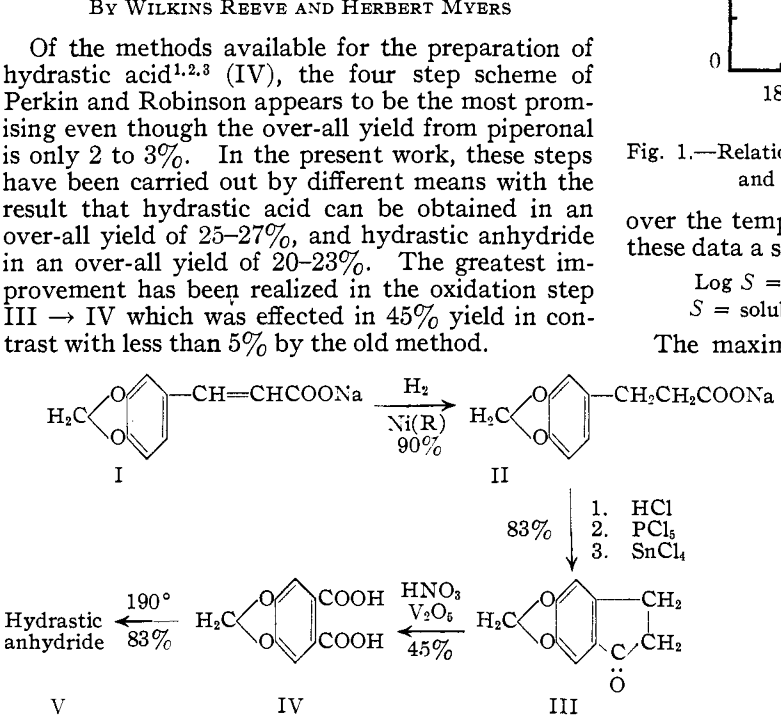
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF BUFFALO
BUFFALO, NEW YORK

RECEIVED OCTOBER 6, 1950

The Synthesis of Hydrastic Acid

BY WILKINS REEVE AND HERBERT MYERS

Of the methods available for the preparation of hydrastic acid[1,2,3] (IV), the four step scheme of Perkin and Robinson appears to be the most promising even though the over-all yield from piperonal is only 2 to 3%. In the present work, these steps have been carried out by different means with the result that hydrastic acid can be obtained in an over-all yield of 25–27%, and hydrastic anhydride in an over-all yield of 20–23%. The greatest improvement has been realized in the oxidation step III → IV which was effected in 45% yield in contrast with less than 5% by the old method.



Melting points ranging from 172 to 188°[1,4] have been reported for hydrastic acid. We have found its melting point to be approximately 225° by a procedure which corrects for the lowering of the observed melting point occurring, due to decomposition, during the time the melting point sample is heated. The time necessary for the sample to melt when placed in a bath at a given temperature is plotted against the temperature as shown in Fig. 1. The straight line AB represents the time required for the heat to flow through the capillary tube and the sample; the temperature of immediate melting is where the lines meet. This procedure may prove useful with other thermally unstable materials.

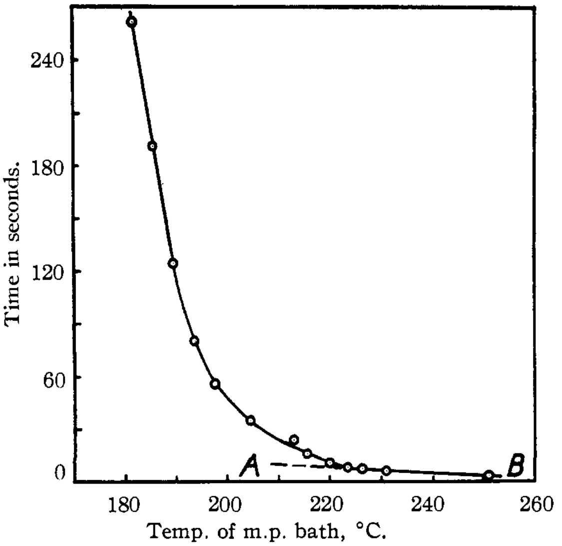


Fig. 1.—Relationship between m.p. of pure hydrastic acid and time sample is in the m.p. bath.

In view of the unsuitability of the melting point as a measure of purity, the solubility temperature[5] was determined, and found to be 86.5° at a 12:1 ratio of water to hydrastic acid. The solubility temperatures at other ratios were also determined over the temperature range of 34 to 87°, and from these data a solubility equation was calculated.

$$\log S = 0.2879 + 0.01384t + 5.82 \times 10^{-5}\, t^2$$

S = solubility in g./l. water; t = temp. in °C.

The maximum deviation between the observed and the calculated solubility data using the above equation is 2%. Some values for the calculated solubility are: at 20° (3.9 g./l.), 40° (8.6), 60° (21.3), 80° (57), 100° (180). By differentiation of the above equation, it can be calculated that the solubility temperature at a 12:1 ratio is lowered 0.18° for each per cent. of soluble impurity.

Experimental

All melting points are corrected. Analyses are by Mrs. Mary Aldridge and Mr. Byron Baer of this Laboratory.

3,4-Methylenedioxydihydrocinnamic acid was prepared by hydrogenating a slurry of the sodium salt of 3,4-methylenedioxycinnamic acid[6] (from 380 g. (1.98 moles) of the acid and 80 g. of sodium hydroxide) in 1300 ml. of distilled water under 3000 lb. (200 atm.) pressure at 110–130° over 50 g. of Raney nickel for 2 hours. The reaction mixture was filtered to remove the catalyst and acidified with concentrated hydrochloric acid to congo red. Water was added as necessary to thin the thick slurry of the insoluble acid which precipitated. After filtering and air drying, 345 g. (90%) was obtained, m.p. 83–84°; reported m.p. 87–88°.[1] This light tan colored material was satisfactory for the next step. A pure white product, m.p. 87–88°, was obtained after two recrystallizations from water, using 2 g. of acid and 0.4 g. of activated carbon (Darco G-60) per 100 ml. of water. The yield after two recrystallizations was 1.4 g.

5,6-Methylenedioxyhydrindone-1.—The acid chloride of the dihydrocinnamic acid was prepared by adding 208 g. (1 mole) of phosphorus pentachloride to a chilled solution of 194 g. (1 mole) of the crude 3,4-methylenedioxydihydrocinnamic acid, dissolved in 1500 ml. of dry, thiophene-free benzene, and stirring for 1.5 hours at room temperature. An excess of the phosphorus pentachloride attacks the methylenedioxy bridge and lowers the yield.

The cyclization was carried out by the dropwise addition

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(1) W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **91**, 1084 (1907).

(2) E. Oertly and A. Pictet, *Ber.*, **43**, 1336 (1910).

(3) T. S. Stevens and M. C. Robertson, *J. Chem. Soc.*, 2790 (1927).

(4) M. Freund, *Ann.*, **271**, 370, 381 (1892).

(5) W. Reeve and R. K. Adams, *Anal. Chem.*, **22**, 755 (1950).

(6) R. D. Haworth, W. H. Perkin, Jr., and J. Rankin, *J. Chem. Soc.*, **125**, 1693 (1924).

over a 3-hour period of the above benzene solution to a chilled and stirred solution of 521 g. (2 moles) of anhydrous stannic chloride dissolved in 300 ml. of benzene and stirring for 15 minutes. The solid tin complex was changed to a liquid complex by adding 300 ml. of ordinary ether. The reaction mixture was poured into a mixture of 4 l. of 6 *N* NaOH and 2 to 3 liters of chopped ice and stirred for 15 minutes. The benzene layer was separated, and the hydrindone suspended in the alkaline solution allowed to stand overnight. It was then filtered, washed with water, thoroughly air-dried, dissolved in 5 l. of boiling benzene to remove inorganic salts and filtered hot. The benzene solutions were combined and steam distilled to remove the benzene, and the resulting insoluble hydrindone filtered and washed with water. A light yellow material (148 g., 83% of theory) m.p. 159–164° was obtained which was pure enough for the next step. A pure white product was obtained by crystallizing 10 g. of the hydrindone from 150 ml. of a 2:1 ethanol–water mixture in the presence of 3.5 g. of activated carbon. There was obtained 8.2 g., m.p. 163–164°; reported m.p. 160°[1] and 161°.[7]

Hydrastic Acid.—A mixture of 100 g. (0.57 mole) of 5,6-methylenedioxyhydrindone-1, 6 g. (0.03 mole) of vanadium pentoxide, 1200 ml. of distilled water, and 300 ml. of concentrated nitric acid was heated in a 5-l. flask under reflux until the reaction started, and then for 1.5 hours, with occasional swirling, after the violent phase of the reaction had subsided. The hot reaction mixture was quickly filtered through asbestos to remove the vanadium pentoxide before some of the hydrastic acid crystallized. The filtrate was neutralized to litmus with 15% sodium hydroxide solution, acidified with glacial acetic acid to a congo red end-point, and then heated to the boiling point. Lead acetate solution (500 ml., 10%) was added until the lead salt of hydrastic acid was completely precipitated, the mixture allowed to cool, filtered, and the yellowish-white precipitate washed with three 100-ml. portions of 3% acetic acid.

The lead salt was converted to crude hydrastic acid by making a slurry with 900 ml. of tap water, heating to boiling, and adding concentrated nitric acid (75 ml.) dropwise from a buret until solution was effected. The hot solution was filtered by gravity through a heated funnel, and the filtrate cooled slowly to ice-bath temperature, allowed to stand 0.5 hour, filtered, washed with two 75-ml. portions of ice-water, and air-dried (yield 66 g.). An additional 17 g. of crude hydrastic acid was obtained from the filtrate by neutralizing as before to precipitate the hydrastic acid as lead hydrastate, filtering, washing and converting this to the crude hydrastic acid as above. The material was often contaminated with small amounts of lead hydrastate.

The combined, crude fractions of hydrastic acid were purified by two precipitations as the lead salt and a recrystallization from water. This was done by dissolving the material in 800 ml. of boiling tap water (adding a little nitric acid if an appreciable amount of the insoluble lead hydrastate was present), and precipitating the lead hydrastate with 10% lead acetate solution (approximately 500 ml. was required). If nitric acid was added, an equivalent amount of sodium hydroxide was added at this point. The lead salt was filtered, dissolved again in dilute nitric acid, filtered, neutralized to litmus with sodium hydroxide solution and acidified to congo red with acetic acid as before, and the lead hydrastate then converted to hydrastic acid as before. The yield was 57 g., solubility temperature 86.1° at 12:1 (corresponding to a purity of 98%), with a neutralization equivalent of 104.7 (theory, 105.0). An additional 5 g. was recovered from the filtrate by precipitating the lead salt, etc., as previously described. The combined 62 g. of pale yellow hydrastic acid was recrystallized from 620 ml. of distilled water, using 6 g. of activated carbon (Darco G-60) to remove the color. An almost white product resulted (53 g., 44.5% of theory), solubility temperature 86.5° at 12:1. This material was used to prepare the anhydride.

A pure white product, having the same solubility temperature, was obtained after three more recrystallizations from water with activated carbon. *Anal.* Calcd. for $C_9H_6O_6$: C, 51.44; H, 2.88. Found: C, 51.42; H, 2.91. The following solubility temperatures were determined: 12:1, 86.5°; 25:1, 73.8°; 50:1, 58.7°; 100:1, 42.8°; 150:1, 33.9°.

Hydrastic Anhydride.—This was prepared by stirring and heating 50 g. of hydrastic acid for 5 minutes after melting in a 1000-ml. beaker immersed in an oil-bath maintained at 190°.[4] A light tan product (44 g., 96%), m.p. 178.5–181° was obtained. This was dissolved in 1000 ml. of hot benzene, 9 g. of activated carbon added, filtered hot through asbestos, cooled to 10°, and filtered. There was obtained 29 g. of a pure white product (64% of theory), m.p. 179–180° (determined in a sealed tube); reported m.p., 175°.[4] *Anal.* Calcd. for $C_9H_4O_5$: C, 56.59; H, 2.11. Found: C, 56.48; H, 2.30. An additional 9 g. of white material, m.p. 177.5–179.5°, was isolated by concentrating the filtrate (total yield, 83%).

Acknowledgment.—We wish to express our appreciation to the National Institutes of Health for a grant which made this work possible. Mr. Roy G. Weston of these laboratories worked out the conditions for the hydrogenation of the 3,4-methylenedioxycinnamic acid.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MARYLAND
COLLEGE PARK, MARYLAND
RECEIVED OCTOBER 16, 1950

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[7] W. Borsche and W. Eberlein, *Ber.*, **47**, 1469 (1914).

Quinazolines. XI. Synthesis of Several Aminoquinazolines and Their Sulfa Derivatives[1]

BY M. B. NAFF AND B. E. CHRISTENSEN

Although the search for new sulfa drugs has been most extensive very little attention has been given to the sulfaquinazolines. For this reason the work in this Laboratory was extended to include the synthesis of a number of such compounds.

The principal task in the execution of such a program is the synthesis of the various aminoquinazolines required for the coupling. In this study all the isomeric aminoquinazolines were prepared with the exception of the 2- and 4-aminoquinazolines. The 2-aminoquinazoline in contrast to the 4-amino isomer, had been previously successfully coupled with acetylsulfanilyl chloride by Dewar.[2] Macbeth and Rodda,[3] however, report the successful preparation of a sulfaquinazoline using 4-aminoquinazoline but failed to give any details or analytical data. Earlier work in this Laboratory had indicated that it would be difficult if not impossible to couple the 4-amino isomer due to its amide-like characteristics, thus confirming the experiments of Dewar.

5-Aminoquinazoline was synthesized from 5-nitro-4-quinazolone which had been prepared according to the directions of Bogert.[4] This nitroquinazolone was converted to the 4-chloro derivative. The reduction of 4-chloro-5-nitroquinazoline was extremely difficult; it was necessary to subject this material to prior purification using Raney nickel, remove the nickel and then proceed with the reduction using palladized calcium carbonate at 0° following essentially the directions of Elderfield.[5] This critical operation yields the dihydro-derivative of 5-aminoquinazoline which was found to be very sensitive to air oxidation. For this reason it was necessary to remove the palladized

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[1] The work in this paper was made possible by a grant-in-aid from the Research Corporation. Published with the approval of the Monograph Publications Committee, Oregon State College, as Research Paper No. 169, School of Science, Department of Chemistry.

[2] Dewar, *J. Chem. Soc.*, **2**, 619 (1944).

[3] Macbeth and Rodda, *Nature*, **156**, 207 (1945).

[4] Bogert and Chambers, THIS JOURNAL, **27**, 649 (1905).

[5] Elderfield and co-workers, *J. Org. Chem.*, **12**, 405 (1947).

calcium carbonate by filtration. The dehydrogenation was then effected by immediately refluxing in the presence of palladized charcoal to yield 5-aminoquinazoline which was stable in air. No sulfaquinazoline could be isolated from the reaction product of the 5-amino derivative with acetylsulfanilyl chloride.

The 6-aminoquinazoline was prepared by the directions given by Elderfield. It was advantageous to carry out the final reduction of the 4-chloro-6-nitroquinazoline in a methylcellosolve rather than methanol solvent due to solubility characteristics. The reaction of this intermediate with acetylsulfanilyl chloride was straightforward.

7-Aminoquinazoline was obtained by essentially the same sequence of reactions from 7-nitro-4-quinazolone.[6] The 4-chloro-7-nitroquinazoline reduced readily to the dihydro derivative which was in turn dehydrogenated with ferricyanide to yield 7-aminoquinazoline. For some unknown reason, the coupling of 7-aminoquinazoline with acetylsulfanilyl chloride was not successful in either glacial acetic acid, dioxane or pyridine.

The preparation of 8-aminoquinazoline[5] was essentially the same as for the 6-amino isomer. The coupling of this intermediate with acetylsulfanilyl chloride did not pose any new problems.

The over-all yields in all these preparations were small by reasons of the great losses entailed in purifying the chloroquinazolines prior to reduction and low yields on hydrogenation–dehydrogenation operations. A number of the aminoquinazolines were light sensitive, making it necessary to carry out several of the operations in the absence of light.

Experimental

4-Chloro-5-nitroquinazoline.—Forty-two ml. of phosphorus oxychloride was added to a mixture consisting of 14 g. (0.073 mole) of 5-nitro-4-hydroxyquinazoline and 24 g. (0.12 mole) of phosphorus pentachloride. This mixture was heated under reflux for 2 hours, cooled for 1 hour, and the crystalline mass of 4-chloro-5-nitroquinazoline which formed removed by filtration. The crystals were washed several times with dry ether, ground with ether in a mortar, and again washed twice with more ether to remove the chlorides of phosphorus. The washed material was twice recrystallized from pure *n*-heptane to give 5.1 g. of white crystals, m.p. 137–139°.

The phosphorus oxychloride filtrate was evaporated to dryness under reduced pressure. The solid residue was then treated with ether and poured into a separatory funnel containing a cold mixture of chopped ice and water. The 4-chloro-5-nitroquinazoline was removed by extraction with ether; the ether extracts were shaken with sodium bicarbonate, decanted, and dried over anhydrous sodium sulfate. Evaporation of the ether solution gave a yellow material which on recrystallization from *n*-heptane yielded 2.7 g. of the chloro compound. The total yield of 4-chloro-5-nitroquinazoline was 7.8 g. (51%). An analytical sample was prepared by sublimation at 0.1 mm. and 140°, m.p. 138.5–139°.

Anal. Calcd. $C_8H_4ClN_3O_2$: C, 45.8; H, 1.9; N, 20.0. Found: C, 45.3; H, 2.2; N, 20.2.

5-Aminoquinazoline.—4-Chloro-5-nitroquinazoline (0.5 g., 0.0024 mole) was dissolved in 70 ml. of dry cold methyl cellosolve which had been placed in a round-bottom flask surrounded with ice. About 0.4 g. of Raney nickel was added and the flask vigorously swirled for a few minutes in order to assure thorough mixing. The Raney nickel was then allowed to settle and the supernatant liquid decanted into a cold hydrogenation bottle containing 1.5 g. of palladized calcium carbonate (2% Pd). The bottle was packed in ice, evacuated of air, and hydrogen admitted at 30 pounds pressure. After shaking for 30 minutes hydrogen absorption was virtually complete; the catalyst was then filtered and the brownish-yellow filtrate transferred to a flask containing 0.5 g. of palladized charcoal (10% Pd). After refluxing for 20 hours, filtration, and removal of the solvent *in vacuo*, the residue, 5-aminoquinazoline was isolated as a dirty yellow solid. The product was again dissolved in a 33% solution of potassium hydroxide and extracted with ether. Evaporation of the extracts gave 0.165 g. of a bright yellow solid, m.p. 183–187°; 47.8% yield. An analytical sample was prepared by sublimation and recrystallization from benzene, m.p. 192.5–193.5°.

Anal. Calcd. for $C_8H_7N_3$: C, 66.2; H, 4.83. Found: C, 65.6; H, 4.95.

7-Aminoquinazoline.—Two grams of palladized calcium carbonate (5% Pd) and 2 g. (0.0138 mole) 4-chloro-7-nitroquinazoline were added to 60 ml. of dry methanol in a hydrogenation bottle. Hydrogenation at 30 lb. initial pressure was complete in 30 minutes. The catalyst was then removed by filtration, the filtrate concentrated to approximately 5 ml. *in vacuo* and then diluted with 50 ml. of water. To this solution was added 15.2 ml. of 33% potassium hydroxide and gradually over a period of 20 minutes 50 ml. of a warm aqueous solution containing 6.5 g. of potassium ferricyanide. After standing 5 minutes, 63 ml. of 33% potassium hydroxide solution was added and the reaction mixture then extracted with ether. Evaporation of the dry ether extracts gave 0.67 g. of 7-aminoquinazoline; 48.4% yield. A sample which had been sublimed at 210° and 3 mm. after recrystallization from benzene gave a m.p. 190.5–191°.

Anal. Calcd. for $C_8H_7N_3$: C, 66.2; H, 4.83; N, 29.0. Found: C, 66.4; H, 5.13; N, 28.6.

N^1-Acetyl-N^4-6-quinazolylsulfanilamide.—N-Acetylsulfanilyl chloride (0.214 g., 0.0009 mole) was added in four portions at 10-minute intervals to a stirred solution of 0.120 g. (0.00083 mole) of 6-aminoquinazoline in 6 ml. of dry pyridine at room temperature following essentially the directions of Wolf.[7] The reaction mixture was then stirred for 1 hour at room temperature and for an additional half-hour at 60°. The amber colored solution which formed was placed in the refrigerator overnight; 75 mg. of yellow material in the form of lumps settled from the solution; yield 27.5%. Recrystallization of the solid from an alcohol–benzene mixture (1:2) yielded small irregular shape yellowish-white crystals which darkened at 285° and melted with decomposition at 290–292°.

Anal. Calcd. for $C_{16}H_{14}N_4O_3S$: C, 56.2; H, 4.1. Found: C, 55.9; H, 4.3.

N^1-Acetyl-N^4-8-quinazolylsulfanilamide.—A solution of 90 mg. (0.00062 mole) of 8-aminoquinazoline in 2 ml. of dry pyridine was added dropwise to a solution of 160 mg. (0.00069 mole) of N-acetylsulfanilyl chloride in 3 ml. of pyridine maintained at 60°. The entire reaction was carried out for 1 hour in semi-darkness, then the reaction mixture was concentrated *in vacuo* to 1 ml. and 30 ml. of water added. A cream-colored suspension formed together with a red gummy deposit. The suspension cleared upon standing in the refrigerator several hours. The supernatant liquid was then decanted and on storage overnight in the refrigerator a small amount of the sulfa derivative crystallized. The reddish gum remaining in the flask was dissolved in 2 ml. of half normal sodium hydroxide, diluted to 12 ml., filtered, and the clear filtrate neutralized with glacial acetic acid. The precipitates which formed were filtered and dried; yield of crude product 0.146 g. (69%). An analytical sample prepared by crystallization from ethyl alcohol had a m.p. of 215.5–216°.

Anal. Calcd. for $C_{16}H_{14}N_4O_3S$: C, 56.2; H, 4.1; N, 16.4. Found: C, 55.8; H, 4.3; N, 16.3.

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[6] Morley and Simpson, *J. Chem. Soc.*, 364 (1948).

[7] Wolf and co-workers, THIS JOURNAL, **71**, 6 (1949).

Semicarbazones of α,β-Unsaturated 20-Ketosteroids

BY HANS REICH AND RAYMOND W. COLLINS[1]

Some time ago Klyne and co-workers[2] isolated Δ^{16}-allopregnen-3(β)-ol-20-one sulfate from pregnant mare's urine and reported that the free ketoalcohol failed to give a semicarbazone. However, three semicarbazones of 16,17-unsaturated 20-ketosteroids are described in the literature: Δ^{16}-pregnene-3,20-dione disemicarbazone,[3] Δ^{16}-pregnen-3-(β)-ol-20-one semicarbazone[4] and Δ^{16}-pregnen-3(β)-ol-20-one acetate semicarbazone.[4] These semicarbazones were prepared "by treatment with semicarbazide acetate under the usual conditions." In the present experiments we have studied the conditions under which semicarbazones of Δ^{16}-20 ketosteroids are formed, and have prepared three additional compounds of this type.

We found that the reaction of $\Delta^{5,16}$-pregnadien-3-(β)-ol-20-one, its acetate and Δ^{16}-allopregnen-3(α)-ol-20-one acetate with semicarbazide acetate in ethanol was incomplete after refluxing for 1.5 hours. The crude reaction products showed maximum absorption at 240 mμ (starting material) and only an inflection between 260 and 270 mμ. When the ketosteroids were refluxed with the same semicarbazide acetate solution for 24 hours, the crude reaction products as well as the crystals isolated from them showed only a single maximum at 267 mμ. The same was the case when the reaction was carried out at room temperature in the presence of pyridine.[5] A similar absorption maximum was found by Wettstein[6] for the semicarbazone of $\Delta^{5,16}$-16-methylpregnadien-3(β)-ol-20-one acetate. Since displacement to longer wave lengths is usually observed in passing from the carbonyl compound to its semicarbazone,[7] the absorption maximum at 267 mμ indicates that normal semicarbazones of 16,17-unsaturated 20-ketosteroids were formed. This maximum excludes the formation of a pyrazoline derivative as well as the addition of one mole of semicarbazide to the quite reactive Δ^{16}-double bond.[6,8] In the latter case there would result a saturated ketone which should show only a band of low intensity with a maximum in the region of 280–300 mμ,[9] while pyrazoline derivatives show nearly the same absorption maxima as the parent ketones.[10]

In contrast to the slow formation of semicarbazones of 16,17-unsaturated 20-ketosteroids the corresponding saturated ketones and those with a hydroxyl group in 17α-position react readily with semicarbazide.[11]

Experimental[12]

Semicarbazide Acetate Solution.—One hundred mg. of semicarbazide hydrochloride and 150 mg. of sodium acetate trihydrate were ground until the mixture liquefied. Then it was taken up in absolute ethanol, filtered and the filtrate diluted to 10 cc.

Semicarbazones.—20–30 mg. of ketone was refluxed for 24 hours with 2–3 cc. of semicarbazide acetate solution. After cooling the solution was concentrated *in vacuo*, diluted with water and extracted twice with chloroform. The chloroform solutions were washed once with water, dried and evaporated. The residue was recrystallized twice from abs. ethanol.

$\Delta^{5,16}$-Pregnadien-3(β)-ol-20-one Semicarbazone.—This semicarbazone decomposed gradually above 230° and did not melt up to 300°; maximum at 267 mμ (log *E* 4.342). *Anal.* Calcd. for $C_{22}H_{33}O_2N_3$: N, 11.31. Found: N, 11.76.

$\Delta^{5,16}$-Pregnadien-3(β)-ol-20-one Acetate Semicarbazone.[13]—M.p. 209.5–212°; maximum at 267 mμ (log *E* 4.380). *Anal.* Calcd. for $C_{24}H_{35}O_3N_3$: C, 69.70; H, 8.53; N, 10.16. Found: C, 69.24; H, 8.09; N, 10.13.

Δ^{16}-Allopregnen-3(α)-ol-20-one Acetate Semicarbazone.—M.p. 216–219°; maximum at 267 mμ (log *E* 4.387). *Anal.* Calcd. for $C_{24}H_{37}O_3N_3$: N, 10.11. Found: N, 9.80.

The same semicarbazone was also obtained as follows: a solution of 500 mg. of semicarbazide hydrochloride in 1.5 cc. of water was mixed with a solution of 500 mg. of potassium acetate in 5 cc. of abs. ethanol. The potassium chloride was filtered off, and 0.5 cc. of the filtrate was added to a solution of 11 mg. of the ketone in 0.5 cc. of abs. ethanol–pyridine 1:1. After addition of one drop of water the mixture was allowed to stand at room temperature for 4 days. It was then diluted with water and extracted three times with ether. The ether solutions were washed neutral, dried and evaporated. Two recrystallizations from abs. ethanol gave crystals of m.p. 214–217°; maximum at 267 mμ.

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[1] This investigation was supported in part by research grants from the National Cancer Institute of the National Institutes of Health, Public Health Service, and from Ciba Pharmaceutical Products, Inc., Summit, N. J.

[2] W. Klyne, B. Schachter and G. F. Marrian, *Biochem. J.*, **43**, 231 (1948).

[3] R. E. Marker and E. Rohrmann, THIS JOURNAL, **62**, 518 (1940).

[4] R. E. Marker and E. Rohrmann, *ibid.*, **62**, 521 (1940).

[5] J. D. Dutcher and O. Wintersteiner, *ibid.*, **61**, 1992 (1939).

[6] A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944).

[7] L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 565 (1943).

[8] D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **72**, 2306 (1950).

[9] L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publishing Corp., New York, N. Y. 1949, p. 190.

[10] K. Dimroth and O. Lüderitz, *Ber.*, **81**, 242 (1948).

[11] For instance pregnenolone acetate, *ibid.*, **67**, 1611 (1934); progesterone, *J. Biol. Chem.*, **107**, 321 (1934); Cpd. E, *Helv. Chim. Acta*, **19**, 29 (1936).

[12] M.p.'s. were taken on a Kofler micro hot stage and are corrected. The quantitative ultraviolet spectra were carried out by Mr. L. Dorfman, Ciba Pharmaceutical Products, Summit, N. J. Two samples of ketones were kindly supplied by Dr. M. Tishler, Merck & Co., Inc., Rahway, N. J., and Dr. J. J. Pfiffner, Parke, Davis & Co., Detroit, Mich.

[13] After completion of our experiments an article by R. Fischer, G. Lardelli and O. Jeger appeared (*Helv. Chim. Acta*, **33**, 1335 (1950)) in which the preparation of this semicarbazone is described. After reflux for 8 hours only half of the ketone had been converted to the semicarbazone.

No Insecticidal Activity of 1,1,4,4-Tetra-[p-chlorophenyl]-2,2,3,3-tetrachlorobutane

BY R. RIEMSCHNEIDER

Bernimolin[1] has reported that 1,1,4,4-tetra-[p-chlorophenyl]-2,2,3,3-tetrachlorobutane (I), mol. wt. 638, shows the same degree of toxicity as p,p'-DDT (II) against *Drosophila melanogaster M.* High toxicity of I is unexpected because of its molecular weight, high melting point (270°) and slight lipoid solubility.

We have determined by means of film tests (Petri dishes) the toxicity of I against *Drosophila*. No symptoms of poisoning were exhibited after 300 minutes when 2000 γ of I were used; under the

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[1] J. Bernimolin, THIS JOURNAL, **71**, 2274 (1949).

same conditions 10 γ of II caused 100% mortality. It is possible that Bernimolin's I contained II or even that it was not identical with I prepared from II by the method of Brand and Bausch.[2] Bernimolin's assumption that the presence of I (perhaps formed by irradiation of II) may be partly responsible for the extraordinary residual effect of II cannot be correct. Likewise Bernimolin's conclusion, based on the supposed insecticidal activity of I, that the molecular weight of residually active contact insecticides of the halohydrocarbon type is not limited, is without foundation.

The alteration of physical properties, *e.g.*, the decrease in lipoid solubility, with increase in molecular weight corresponds in our experience[3] with a quite general lowering of contact insecticidal activity of halogenated hydrocarbons when their molecular weight exceeds 430–450. Halogenated hydrocarbons whose molecular weight exceeds this limiting value are not necessarily completely inactive as contact insecticides. Thus in 1947 we reported[4] insecticidal activity for the substance M 490 (so called because of its approximate molecular weight). This activity, however, was much less than that of M 410[5] (Chlordane).

(2) Brand and Bausch, *J. prakt. Chem.*, **127**, 232 (1930).

(3) R. Riemschneider, "Zur Kenntnis der Kontakt-Insektizide I," Beiheft 2, Ergänzungsband 1 zur "Pharmazie" 1947. A paper of Lord (*Ann. Appl. Biol.*, **35**, 505 (1948)) confirms the supposition made in this book that the molecular weight of highly active contact insecticides of the halohydrocarbon type with residual effect is limited.

(4) Riemschneider, *Mitt. Physiol. Chem. Inst.*, *R***12**, Dec., 1947, and *R*11, Oct., 1947.

(5) Riemschneider, *Pharmazie*, **3**, 115 (1948); *Chem. Z.*, II, 344 (1948); *Chim. et Ind.*, **64**, 695 (1950).

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The System $Ba(IO_3)_2$–$BaCl_2$–H_2O at 25°

BY JOHN E. RICCI

In connection with studies on the aqueous phase relations of the halates, the 25° isotherm of the system $Ba(IO_3)_2$–$BaCl_2$–H_2O was investigated, revealing the formation of an incongruently soluble hydrated double salt with the probable formula $Ba(IO_3)_2 \cdot BaCl_2 \cdot 2H_2O$. The results, in terms of weight percentage, are listed in Table I and plotted in Fig. 1.

The general procedure was that described in similar reports. Complexes were made up from water and the solids $Ba(IO_3)_2 \cdot H_2O$ and $BaCl_2 \cdot 2H_2O$, which were C.P. samples checked for purity by direct analysis. After 1 or 2 weeks of stirring the filtered saturated solution was analyzed for iodate with standard thiosulfate and for total solid by evaporation. Reanalysis after a similar additional period of stirring was used to prove equilibrium. The double salt did not form readily. A practically complete but metastable diagram was obtained with the separate hydrated salts as sole solid phases, before the double salt, suspected because of unsatisfactory aspects of the first diagram, could be made to form; thereafter it was used to seed the various complexes. After such seeding, for example, the remaining liquid of complex no. 6 dropped in composition to that shown as line 8 of the table; the "total complex" composition for line 8 was estimated from that of no. 6 corrected for the amount of liquid withdrawn for analysis before seeding. Line 9 bears the same relation to line 7.

TABLE I

SYSTEM $Ba(IO_3)_2$–$BaCl_2$–H_2O AT 25°

	Saturated solution Wt. %			Total complex wt. %		
	$Ba(IO_3)_2$	$BaCl_2$	Density	$Ba(IO_3)_2$	$BaCl_2$	Solid phase[b]
1	0.0400	0.00	0.997	...	0.00	A
2	.0189	19.63	1.194	8.00	18.00	A
3	.0187	20.50	1.206	25.99	14.99	A
4	.0198	21.56	1.218	7.00	20.00	A
5	.0231	25.29	1.268	23.82	19.07	A^m
6	.0240	25.59	1.273	23.52	21.47	A^m [a]
7	.0267	27.09	1.286	23.58	21.54	$(A + C)^m$
8		22.06	1.222	35.3	19.6	A + B
9		22.05	1.223	29.5	20.2	A + B
10	.0201	(22.38)?		6.01	21.36	A + B
11	.0201	22.06	1.225	6.03	22.16	A + B
	.0201	22.06	1.223	= average		A + B
12	.0189	22.72	1.232	6.03	23.24	B
13	.0186	23.76	1.245	5.99	24.17	B
14	(.020)	24.25	1.255	10.96	24.96	B
15	.0179	24.73	1.258	6.00	25.04	B
16	.0171	25.45	1.266	6.00	25.72	B
17	(.019)	25.51	1.269	10.02	25.96	B
18	.0165	26.01	1.274	6.04	26.22	B
19	.0152	26.82	1.285	5.89	26.95	B
20	.0153	27.09	1.289	4.99	27.95	B + C
21	.0153	27.11	1.289	2.00	39.95	B + C
22	.00	27.11	1.289	0.00	...	C

[a] Probably in course of change, not completely at equilibrium. [b] A = $Ba(IO_3)_2 \cdot H_2O$; B = $Ba(IO_3)_2 \cdot BaCl_2 \cdot 2H_2O$; C = $BaCl_2 \cdot 2H_2O$; *m* = metastable.

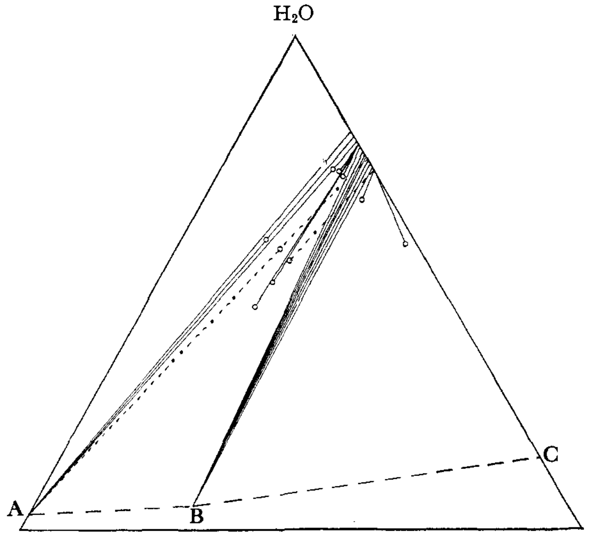

Fig. 1.—25° isotherm of system $(BaIO_3)_2$–$BaCl_2$–H_2O; A = $Ba(IO_3)_2 \cdot H_2O$, B = $Ba(IO_3)_2 \cdot BaCl_2 \cdot 2H_2O$, C = $BaCl_2 \cdot 2H_2O$.

The formula of the double salt was determined by the intersection of the tie-lines fixed by the compositions of saturated solution and total complex.[1] For greater dependability of the extra-

(1) A. E. Hill and J. E. Ricci, THIS JOURNAL, **53**, 4305 (1931).

polation the two runs numbered 14 and 17 were made with much larger amounts of solid to be transformed into double salt, and these were rotated for about a year before analysis. Although the equimolar ratio of the salts in the compound is quite clear from mere graphical extrapolation, it is more difficult to fix the hydration of the double salt, since the weight percentages of water in the mono-, di- and trihydrates of a 1:1 double salt are not very different, being 2.53, 4.93 and 7.21, respectively.

The tie-lines for complexes 12–19, in which the double salt was the sole saturating solid, were extrapolated algebraically to their intersections with the line representing the 1:1 salt ratio. The average number of moles of H_2O per $Ba(IO_3)_2 \cdot BaCl_2$ thus calculated is 2.13 with an average deviation from the mean of 0.18. The tie-lines were also extrapolated to the line representing the percentage of $Ba(IO_3)_2$ in a 1:1 double salt with 1, 2 and 3 moles of H_2O, respectively, in the formula. The intersections of the tie-lines with each of these fixed lines was then expressed as an "error" in terms (positive or negative) of percentage of $BaCl_2$ in the solid. The average (algebraic) error of extrapolation is then −0.71% $BaCl_2$ at the monohydrate, −0.08% at the dihydrate and +0.52% at the trihydrate.

The various tie-line extrapolations therefore seem to be sufficient to justify accepting the formula $Ba(IO_3)_2 \cdot BaCl_2 \cdot 2H_2O$ for the double salt. The other solid phases of the isotherm are $Ba(IO_3)_2 \cdot H_2O$ and $BaCl_2 \cdot 2H_2O$.

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Exchange of Deuterium Oxide with Bromodichloromethane and Chlorodibromomethane

BY R. H. SHERMAN AND R. B. BERNSTEIN

The base-catalyzed exchange of trichloromethane with deuterium oxide has been studied by Sakamoto,[1] who found that the rate of exchange was rapid compared with the rate of hydrolysis. Hine,[2] in a study of the basic hydrolysis of trichloromethane, proposed mechanisms involving the intermediates CCl_3^- and CCl_2 which were in concordance with the observed rapid exchange rates reported by Sakamoto. Newton and Rollefson[3] utilized the base-catalyzed exchange reaction as a method of preparation of trichloromethane-*d*.

Bromodichloromethane-*d* and chlorodibromomethane-*d* have been obtained in this Laboratory by the exchange reaction between the protium analogs and deuterium oxide in the presence of deuteroxide ion.[4] The reactions were carried out in heavy-walled Pyrex vessels of about 30 ml. volume, into which were placed 0.1 mole of purified halomethane, 0.1 mole of 98% deuterium oxide and 0.01 mole of sodium deuteroxide. After outgassing the contents at −78°, the vessel was sealed and maintained at 105° in the absence of light for four days, with periodic shaking. The reactor was then cooled to −195° and opened. The non-aqueous layer was dried and distilled through a small packed column.

The infrared absorption spectra of the purified products revealed appropriate bands attributed to the C–D bond stretching and bending vibrations. A determination of the isotopic purity of the deuterohalomethanes was carried out on the basis of the 3020 $cm.^{-1}$ band of the C–H bond. The results were 43% CBr_2ClD and 16% CCl_2BrD. Upon recharging the reactor with the enriched compound and a new supply of deuterium oxide and sodium deuteroxide in the original proportions the exchange reactions were repeated under similar conditions, resulting in 64% CBr_2ClD and 36% CCl_2BrD, respectively.

Considerable gas pressure (non-condensable at −195°) was observed at the end of each run. In one control experiment of two days using CBr_2ClH, the non-condensable gas was analyzed mass-spectrometrically and found to be essentially pure carbon monoxide, in a quantity accounting for approximately 3.5% of the total halomethane used. The aqueous phase was acid. The total halide ion found in the aqueous phase[5] corresponded to about 3% halomethane decomposition. In several experiments the ratio of Br^- to Cl^- exceeded 2:1. This ratio was found to vary; no explanation has yet suggested itself.

In one experiment of 16 days with CBr_2ClH, the total halide ion recovered was 10.5 millimoles; originally 11.8 millimoles of deuteroxide ion was available. This ratio of OD^-/X^- of 1.12 is in reasonable agreement with the stoichiometry of the hydrolysis according to the mechanisms of Hine.[2] The over-all reaction for decomposed halomethane may be written: $2CX_3H + 7OH^- = CO + 6X^- + HCO^-_2 + 4H_2O$, so that the ratio of hydroxyl consumed to halide produced would be 7/6 or 1.17. It thus appears that the extent of decomposition is limited by the hydroxyl ion available. It should also be noted that both of the purified halomethanes (and their deuterium analogs) were extremely stable to heat and light in the absence of oxygen, in contrast to the decomposition usually observed when exposed to the atmosphere.

It is clear from these results that the rate of exchange of bromodichloromethane and chlorodibromomethane is indeed more rapid than the rate of hydrolysis, in agreement with the previous data for chloroform. However, the apparent order of reactivity toward exchange for these two compounds is somewhat surprising from a point of view of electronegativity. Further kinetic studies in a single phase system appear necessary for an understanding of this observation.

Thanks are due to D. V. Kniebes, S. Katz and V. H. Dibeler for their valuable assistance. The D_2O

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(1) Y. Sakamoto, *Bull. Chem. Soc. Japan*, **11**, 627 (1936).

(2) J. Hine, THIS JOURNAL, **72**, 2438 (1950).

(3) T. W. Newton and G. K. Rollefson, *J. Chem. Phys.*, **17**, 718 (1949).

(4) The procedure of ref. 3 employed carbonate as the base and was found to be unsatisfactory in the case of the bromomethanes. The carbonate was completely decomposed, resulting in explosion of the reaction vessels.

(5) The concentrations of Br^- and Cl^- ions in the aqueous phas were obtained by potentiometric titration with silver nitrate.

was obtained through the courtesy of the Atomic Energy Commission.

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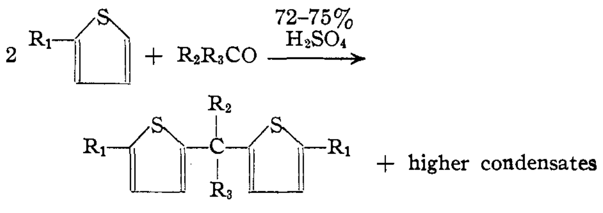
Condensation of Thiophene and Homologs with Ketones

By John W. Schick and Duncan J. Crowley

The reaction of thiophene with aldehydes,[1] particularly formaldehyde,[2] in an acidic medium is known to produce 1,1-(2′,2″-dithienyl)-alkanes which on further reaction result in resins and substituted resinous oils. However, no description of the reaction of thiophene and/or substituted thiophenes with ketones has been found in the literature.

The condensation is illustrated in the equation



R_1 = H–. Cl–, CH_3–, R_2 = CH_3–
R_3 = CH_3–, C_4H_3S–, C_6H_5–, C_2H_5–
$R_2R_3C<$ may be cyclic, *e.g.*, in cyclohexanone

This condensation has been carried out with thiophene, 2-methylthiophene and 2-chlorothiophene with ketones, such as acetone, methyl ethyl ketone, cyclohexanone, acetophenone and 2-acetylthiophene. For this particular reaction, the conditions are somewhat similar to those described for the phenol–ketone condensations.[3,4,5,6,7]

Although 72–75% sulfuric acid was the principal condensing agent employed, it was noted that 37% hydrochloric acid resulted in product yields comparable to sulfuric acid, while 85% phosphoric acid resulted in poorer yields. Table I summarizes the experimental data using 72% sulfuric acid as the condensing agent.

General Experimental Conditions

Thiophene or substituted thiophene (0.8–2.0 moles) and the ketone (1.0 mole) were allowed to react in the presence of 72–75% sulfuric acid (acid–thiophene ratio 1.5:1) at 50–90° for 3–8 hours. The reaction product was separated from the acid layer and washed with water, dilute carbonate, water again, then dried over anhydrous sodium sulfate. The unreacted thiophene or substituted thiophene was removed and the residue distilled at reduced pressure.

Table I

Thiophene–Ketone Condensations[a]

Thiophene	Ketone	Mole ratio, thiophene: ketone	Product structure[b]	Formula	Yield,[c] %	B.p., °C.	Mm.	$n^{20}D$	Sulfur, % Calcd.	Found
Thiophene	Acetone	1.6	T–K–T	$C_{11}H_{12}S_2$	47	86	0.3	1.5855	30.8	30.9
			T–K–T–K–T	$C_{18}H_{20}S_3$	19	188	.3	1.6029	28.9	28.9
Thiophene	Methyl ethyl	2	T–K–T	$C_{12}H_{14}S_2$	66	97.5	.1	1.5806	28.8	29.0
			T–K–T–K–T[d]	$C_{20}H_{24}S_3$	8				26.6	25.9
			T–K–T_4–K–T[e]	$C_{44}H_{54}S_6$	11	. . .	[f]		24.8	24.3
Thiophene	Cyclohexanone	1.6	T–K–T[g]	$C_{14}H_{16}S_2$	39	158	.3		25.8	25.7
			T–K–T_2–K–T	$C_{34}H_{40}S_4$	45	. . .	[f]		22.3	22.4
Thiophene	Acetophenone	1.6	T–K–T	$C_{16}H_{14}S_2$	49	153	.5	1.6319	23.7	23.6
			T–K–T_2–K–T[h]	$C_{40}H_{34}S_4$	30	. . .	[f]		19.9	20.2
Thiophene	Acetylthiophene	1.6	T–K–T	$C_{14}H_{12}S_3$	54	164	.1	1.6399	34.8	34.6
2-Chlorothiophene	Acetone	0.8	T–K–T	$C_{11}H_{10}S_2Cl_2$	61	143	.5		23.1	22.7
2-Methylthiophene	Acetone	1.6	T–K–T	$C_{13}H_{16}S_2$	79	110	.5	1.5691	27.1	26.5

[a] Condensation carried out in 72–75% H_2SO_4 with an acid:thiophene mole ratio of 1.5:1. [b] T = thiophene, K = ketone. [c] Yield based on thiophene consumed. [d] Mol. wt., calcd. 360, found 376. [e] Mol. wt., calcd. 774, found 772. [f] Resinous composition. [g] M.p. 61–62.5°. [h] Mol. wt., calcd. 642, found 639.

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The Separation of Mixtures of Mono- and Disubstituted Alkyl Phosphoric Acids[1]

By D. C. Stewart and H. W. Crandall

A number of alkyl phosphoric acids are available commercially, but only as mixtures of the mono- (H_2RPO_4) and di- (HR_2PO_4) substituted forms. It seems probable that for many purposes it would be desirable to use one or the other of these in a separated state, as, for example, in studying the mechanisms involved in the extraction of amino acids by their use.[2] It has been found that this separation may be readily accomplished by taking advantage of the differences in the distribution of the two forms between two immiscible phases, generally water and some organic solvent. In this latter case, the disubstituted acid favors the organic phase, whereas the monosubstituted compound shows more affinity for the aqueous layer. By choosing the appropriate solvent, it is then possible to water wash all of the H_2RPO_4 out of the organic layer by a series of batch extractions, leaving only the HR_2PO_4;

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(1) Steinkopf, "Die Chemie des Thiophens," Edwards Brothers, Ann Arbor, Michigan, 1944, p. 138.

(2) Caesar and Sachanen, *Ind. Eng. Chem.*, **40**, 922 (1948).

(3) Greenalgh, U. S. Patent 1,977,627.

(4) Jordan, U. S. Patent 1,854,940.

(5) Baker and Besly, *J. Chem. Soc.*, 1103 (1940).

(6) McGreal, Niederl and Niederl, This Journal, **61**, 345 (1939).

(7) DeBell, Goggin and Gloor, "German Plastic Practices," DeBell and Richardson, Springfield, Mass., 1946, p. 260.

(1) A portion of this work was performed under the auspices of the Atomic Energy Commission.

(2) E. V. McCollum, A. A. Rider and H. Suss, *Proc. Soc. Exp. Biol. Med.*, **72**, 709 (1949).

and, conversely, similarly to solvent-wash all the di- form away from the mono- form, leaving the latter in a water solution. In the case of the octyl phosphoric acids it was found that the substitution of diethylene glycol for the water phase eliminated difficulty with emulsions and gave distribution coefficients of the right order of magnitude to give satisfactory separation of the two forms.

The distribution of the acids was followed by titrating aliquots of the phases potentiometrically with standardized base, using a Beckman Type G glass electrode *p*H meter. It was assumed throughout that no free phosphoric acid was present, so that the difference in titer between the two breaks of the curve could be taken to represent the amount of H_2RPO_4 present, and the difference between this quantity and the titer to the first break to represent the HR_2PO_4. Using this method, the values shown in Table I were obtained for the acid strengths of the commercial mixtures as purchased. The distribution coefficients of the acids between the various pairs of immiscible phases were then similarly obtained, and these are summarized in Table II.

TABLE I

COMPOSITION OF COMMERCIAL ALKYL PHOSPHORIC ACIDS

Phosphoric acid	Source	Concentrations, *M* H_2RPO_4	 HR_2PO_4
Ethyl-	Eastman	4.66	4.36
n-Propyl-	Eastman	4.36	3.15
n-Butyl-	Eastman	3.28	2.48
Isobutyl-	Monsanto	3.57	2.56
n-Amyl-	Monsanto	3.48	1.81
n-Octyl-	Monsanto	2.01	1.75

TABLE II

DISTRIBUTION OF ACIDS BETWEEN IMMISCIBLE PHASES

Phosphoric acid	Distribution coefficient (*E*) into solvents from water Solvent	 $E_{H_2RPO_4}$	 $E_{HR_2PO_4}$
Ethyl-	*n*-Primary amyl alcohol	0.69	1.7
	Dibutyl carbitol	.14	0.51
n-Propyl-	*n*-Primary amyl alcohol	.86	5.4
	Dibutyl carbitol	1.4	1.2
n-Butyl-	*n*-Primary amyl alcohol	2.9	>1000?
	Dibutyl carbitol	2.1	39
	Dibutyl ether	0.66	15
Isobutyl-	Dibutyl ether	.54	11
n-Amyl-	Dibutyl ether	.72	6.2
n-Octyl-	Diethyl ether	42	~760
	Methyl isobutyl ketone	28	~106
n-Octyl-	Dibutyl ether	0.44[a]	7.0[a]

[a] Out of diethylene glycol rather than water.

For batch type washing, the most satisfactory separation is obtained when the HR_2PO_4 distribution coefficient is greater than 5, coupled with a corresponding *E* value of less than 1 for the H_2RPO_4 form. The use of counter-current column extraction techniques, however, should make separations feasible even though the two *E* values differ by a much smaller factor.

Using this technique, completely separated solutions of diethylphosphoric acid in *n*-amyl alcohol, dipropylphosphoric acid in isopropyl and dibutyl ethers, dibutylphosphoric acid in *n*-amyl alcohol and in dibutyl ether, diisobutylphosphoric acid in dibutyl ether, diamylphosphoric acid in dibutyl ether, dioctylphosphoric acid in dibutyl ether and monobutylphosphoric acid in water have all been prepared.

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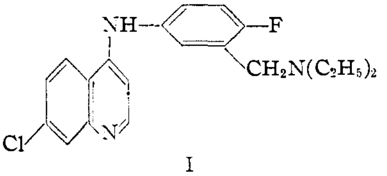
Synthesis of 2-Diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene Dihydrobromide

BY AUGUST SVEINBJORNSSON AND CALVIN A. VANDERWERF

In continuation of our studies on the replacement of amino and hydroxyl groups with the isosteric fluorine atom in medicinal agents of proved value, we have synthesized 2-diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene (I) the fluoro isostere of the antimalarial drug Camoquin



I

[4-(7-chloro-4-quinolylamino)-α-diethyl-amino-*o*-cresol][1] in which the OH-group in Camoquin is replaced by a fluorine atom.

Of the various synthetic routes explored, the best method for the preparation of the desired compound involved the following steps: *o*-toluidine → *o*-fluorotoluene → *o*-fluorobenzoic acid → *o*-fluorobenzyl alcohol → *o*-fluorobenzyl bromide → 2-fluoro-5-nitrobenzyl bromide → 2-diethylaminomethyl-4-nitrofluorobenzene hydrobromide → 2-diethylaminomethyl-4-aminofluorobenzene dihydrobromide → dihydrobromide of I.

The antimalarial activity of I was found to be considerably less than that of Camoquin.

Experimental

Preparation of Known Intermediates.—*o*-Fluorotoluene was prepared in 60% yield by direct diazotization of *o*-toluidine in anhydrous hydrogen fluoride, followed by decomposition of the diazonium fluoride in refluxing hydrogen fluoride. The *o*-fluorotoluene was oxidized to *o*-fluorobenzoic acid in 75% yield by the general method of Clark and Taylor,[2] and the acid was reduced to *o*-fluorobenzyl alcohol in 81% yield by means of a 2.5 molar quantity of lithium aluminum hydride.[3] Treatment of the alcohol with anhydrous hydrogen bromide in benzene gave an 81% yield of the highly lachrymatory *o*-fluorobenzyl bromide.

2-Fluoro-5-nitrobenzyl Bromide.—To 200 ml. of fuming nitric acid (sp. gr. 1.5) at 0°, 25.0 g. (0.13 mole) of *o*-fluorobenzyl bromide was added dropwise with stirring. The mixture was then allowed to come to room temperature with stirring and poured onto ice. The yellow product which precipitated was filtered, washed with cold water, and recrystallized from ethanol to yield 25.0 g. (81%) of pure **2-fluoro-5-nitrobenzyl bromide**, m.p. 76.6–77.4°.

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(1) J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb and A. L. Rawlins, THIS JOURNAL, **70**, 1363 (1948).

(2) A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 135.

(3) See R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 2548 (1947), for the general method.

Anal. Calcd. for $C_7H_5O_2NFBr$: C, 35.9; H, 2.1; N, 6.0. Found: C, 35.9; H, 2.1; N, 6.0.

Permanganate oxidation of the product gave in 67% yield a single acid whose m.p. (137.2–138.0°) was not depressed by admixture with an authentic sample of 2-fluoro-5-nitrobenzoic acid, prepared by the method of Slothouwer.[4]

2-Diethylaminomethyl-4-nitrofluorobenzene Hydrobromide.—In a typical run made according to the general directions of Burckhalter, *et al.*,[1] for the preparation of α-alkylamino-4-nitro-*o*-cresols from α-chloro-4-nitro-*o*-cresol, 22.0 g. (0.094 mole) of 2-fluoro-5-nitrobenzyl bromide and 14.6 (0.2 mole) of diethylamine gave 19.0 g. (66%) of pure product, m.p. 162° (dec.).

Anal. Calcd. for $C_{11}H_{15}N_2O_2F \cdot HBr$: C, 43.0; H, 5.2; N, 9.1. Found: C, 42.9; H, 5.2; N, 9.3.

2-Diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene Dihydrobromide.—A suspension of 18.0 g. (0.059 mole) of 2-diethylaminomethyl-4-nitrofluorobenzene hydrobromide in 50 ml. of absolute ethanol was reduced at a hydrogen pressure of 40 lb. in the presence of platinum oxide catalyst. The resulting mixture was filtered and the filtrate treated with a slight excess of alcoholic hydrogen bromide. Then 11.9 g. (0.06 mole) of 4,7-dichloroquinoline was added and the mixture heated on a steam-bath for 2 hours. The mixture was cooled and ether added until precipitation of the crude product was complete. Recrystallized from methanol, the pure **2-diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene dihydrobromide**, m. p. 203.8° (dec.), weighed 19.0 g. (60%).

Anal. Calcd. for $C_{20}H_{21}N_3ClF \cdot 2HBr$: C, 46.2; H, 4.4; N, 8.1. Found: C, 46.1; H, 4.7; N, 7.9.

Acknowledgment.—These studies were aided by a contract between the Office of Naval Research, Department of the Navy, and the University of Kansas.

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[4] J. H. Slothouwer, *Rec. trav. chim.*, **33**, 324 (1914).

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New Derivative of Dinaphthylethane

By M. Szwarc and A. Shaw

Previous studies of the pyrolysis of toluene and its derivatives[1,2,3,4] have demonstrated that the initial decomposition of these compounds is represented by the equation

$$C_6H_5CH_3 \longrightarrow C_6H_5CH_2 + H\cdot$$

Benzyl radicals (or their derivatives) dimerize, and this process accounts for the presence of dibenzyl (or its derivatives) among the products of pyrolysis. We have found recently[5] that the pyrolysis of 1- and 2-methylnaphthalenes takes place according to the same scheme to yield 1,2-bis-(1-naphthyl)-ethane, m.p. 162–163°, reported[6] 162–163°, picrate m.p. 204–205°, reported[7] 205°, and 1,2-bis-(2-naphthyl)-ethane, m.p. 182–184°, reported[8] 182–183°, picrate m.p. 198°, reported[8] 198°, respectively.

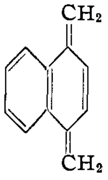
We find that the same scheme applies to the pyrolysis of 2,6-dimethylnaphthalene. The dimer was identified as 1,2-bis-(6-methyl-2-naphthyl)-ethane, m.p. 213–215°.

Anal. Calcd. for $C_{24}H_{22}$: C, 92.9; H, 7.1; mol. wt., 310. Found: C, 92.4; H, 6.95; mol. wt., 304.

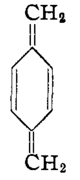
Its picrate melts at 210°.

Anal. Calcd. for $C_{30}H_{25}O_7N_3$: N, 7.9. Found: N, 8.1.

It is interesting to note that the pyrolysis of 1,4-dimethylnaphthalene results in the formation of quinono-hydrocarbon (A),[9] which is a homolog of a similar compound (B) produced in the pyrolysis of *p*-xylene.[10]



A



B

One could expect that a similar compound would be produced in the pyrolysis of 2,6-dimethylnaphthalene, but that is not the case.

These pyrolyses have been carried out in a flow system essentially similar to that described previously by one of us.[1] The decomposition was investigated at temperatures of about 800°, pressures of the order of 5–10 mm., and times of contact of the order 0.5–1 sec. Due to the low volatility of these compounds it was necessary to heat electrically the tubes and taps composing this section of the apparatus, through which the compounds investigated were introduced into the reaction vessel. The dimers formed in the pyrolysis crystallized on the walls of a tube leading from the reaction vessel. This tube was maintained at a temperature of about 50° which was sufficiently high to prevent crystallization of the undecomposed methylnaphthalenes present in the gas phase. The dimers collected in the tube were subsequently dissolved in the appropriate solvents and purified by crystallization.

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[1] M. Szwarc, *Nature*, **160**, 403 (1947); *J. Chem. Phys.*, **16**, 128 (1948).

[2] M. Szwarc and J. S. Roberts, *ibid.*, **16**, 609 (1948).

[3] J. S. Roberts and M. Szwarc, *ibid.*, **16**, 981 (1948).

[4] M. Szwarc and J. S. Roberts, This Journal, **70**, 2831 (1948).

[5] A. Shaw and M. Szwarc, unpublished results.

[6] P. Schorigin, *Ber.*, **59**, 2512 (1926).

[7] W. Friedmann, *ibid.*, **49**, 281 (1916).

[8] W. Friedmann, *ibid.*, **49**, 1354 (1916).

[9] M. Szwarc, *J. Polymer Sci.*, in press; summary in *J. Polymer Sci.*, June, 1950.

[10] M. Szwarc, Discussions Faraday Soc., No. 2, 46, 1947.

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Preparation and Purification of Potassium Ferrate. VI

By G. W. Thompson,[1] L. T. Ockerman[2] and J. M. Schreyer

Numerous investigators[3,4,5] have reported wet methods for the preparation of solutions and impure crystalline samples of potassium ferrate(VI).

A procedure for the preparation of pure potassium ferrate(VI) has been reported by Schreyer.[6]

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[1] Richfield Oil Corp., Bakersfield Laboratory, Bakersfield, Calif.

[2] Deceased April 11, 1950.

[3] E. F. Fremy, *Compt. rend.*, **12**, 23 (1841); **14**, 424 (1842).

[4] L. Moser, *J. prakt. Chem.*, [2] **56**, 425 (1897).

[5] L. Losana, *Gazz. chim. ital.*, **55**, 468 (1925).

[6] J. M. Schreyer, Thesis, "Higher Valence Compounds of Iron," Oregon State College, Corvallis, Oregon, 1948.

This procedure involved the oxidation of hydrous ferric oxide suspended in 8 *M* potassium hydroxide by bubbling chlorine gas through the solution which was maintained at a temperature of 50–55°. This procedure was laborious and gave low yields.

Hrostowski and Scott[7] reported the preparation of 96.9% potassium ferrate by an analogous method, except that they utilized sodium hypochlorite as an oxidizing agent and precipitated potassium ferrate from the solution of sodium ferrate by addition of solid potassium hydroxide until saturation was attained. Yields were reported from 10 to 15% of the theoretical.

Experimental

Preparation of Potassium Ferrate.—Preparations of samples of potassium ferrate were made using the methods of Schreyer[6] and Hrostowski and Scott.[7]

Additional preparations of potassium ferrate were made by the hypochlorite method except that hydrous ferric oxide was formed by the addition of ferric nitrate, rather than ferric chloride, to concentrated sodium hypochlorite solutions. The oxidation took place almost immediately at room temperature in contrast to the 50–55° temperature necessary with the ferric chloride–sodium hypochlorite method. Although no purification of the samples was carried out, yields were determined analytically by the arsenite–bromate method.[8] The results are shown in Table I.

TABLE I

COMPARISONS OF YIELDS OF POTASSIUM FERRATE BY DIFFERENT METHODS OF SYNTHESIS

Salts of iron	Oxidizing agent	Yield in grams	Purity, %	Theoretical yield, %
$FeCl_3 \cdot 6H_2O$[a]	Cl_2	8.36	15.46	7.0
25 g.		5.27	16.81	4.8
		10.38	14.72	8.3
$FeCl_3 \cdot 6H_2O$[b]	NaOCl	6.90	67.21	25.3
25 g.		10.74	52.46	30.7
		9.64	74.71	39.3
$Fe(NO_3)_3 \cdot 9H_2O$	NaOCl	12.13	51.20	50.6
25 g.		10.43	63.40	53.9

[a] Method of Schreyer. [b] Method of Hrostowski and Scott.

Purification.—Previous methods of purification removed chloride impurities by taking advantage of the fact that a portion of this impurity remained in the saturated potassium hydroxide solution from which the potassium ferrate had been precipitated. Brönsted's data[9] show a pronounced increase in the solubility of both potassium chloride and potassium nitrate as the potassium hydroxide molarity is decreased. The solubility at 20° of potassium ferrate in various concentrations of potassium hydroxide was determined by the recommended total iron method.[8] An impure K_2FeO_4 sample was selected in order to simulate the conditions encountered during actual purifications by means of the reprecipitation method. The chloride ion present in the solutions of known potassium hydroxide concentrations saturated with potassium ferrate was determined by the Mohr method.[10] The concentration of potassium ferrate in these solutions was determined by the total iron method.[8] Results are shown in Table II. These data indicate that the precipitation of the bulk of the dissolved potassium ferrate would be accomplished by making the solution 11 *M* in potassium hydroxide, but the major part of the potassium chloride impurity as well as the potassium nitrate would still be in solution. Brönsted[9] reports that the solubility of potassium chloride in 10.95 *M* potassium hydroxide is 20.35 g./l.

TABLE II

CONCENTRATION OF POTASSIUM CHLORIDE AND POTASSIUM FERRATE IN AQUEOUS SOLUTIONS OF POTASSIUM HYDROXIDE

Sample number	KOH, m./l.	KCl, g./l.	Saturated K_2FeO_4, g./l.
1	6.15	23.8	13.35
2	6.86	23.6	11.80
3	7.60	23.3	8.81
4	8.22	22.9	7.52
5	9.41	21.6	5.06
6	10.92	20.4	3.02
7	11.55	17.2	2.66
8	13.03	12.4	2.09
9	14.58	..	1.80

Combined Preparation and Purification of Potassium Ferrate.—A combined preparation and purification process is advantageous in that mechanical losses are minimized and less time is consumed in drying and washing the reaction products. The following procedure is recommended.

Thirty grams of sodium hydroxide is dissolved in 75 ml. of water and the cooled solution is chlorinated with vigorous stirring while maintaining the temperature under 20°. Chlorination is continued until the weight of the solution has increased by 20 g. Seventy grams of solid sodium hydroxide is added slowly with stirring, permitting the temperature to rise as high as 25–30° to aid solution of the sodium hydroxide; finally, the mixture is cooled to 20°. The precipitated sodium chloride is removed by filtration through a fritted glass filter.

To the alkaline hypochlorite solution at 25–30°, 25 g. of ferric nitrate is added slowly. The temperature is maintained at 30° while saturating with sodium hydroxide. The mixture is then filtered with suction through a coarse fritted glass filter.

The filtrate of sodium ferrate is transferred to a 250-ml. beaker placed in a 20° water-bath and 100 ml. of saturated potassium hydroxide solution is added with stirring. Stirring is continued for 5 minutes, finally, filtering through a fritted glass filter of medium porosity. The filtrate is discarded.

The precipitate is leached on the filter with 4 or 5 successive 10-ml. portions of 3 *M* potassium hydroxide solutions. The liquid is drawn each time through the filter into 50 ml. of chilled saturated potassium hydroxide solution. The residue remaining on the filter has a light gray cast and is discarded.

The filtrate is transferred to a 250-ml. beaker and 50 ml. of chilled, saturated potassium hydroxide solution is added. Any solid potassium ferrate remaining in the filter flask is washed out with a few ml. of saurated potassium hydroxide solution. The final solution is approximately 11 *M* in potassium hydroxide. The solution is stirred for 5 minutes and is filtered through fritted glass of medium porosity.

The precipitate remaining on the filter is washed with 10 ml. of benzene. After three to five 20-ml. portions of 95% ethyl alcohol are drawn through the filter, the precipitate is transferred to a beaker containing 1000 ml. of 95% ethyl alcohol and stirred for 20 minutes. This washing is repeated three times. The precipitate is removed by filtration and dried by drawing 50 ml. of ethyl ether through the filter. During this drying operation, a calcium chloride tube is used to protect the potassium ferrate from the moisture of the atmosphere. Suction is continued for 20 minutes and final drying is accomplished by the use of a vacuum desiccator. Dry potassium ferrate is stable and should be kept in a desiccator.

Numerous samples were prepared by this method. Results of analysis, using the chromite method[11] gave yields of 44.1 to 76.4% of theory, and purities from 92.34 to 96.3% K_2FeO_4. These maximum yields were obtained when using centrifugation instead of filtration during the preparation.

If it is desirable to obtain a sample of greater purity than

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[7] Hrostowski and Scott, *J. Chem. Physics*, **18**, 105 (1950).

[8] Schreyer, Ockerman and Thompson, *Anal. Chem.*, **22**, 691 (1950).

[9] Brönsted, THIS JOURNAL, **42**, 1448-1454 (1920).

[10] Pierce and Haenisch, "Quantitative Analysis," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 258.

[11] Schreyer, Ockerman and Thompson, *Anal. Chem.*, in publication.

those prepared by the procedure recommended above, the sample is subjected to an additional reprecipitation from 6 *M* potassium hydroxide solution. In this Laboratory, such additional purifications of samples obtained by the recommended procedure gave products ranging in purity from 98.5 to 99% potassium ferrate, as analyzed by the chromite method,[11] although a great reduction in the quantity of potassium ferrate resulted.

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LEXINGTON, KENTUCKY

RECEIVED AUGUST 9, 1950

Phosphorus Oxychloride in the Preparation of Ketimines

BY ARTHUR W. WESTON AND R. J. MICHAELS, JR.

It has been found that phosphorus oxychloride is an excellent agent for promoting the formation of anils derived from 2-thienyl aryl and 2-thienyl alkyl ketones. Recently Hartough[1] reported that propyl 2-thienyl ketone yielded 28% of the Schiff base when condensed with aniline in the presence of iodine. However, by adding a small amount of phosphorus oxychloride to a refluxing solution of the reactants we were able to isolate 88% of the desired condensation product. Similarly, an improved yield of N-phenyl methyl 2-thienyl ketimine[1] resulted when phosphorus oxychloride was used. High yields were obtained with the other thienyl ketones employed.

The use of phosphorus oxychloride is particularly indicated for the 2-acylthiophenes which form insoluble complexes[1] with zinc chloride, a commonly employed condensing agent, and for other compounds that are sensitive to zinc chloride.

The addition of 0.5 cc.[2] of phosphorus oxychloride to a mixture of 0.25 mole of ketone and 0.3 mole of aniline was sufficient to ensure complete condensation, except in the case of phenyl 2-thienyl ketone. In this instance it was necessary to use twice the quantity of catalyst in order to obtain a good yield of N-phenyl phenyl 2-thienyl ketimine. In all condensations a slight excess of aniline was employed to compensate for the material removed by salt formation.

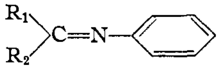
If the phosphorus oxychloride added at the start of the reaction proved to be inadequate, more could be added later without impairing the yield, as illustrated in the experimental section. An amount of concentrated hydrochloric acid, sirupy phosphoric acid, or a mixture of the two equivalent to the quantity of phosphorus oxychloride employed gave inferior results in the preparation of N-phenyl methyl 2-thienyl ketimine. With benzophenone and aniline, comparable results were realized when the phosphorus oxychloride was replaced by phosphorus oxybromide, phosphorus trichloride or phosphorus pentachloride. Phosphorus pentoxide was not effective, indicating that a halogen-containing catalyst is probably required.

Experimental

N-Phenyl Ethyl 2-Thienyl Ketimine.—A mixture of 27.9 g. (0.30 mole) of aniline, 35 g. (0.25 mole) of ethyl 2-thienyl ketone[3] and 0.5 cc. (0.0055 mole) of phosphorus oxychloride in 150 cc. of toluene was refluxed overnight in a flask equipped with a reflux condenser and a conventional water separator. At the end of this time, the theoretical amount (4.5 cc.) of water had been collected. After the reaction mixture was filtered to remove the aniline salt which had separated, the toluene was removed under reduced pressure and the residue distilled. There was obtained 10.2 g. of forerun followed by 40.4 g. (75%) of product, b.p. 133° at 1 mm., n^{24}_D 1.6347.

TABLE I

N-PHENYL KETIMINES



R_1	R_2	B.p. °C.	Mm.	M.p., °C.	Yield,[g] %	Formula	Nitrogen, %[h] Calcd.	Nitrogen, %[h] Found
2-Thienyl	Methyl	137–138	1.5	69–70[a,b]	68	$C_{12}H_{11}NS$	6.96	6.87
2-Thienyl	Ethyl	130–133	1.0	[c]	75	$C_{13}H_{13}NS$	6.51	6.42
2-Thienyl	*n*-Propyl	130–132	0.8	[d]	88	$C_{14}H_{15}NS$	6.11	6.04
2-Thienyl	Phenyl	158–162	1.7	123–124[b]	80	$C_{17}H_{13}NS$	5.32	5.35
Phenyl	Phenyl	160–163	0.8	113–114[e,f]	86	$C_{19}H_{15}N$	..	..

[a] Reported (ref. 1) m.p. 69–70°. [b] Crystallized from absolute alcohol. [c] n^{24}_D 1.6347. [d] n^{25}_D 1.6199; reported (ref. 1) b.p. 128–130 at 1 mm. [e] C. M. Rosser and J. J. Ritter, THIS JOURNAL, 59, 2179 (1937), report m.p. 113–114°. [f] Crystallized from acetone. [g] In most instances, some of the original ketone was recovered so that the yields are actually higher than reported. [h] We are indebted to Mr. E. F. Shelberg and members of the Microanalytical Department for these microanalyses.

In addition, it was observed that benzophenone, which does not condense directly with aniline, readily produced the anil when these reactants were treated with phosphorus oxychloride. On the other hand, the condensation of acetophenone with aniline was complicated by the formation of both acetophenone anil and dypnone anil. The latter product is to be expected in view of the tendency of acetophenone to undergo molecular condensation in the presence of acid. It is interesting to note, however, that the isostere, methyl 2-thienyl ketone, yielded little or no self condensation product under the same reaction conditions.

N-Phenyl Phenyl 2-Thienyl Ketimine.—By refluxing a mixture of 47 g. (0.25 mole) of phenyl 2-thienyl ketone,[4] 27.9 g. (0.30 mole) of aniline and 0.5 cc. (0.0055 mole) of phosphorus oxychloride for 17 hours, 2 cc. of water was liberated. After the addition of another 0.5 cc. (0.0055 mole) of phosphorus oxychloride along with 4.7 g. (0.05 mole) of aniline to combine with the acid subsequently formed, the mixture was again refluxed overnight. The theoretical amount of water (4.5 cc.) had then been liber-

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(1) H. D. Hartough, THIS JOURNAL, **70**, 1282 (1948).

(2) The importance of this quantity was not determined but it was noted that the use of appreciably smaller amounts of the agent lowered the yield considerably.

(3) H. D. Hartough and A. I. Kosak, THIS JOURNAL, **69**, 3099 (1947).

(4) The phenyl 2-thienyl ketone and methyl 2-thienyl ketone were furnished through the courtesy of Dr. G. A. Harrington of the Socony-Vacuum Oil Company.

ated. The crude product was isolated as described above and then distilled. A forerun of 6.6 g. was followed by the main fraction b.p. 158–162° at 1.7 mm. The 52.5 g. (80%) of ketimine thus obtained melted at 121–123°. Crystallization from absolute alcohol gave pure material m.p. 123–124°.

Data pertaining to the anils prepared in this study are recorded in Table I.

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Trypsin Hydrolysis of Lysine Ethyl Ester

BY HAROLD WERBIN AND ANN PALM

In a recent review Neurath and Schwert[1] have discussed the specificity requirements of synthetic substrates for trypsin. L-Lysine ethyl ester (LyEE) which possesses the necessary configuration, (1) a lysyl side chain, (2) a susceptible ester linkage and (3) a polar group (NH_2) alpha to the carbonyl of the susceptible bond, has been found to be hydrolyzed by trypsin. The rate of hydrolysis was measured by using the Hestrin technique[2] for the quantitative determination of esters. Figure 1 shows that the hydrolysis follows zero order kinetics at *p*H 7.88 and 25.0°. The calculated rate constant was found to be a linear function of the enzyme concentration as illustrated in Fig. 2.

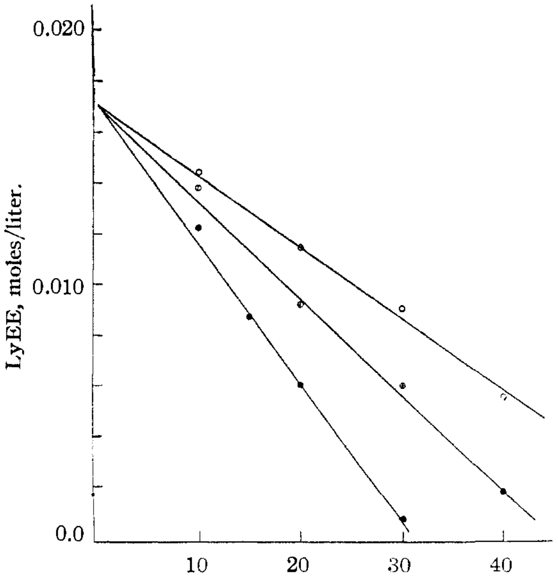

Fig. 1.—Zero order hydrolysis of 0.017 *M* lysine ethyl ester by trypsin at 25° and *p*H 7.88: ○, 2.73 × 10^{-3} mg. TPN/ml.; ◐, 3.66 × 10^{-3} mg. TPN/ml.; ●, 5.46 × 10^{-3} mg. TPN/ml.

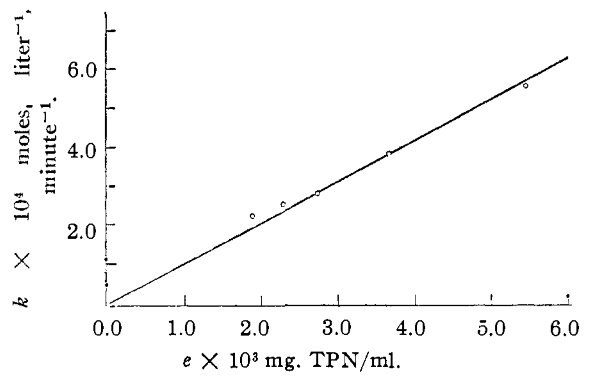

Fig. 2.—Specific rate constant for the hydrolysis of lysine ethyl ester by trypsin.

Recently Iselin, *et al.*,[3] have employed a colorimetric procedure similar to the one described below to measure the hydrolysis of hydroxamides by chymotrypsin, while the use of the Hestrin method to measure the extent of hydrolysis of l-arginine methyl ester[4] by trypsin and of l-tyrosine ethyl ester[4] by chymotrypsin has been described by Werbin.[5] Financial aid from the Dazian Foundation for Medical Research is acknowledged.

Experimental

Substrate.—LyEE was prepared by passing dry hydrogen chloride gas through a mixture of 6.0 g. of lysine monohydrochloride and 210 ml. of absolute ethanol until all the lysine had dissolved. The addition of hydrogen chloride was stopped, the solution was refluxed for 2 hours, and placed in the refrigerator overnight. On the following day it was distilled under reduced pressure and the residual oil was reësterified. After removal of the ethanol, crystals appeared and recrystallization from 25 ml. of absolute ethanol yielded 5.0 g. of white crystals, decomposing at 144°. Akabori and Kaneko[6] report 143.5–144.5°.

Kinetic Study.—To 2.0 ml. of 0.06 *M* LyEE and 2.0 ml. of 0.3 *M* phosphate buffer incubated for 10 minutes at 25° ± 0.02 was added 2.0 ml. of crystalline trypsin dissolved in hydrochloric acid solution of *p*H 3.0. The stopwatch was started at the time of half-addition of the trypsin. At the desired time 1.0 ml. of reaction mixture was added to 2.0 ml. of alkaline hydroxylamine solution following the procedure employed by Hestrin.[2] The ferric chloride solution used to develop the color was 0.4 *M*. The transmission of the solution at 520 mμ was read on a brociner-mass photoelectric colorimeter 5 minutes after the addition of the ferric chloride. A blank run demonstrated that there was no spontaneous hydrolysis of the ester.

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[1] H. Neurath and G. W. Schwert, *Chem. Revs.*, **46**, 69 (1950).

[2] S. Hestrin, *J. Biol. Chem.*, **180**, 249 (1949).

[3] B. M. Iselin, H. T. Huang and C. Niemann, *ibid.*, **183**, 403 (1950).

[4] These substrates were suggested by Dr. Harry Goldenberg.

[5] H. Werbin, Ph.D. Thesis, Polytechnic Institute of Brooklyn, June, 1950.

[6] S. Akabori and T. Kaneko, *Bull. Chem. Soc. Japan*, **11**, 208 (1936).

DEPARTMENT OF BIOCHEMISTRY
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RECEIVED AUGUST 16, 1950

Preparation of 1,1,3,3-Tetrachloropropane

BY A. M. WHALEY[1] AND H. W. DAVIS

There are twenty-nine possible chloropropanes, two of which do not have physical properties listed in the literature. Both of these compounds, namely, 1,1,3,3-tetrachloropropane and 1,1,1,3,3,3-hexachloropropane, have all the halogen atoms located on the end carbon atoms, so that it is not easy, if at all possible, to make these chlorides by processes involving addition of chlorine to a double bond; of interest, however, is the fact that the 1,1,1,3,3-pentachloropropane has been pro-

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[1] Halogen Chemicals Inc., 616 King St., Columbia, S. C.

duced by the action of chlorine on 1,1-dichlorocyclopropane.[2]

In the course of a fundamental study of the properties of the chloropropanes, we have prepared and characterized the missing 1,1,3,3-tetrachloropropane. The final step was the chlorination of 1,1,3-trichloropropane followed by fractionation to separate the three possible tetrachlorides, 1,1,1,3-, b.p. 157.5°; 1,1,3,3-, b.p. 162°; 1,1,2,3-, b.p. 178.3°.

Experimental

1,1,3-Trichloropropane was prepared, independently of, but by a method similar to that of Stitz,[3] from β-chloropropionaldehyde and PCl_5. Eight moles (1180 g.) of this trichloride diluted with 1000 g. of carbon tetrachloride was chlorinated at 55–60° in a two-liter flask fitted with a gas dispersion disc, stirrer, thermometer and condenser. Chlorine was passed in slowly until the gain in weight was 221 g., corresponding to 80% monochlorination, 10 hours being required for this operation. The reaction mixture was distilled using a 2.5 × 100 cm. column packed with glass helices, at atmospheric pressure until the carbon tetrachloride was removed and finally at 100 mm. pressure. The yield of 1,1,3,3-tetrachloropropane, boiling range 94–98° (100 mm.) was 320 g. or 30%. Properties of the purified material were: b.p. 161.9° (756 mm.); f.p. −27° (uncor.); d^{20}_{4} 1.4689; d^{25}_{4} 1.4612; n^{20}_{D} 1.4848; n^{25}_{D} 1.4813.

Anal. Calcd. for $C_3H_4Cl_4$: Cl, 77.97. Found: Cl, 77.19.

Acknowledgment.—The authors are grateful to Miss Darien Dorn and Mr. R. J. Breazeale who assisted in this work.

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(2) P. G. Stevens, This Journal, **68**, 620 (1946).

(3) F. Stitz, *Österr. Chem.-Ztg.*, **48**, 186 (1947); *C. A.*, **44**, 7226 (1950).

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Reciprocal Solubility of 4,6-Dimethyl-1,2-pyrone and Water

By Richard H. Wiley and Newton R. Smith

In studies involving reaction of 4,6-dimethyl-1,2-pyrone in water solution, it was observed that this unsaturated lactone possessed lower and upper consolute temperatures between 0 and 100°. Although this compound has been known for a number of years,[1] no comment has been made on this phenomenon. This report presents data on the solubility of 4,6-dimethyl-1,2-pyrone in water which establish upper and lower consolute temperatures.

The occurrence of an upper and lower consolute temperature of organic compounds in water solution has been observed in only a few cases; these compounds include amines,[2] ketones,[3] alcohols[4] and glycol monoethers.[5] This apparently is the first reported occurrence of both upper and lower consolute temperatures for an ester or lactone. The solubility relations between 4,6-dimethyl-1,2-pyrone and water are unusual for this reason and also because the region which consists of two phases occupies such a small area on the phase diagram. The lower and upper consolute temperatures are 59.7 ± 0.5° and 86.3 ± 0.5°, respectively, as shown in Fig. 1. In systems containing concentrations below 25% and above 50% of the pyrone by weight, the two liquids are completely miscible above 51.5°, the melting point of the pyrone. At room temperature the solid pyrone crystallizes from sufficiently concentrated solutions slowly on standing or rapidly if seeded with the pyrone.

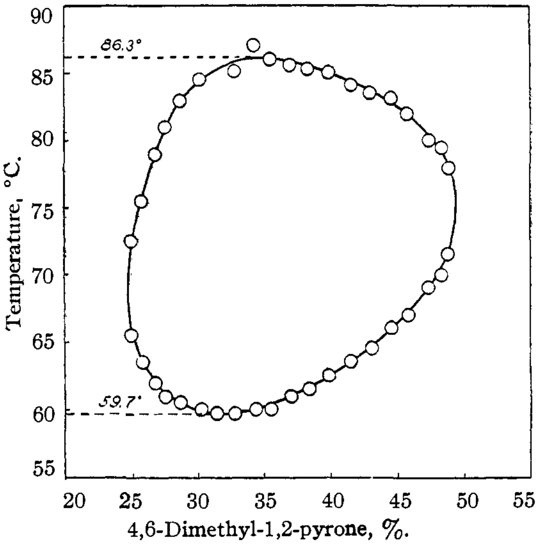

Fig. 1.—The 4,6-dimethyl-1,2-pyrone–water system.

Within the accuracy of the experiment the solubility curve is smooth except for one point on the higher solution curve when an upper consolute temperature of 87° was obtained at a concentration of 34.3% pyrone. The temperatures were read at a point of definite separation of phases. This separation was preceded by a marked opalescence. The exact temperature at which the opalescence occurs was difficult to determine and was obscured by a change from a water white to a yellow color as the experiment progressed.

The usual explanation for this phenomenon is that below the lower critical temperatures compound formation of the hydrogen bond type increases the solubility of the organic compound.[6] This is probably the explanation of the solubility behavior of the dimethylpyrone. There is a possibility that since the dimethylpyrone is easily hydrolyzed the phenomenon may be due to a reversible hydrolysis of the lactone to the corresponding acid. This requires that the pyrone precipitate from cold and the acid from hot solutions. This is not too likely as one would expect the acid to be soluble in the concentration ranges involved at the high temperatures and it is known that the solubilities of ethyl ether and ethyl acetate increase with decreasing temperature.

Experimental

4,6-Dimethyl-1,2-pyrone, prepared by the decarboxylation of isodehydroacetic acid,[1] was distilled repeatedly and

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(1) Hantzsch, *Ann.*, **222**, 9 (1883).

(2) Flaschner, *J. Chem. Soc.*, **95**, 668 (1909).

(3) Kohnstamm and Timmermans. *Verslag Akad. Wetenschappen Amsterdam*, **21**, 783 (1913).

(4) Timmermans. *Arch. Néerland sci.*, **6**, 147 (1922).

(5) Cox, Nelson and Cretcher. This Journal, **49**, 1080 (1927).

(6) Glasstone, "Textbook of Physical Chemistry," second ed., D. Van Nostrand Company, Inc., New York, N. Y., 1946, p. 728.

stored in a vacuum desiccator over calcium chloride. The pyrone melted at 51° (reported 51.5°).

A weighed amount of the pyrone was placed in a 50-ml. flask equipped with a stirrer and a cork stopper. The flask was placed in a water-bath with a thermometer and stirrer. Weighed quantities of freshly distilled water were added from a weighing bottle, the water-bath heated above the upper consolute temperature, and the bath allowed to cool slowly, during which time the upper and lower solution temperatures were recorded; then more water was added and the procedure repeated. These temperatures were reproducible within ±0.5°. Readings were recorded at the temperature at which there was a definite separation into two phases. The data are plotted in Fig. 1.

Acknowledgment.—The authors wish to thank the Research Corporation for a grant made in support of a program under which this work was done.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF LOUISVILLE
LOUISVILLE, KENTUCKY

RECEIVED NOVEMBER 6, 1950

COMMUNICATIONS TO THE EDITOR

NEOMYCINS B AND C, AND SOME OF THEIR DEGRADATION PRODUCTS

Sir:

In the course of purification of the antibiotic complex termed neomycin by Waksman and Lechevalier,[1] we have obtained by chromatography of the hydrochloric acid salt[2] in 80% methanol over alumina two homogeneous biologically active fractions. One of these closely resembles the neomycin B described by Regna and Murphy,[3] while the properties of the other, named by us neomycin C, sharply differentiate it from neomycin A[4] (see Table I).

TABLE I

COMPARISON OF PROPERTIES OF NEOMYCINS

	Neomycin component B, amorphous hydrochloride	Neomycin component C, amorphous hydrochloride	Neomycin A[4] amorphous hydrochloride	Neomycin B[3] amorphous sulfate
Biopotency in[a] nutrient broth *vs. Klebsiella pn.*	265 units/mg.	180 units/mg.	20 units/mg.[b]	260 255 units/mg.
Biopotency on nutrient Agar *vs. B. subtilis*	86 units/mg.	121 units/mg.	1700 units/mg.[b] 710 units/mg.[b]	....
$[\alpha]_D$	+54°	+80°	+83°	+58°

[a] The units are based on a comparison with a Waksman standard preparation. [b] These values determined with a sample of neomycin A hydrochloride kindly supplied by Dr. Karl Folkers.

Crystalline reineckates, picrolonates and *p*-(*p'*-hydroxyphenylazo)-benzenesulfonates have been prepared from both entities. In addition, antibacterially inactive, crystalline N-acetates have been obtained (*Neomycin B N-acetate*, needles from aqueous acetone; m.p. 200–205° with decomposition, after darkening and softening 186–190°; $[\alpha]^{22}_D$ +62°, 0.4% in water. *Anal.* Found:[5] C, 50.71; H, 6.95; N, 9.45; acetyl, 32.4. *Neomycin C N-acetate*, needles from aqueous acetone; m.p. similar to that of neomycin B N-acetate, but showing a depression of 10° in mixed melting point determination; $[\alpha]^{22}_D$ +90°, 0.4% in water. *Anal.* Found: C, 51.09; H, 7.47; N, 9.24; acetyl, 32.7). These data suggest that the two bases may be isomeric. All the nitrogen atoms are present as primary amino groups (Van Slyke).

Methanolysis of the hydrochlorides afforded the following two fragments:

(1) An amorphous hydrochloride, identical from both neomycin B and C, which was devoid of reducing power and yielded all its nitrogen as amino nitrogen in the Van Slyke determination. The empirical formula, $C_9H_{19}O_5N_3 \cdot 3HCl$, may be derived from the analyses of the following crystalline derivatives. *N-acetate*, needles from methanol; decomposes *ca.* 300° without melting, after sintering at 260°; $[\alpha]^{22}_D$ +88°, 0.3% in water. *Anal.* Calcd. for $C_9H_{16}O_5N_3(COCH_3)_3$: C, 48.00; H, 6.71; N, 11.20; acetyl, 34.4. Found: C, 47.76, 47.94; H, 6.95, 7.76; N, 11.46; acetyl, 36.5. *N-Benzoate*, needles from aqueous methanol, decomposes to black tar at 299–300° after darkening at 270°; $[\alpha]^{22}_D$ +70°, 0.5 % in methanol. *Anal.* Calcd. for $C_9H_{16}O_5N_3(COC_6H_5)_3$. C, 64.16; H, 5.57; N, 7.48. Found: C, 64.54; H, 6.02; N, 7.43. *Heptaacetate*, prisms from acetone, dried sample softens at 165°, undergoes transition 190–215°, liquifies at 260–262°; the cooled and solidified material (needles) then melts (without transition) at 262–265°; $[\alpha]^{22}_D$ +49°, 0.5% in methanol. *Anal.* Calcd. for $C_9H_{12}O_5N_3(COCH_3)_7$ (mol. wt., 5.44): C, 50.83; H, 6.12; N, 7.73; total acetyl,

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[1] S. A. Waksman and H. A. Lechevalier, *Science*, **109**, 305 (1949).

[2] The crude neomycin preparations used were produced by the Divisions of Microbiological and Chemical Development, E. R. Squibb & Sons, New Brunswick, N. J.

[3] P. P. Regna and F. X. Murphy, THIS JOURNAL, **72**, 1045 (1950).

[4] R. Peck, C. E. Hoffhine, P. Gale and K. Folkers, *ibid.*, **71**, 2590 (1949).

[5] All analytical determinations were carried out by Mr. J. F. Alicino, Microanalytical Laboratory, E. R. Squibb & Sons, New Brunswick, N. J.