evaporated to dryness and the residue was acetylated as above.

(b) Use of Hydrochloric Acid.—A solution of 50 g. of crude I in 100 ml. of acetic anhydride was treated with 14.9 ml. (1 equiv.) of concd. hydrochloric acid. The mixture was refluxed for two hours, cooled and treated with 12.5 g. of sodium acetate. After oxidation, the reaction mixture was processed as above and gave 5.2 g. of pregnadienolone acetate (IV), m.p. 165–170°; $[\alpha]^{25}_D$ −39.5°; E, 264 (233 mμ) (96.0% pure).

(c) Use of Acetyl Chloride.—A sample of 50 g. of crude I in 100 ml. of acetic anhydride was treated with 8.55 g. (1 equiv.) of acetyl chloride. The mixture was refluxed for four hours, treated with 12.5 g. of sodium acetate and worked up as usual after oxidation. The product weighed 4.4 g., m.p. 165–171°; $[\alpha]^{25}_D$ −38.9°; E, 259 (233 mμ) (94.3% pure).

(d) Use of p-Toluenesulfonic Acid.—Fifty grams of crude I in 100 ml. of acetic anhydride was treated with 2 g. of p-toluenesulfonic acid and refluxed for eight hours. Sodium acetate (1 g.) was added and the mixture was oxidized and worked up as usual. Only 0.9 g. of pregnadienolone acetate (IV) was obtained, m.p. 170–173°; $[\alpha]^{13}_D$ −40.2°; E, 275 (233 mμ) 100% pure). The mother liquor was treated with water and gave 21.5 g. of resin which contained 2.3 g. of pregnadienolone acetate as indicated by the ultraviolet absorption maximum, E, 30 (235 mμ).

(e) Other Catalysts.—Undesired reactions occurred so that the product could not be isolated using the following acid catalysts: SnCl₄, BF₃, ZnCl₂, HClO₄, oxalic acid and tri-chloroacetic acid. There was little reaction with traces of acids. For example, 20 g. of I in 100 ml. of acetic anhydride was unaffected after refluxing with 0.1 cc. H₂SO₄ for eight hours.

Thermal Cleavage of 5-Pregnen-3β,16β-diol-20-one-3-acetate-16-(δ-acetoxy-γ-methylvalerate) (III).—Fifty grams of I was treated according to the directions (a) for the preparation of IV. After the reduction of excess chromic acid with sodium bisulfite solution, the oxidation mixture containing III was concentrated *in vacuo* and extracted with ether. The ether solution was washed neutral and dried over anhydrous magnesium sulfate. A sample evaporated to dryness showed E, 91 (237 mμ) corresponding to 33% of 5,16-pregnadien-3β-ol-20-one acetate (IV) (already formed due to cleavage under the acid conditions in the reaction and processing) in the crude III.

The ether solution was concentrated and mixed with 65 ml. of xylene. The solution was distilled until the temperature reached 135° and the remainder was refluxed for one hour. A sample was evaporated to dryness and showed E, 136.6 (237 mμ). This corresponds to 49.6% of IV, an increase of 50% over the pretreated mixture of III and IV.

The solution was chilled overnight and the product collected. The yield was 9.0 g., m.p. 156.2–165.6°; E, 185 (235 mμ) corresponding to a content of 67.5% of IV. Two recrystallizations from acetic anhydride gave 4.1 g. of pregnadienolone acetate, m.p. 170.5–172.5°; E, 269 (233 mμ); $[\alpha]_D$ −39.1°.
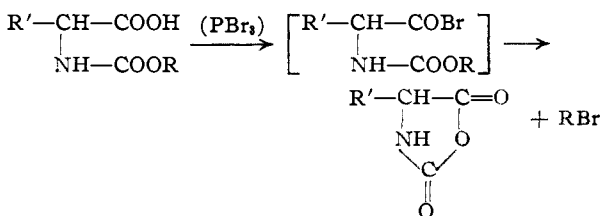
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NOTES

Synthesis of N-Carboxy-α-amino Acid Anhydrides from N-Carbalkoxy-α-amino Acids by the Use of Phosphorus Tribromide

BY DOV BEN-ISHAI AND EPHRAIM KATCHALSKI

The results of the investigation of the cyclization of N-carbalkoxy-β-haloalkylamines[1] and of the reaction between urethans and acetyl bromide and chloride,[2] suggested that N-carbalkoxy-α-amino acid bromides would cyclize more readily than the corresponding chlorides[3] to give N-carboxy-α-α-amino acid anhydrides.

It was, indeed, found that the N-carbalkoxy-α-amino acids given in Table I, when treated at room temperature with phosphorus tribromide, were converted with excellent yields, into the corresponding N-carboxy-α-amino acid anhydrides (oxazolidine-2,5-diones) (*cf.* Table II). The reaction is represented by the general equation

$$\text{R'—CH—COOH} \xrightarrow{\text{(PBr}_3\text{)}} \left[\begin{array}{c} \text{R'—CH—COBr} \\ | \\ \text{NH—COOR} \end{array} \right] \longrightarrow$$

$$\begin{array}{c} \text{R'—CH—C=O} \\ | \quad\quad | \\ \text{NH} \quad \text{O} \\ \searrow_{\text{C}}\swarrow \\ \| \\ \text{O} \end{array} + \text{RBr}$$

Under practically the same experimental conditions, N-carbethoxy- and N-carbobenzoxyanthranilic acid gave nearly quantitative yields of isatoic anhydride.

Experimental

N-Carbalkoxy-α-amino Acids.—The N-carbethoxy- and N-carbobenzoxyamino acids used were prepared by coupling ethyl chloroformate and carbobenzoxy chloride, respectively, with the corresponding α-amino acids in a manner similar to that prescribed for the synthesis of carbobenzoxyglycine.[4] The yields and analytical data are given in Table I.

N-Carboxy-α-amino Acid Anhydrides. General Procedure.—Phosphorus tribromide (0.02 mole) was added slowly to the N-carbalkoxy-α-amino acid (0.05 mole) dissolved or suspended in anhydrous ether (50 ml.). The reaction mixture was kept at room temperature for 12 hours. Dry petroleum ether (100 ml.) was added, and crystallization of anhydride promoted by keeping the reaction mixture for several hours at 4°. The anhydride, which separated out as a crystalline mass, was filtered, washed thoroughly with dry petroleum ether and recrystallized from a dry mixture of ethyl acetate and petroleum ether (Table II).

Isatoic Anhydride.—Phosphorus tribromide (0.035 mole) was added to 0.1 mole of N-carbethoxy or N-carbobenzoxy-anthranilic acid (prepared by coupling anthranilic acid with the corresponding carbalkoxy chloride, in the usual way; *cf.* Table I) dissolved in anhydrous ether (100 ml.). After 24 hours at room temperature isatoic anhydride had separated as a microcrystalline product. It was filtered, washed with dry ether and recrystallized from alcohol; m.p. 240–243°,[5] yield about 90%.

Anal. Calcd. for C₈H₅NO₃: C, 58.9; H, 3.1; N, 8.6. Found: C, 58.5; H, 3.2; N, 8.3.

For further identification, the anhydride was converted

(1) E. Katchalski and D. Ben-Ishai, *J. Org. Chem.*, **15**, 1067 (1950).

(2) D. Ben-Ishai and E. Katchalski, *ibid.*, **16**, 1025 (1951).

(3) H. Leuchs, *Ber.*, **39**, 857 (1906); H. Leuchs and W. Geiger, *ibid.*, **41**, 1721 (1908); F. Wessely, *E. physiol. Chem.*, **146**, 72 (1925).

(4) "Organic Syntheses," **23**, 14 (1943).

(5) E. Erdmann, *Ber.*, **32**, 2165 (1899), gives m.p. 240° (dec.).

TABLE I

N-CARBALKOXY-α-AMINO ACIDS

Compound (Cbzo, carbobenzoxy; Cbetho, carbethoxy.)	Yield, %	M.p. (°C.) uncor.	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
N-Cbetho-DL-phenylalanine	85	76	$C_{12}H_{15}NO_4$	60.8	60.6	6.3	6.4	5.9	6.2
N-Cbzo-DL-phenylalanine	80	102[a]	$C_{17}H_{17}NO_4$	68.2	68.5	5.7	5.8	4.7	4.8
N-Cbetho-DL-alanine	64	83[b]	$C_6H_{11}NO_4$	44.7	44.9	6.8	6.5	8.7	8.5
N-Cbzo-DL-alanine	76	114[c]	$C_{11}H_{13}NO_4$	59.2	59.0	5.8	5.9	6.3	6.5
N-Cbetho-DL-valine	86	56	$C_8H_{15}NO_4$	50.8	51.0	7.9	8.0	7.4	7.3
N-Cbzo-DL-valine	88	71	$C_{13}H_{17}NO_4$	62.2	62.4	6.8	6.6	5.6	5.8
N,N'-Dicbzo-L-lysine	82	150[d]	$C_{22}H_{26}N_2O_6$	63.8	63.6	6.3	6.6	6.8	7.1
N-Cbzo-sarcosine	87	53–54	$C_{11}H_{13}NO_4$	59.3	59.4	5.8	5.6	6.3	6.6
N-Cbetho-anthranilic acid	78	125 dec.	$C_{10}H_{11}NO_4$	57.4	57.4	5.3	5.4	6.7	6.8
N-Cbzo-anthranilic acid	55	141	$C_{15}H_{13}NO_4$	66.4	66.6	4.8	4.9	5.2	5.0

[a] M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932), give m.p. 103°. [b] E. Fischer and W. Axhausen, *Ann.*, **340**, 137 (1905), give m.p. 84° (cor.). [c] M. Bergmann and L. Zervas, ref. a, give m.p. 114–115° (cor.). [d] M. Bergmann, L. Zervas and W. F. Ross, *J. Biol. Chem.*, 111, 245 (1935), give m.p. 150°. J. Bredt and H. Hof, *Ber.*, **33**, 26 (1900), give m.p. 126° (dec.).

TABLE II

N-CARBOXY-α-AMINO ACID ANHYDRIDES (OXAZOLIDINE-2,5-DIONES)

N-Carbalkoxy-α-amino acid	Oxazolidine-2,5-dione	Yield, %	M.p. (°C.) uncorrected	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
N-Cbetho-DL-phenylalanine	4-Benzyl	82	125–126 (dec.)[a]	$C_{10}H_9NO_3$	62.8	62.7	4.7	4.9	7.3	7.4
N-Cbzo-DL-phenylalanine	4-Benzyl	84	125–126 (dec.)[a]	$C_{10}H_9NO_3$	62.8	62.6	4.7	4.7	7.3	7.4
N-Cbetho-DL-alanine	4-Methyl	60	44–45[b]	$C_4H_5NO_3$	41.7	41.9	4.4	4.6	12.2	12.4
N-Cbzo-DL-alanine	4-Methyl	68	44–45[b]	$C_4H_5NO_3$	41.7	41.7	4.4	4.6	12.2	12.3
N-Cbetho-DL-valine	4-Isopropyl	85	77–79[c]	$C_6H_9NO_3$	50.4	50.1	6.3	6.4	9.8	10.0
N-Cbzo-DL-valine	4-Isopropyl	88	77–79[c]	$C_6H_9NO_3$	50.4	50.3	6.3	6.4	9.8	10.1
N,N'-Dicbzo-L-lysine	4-(δ,N-Cbzo-aminobutyl)	85	99 (dec.)[d]	$C_{15}H_{18}N_2O_5$	58.8	58.7	5.9	5.9	9.2	9.0
N-Cbzo-sarcosine	3-Methyl	90	99 (dec.)[e]	$C_4H_5NO_3$	41.7	41.9	4.4	4.1	12.2	12.1

[a] H. Leuchs and W. Geiger, *Ber.*, **41**, 1721 (1908), give m.p. 127–128° (dec.). [b] J. L. Bailey, *J. Chem. Soc.*, 3461 (1950), gives m.p. 45–46°. [c] W. E. Hanby, S. G. Waley and J. Watson, *ibid.*, 3009 (1950), give m.p. 78–79°. [d] M. Bergmann, L. Zervas and W. F. Ross, *J. Biol. Chem.*, 111, 245 (1935), give m.p. 100° (dec.). [e] F. Sigmund and F. Wessely, *Z. physiol. Chem.*, **157**, 91 (1926), give m.p. 99–100° (dec.).

by aqueous ammonia into anthranilamide; from chloroform, m.p. 108–109°.[6]

Anal. Calcd. for $C_7H_8ON_2$: N, 20.6. Found: N, 20.8.

(6) Kolbe, *J. prakt. Chem.*, [2] **30**, 487 (1884).

THE WEIZMANN INSTITUTE OF SCIENCE
REHOVOTH, ISRAEL

Substituted Benzimidazoles[1]

BY CARL TABB BAHNER, HENRY A. RUTTER, JR., AND LYDIA MOORE RIVES

It has been reported[2] that benzimidazole is an antagonist of adenine and it seemed worthwhile to investigate whether substituted benzimidazoles would inhibit the growth of cancers. In addition to a number of previously described compounds the following have been prepared.

5,7(or 4,6)-Dinitrobenzimidazole.—A solution of 1.0 g. of 1,2-diamino-4,6-dinitrobenzene[3] (0.005 mole) and 0.37 g. of formic acid (0.008 mole) in 5 ml. of 4 N HCl was refluxed 40 minutes, cooled and neutralized with ammonia. The precipitate was recrystallized once from water and twice from ethanol (with activated charcoal) to yield 0.50 g. of yellow crystals, m.p. 239–240° (dec.).

(2) D. W. Wooley, *J. Biol. Chem.*, **152**, 225 (1944).

(3) Cf. R. Nietzke and H. Hagenbach, *Ber.*, **30**, 544 (1897).

Anal.[4] Calcd. for $C_7H_4N_4O_4$: C, 40.39; H, 1.94. Found: C, 40.55; H, 1.79.

4(or 7)-Amino-6(or 5)-nitrobenzimidazole.—A solution of 3.36 g. of 5-nitro-1,2,3-triaminobenzene (0.02 mole) and 1.38 g. of formic acid (0.03 mole) in 20 ml. of 4 N HCl was refluxed 40 minutes and cooled to room temperature. The black, needle-shaped crystals (probably a hydrochloride salt of the benzimidazole) were filtered off, dissolved in boiling concentrated HCl, diluted with water, and neutralized with ammonia to produce a red precipitate which, after one recrystallization from water and two recrystallizations from alcohol (with activated charcoal), yielded 0.8 g. of yellow crystals, m.p. 240–241° (dec.). An additional 0.2 g. of product was obtained by neutralizing the original reaction mixture with ammonia and recrystallizing the precipitate.

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.19; H, 3.37. Found: C, 47.37; H, 3.35.

5(or 6)-Chloro-2-hydroxymethylbenzimidazole.—Prepared from p-chloro-o-phenylenediamine and glycolic acid and recrystallized from ethyl acetate this product melted at 206–208° (dec.). (Water and ethyl alcohol were unsatisfactory solvents for recrystallization.)

Anal. Calcd. for $C_8H_7ClN_2O$: C, 52.71; H, 3.86. Found: C, 52.78; H, 3.60.

5(or 6)-Nitro-2-hydroxymethylbenzimidazole.—Prepared from p-nitro-o-phenylenediamine and glycolic acid and recrystallized from ethyl acetate the yellow crystals melted at 194–195° (dec.).

Anal. Calcd. for $C_8H_7N_3O_3$: C, 49.74; H, 3.63. Found: C, 49.56; H, 3.60.

5(or 6)-Chlorobenzimidazole Hydrochloride.—A solution of 5(or 6)-chlorobenzimidazole[5] in concentrated HCl was

(4) All carbon and hydrogen analyses by Galbraith Microanalytica Laboratories, Knoxville, Tennessee.

(5) O. Fischer, *Ber.*, **37**, 556 (1904).

evaporated to dryness. The residue was dissolved in warm isopropyl alcohol and thrown out by addition of acetone, m.p. 239–240° (dec.); solubility in water at 25° about 5%. *Anal.* Calcd. for $C_7H_6Cl_2N_2$: ionic Cl, 18.75. Found: Cl, 18.48, 18.71.

5(or 6)-Aminobenzimidazole Dihydrochloride.—Isopropyl alcohol was added to a saturated solution of 5(or 6)-aminobenzimidazole[6] in dilute HCl and the resulting light pink crystals were washed with isopropyl alcohol and with ether. A sample kept in a vacuum desiccator gave a low analysis, apparently because of gradual loss of HCl, but a sample dried at atmospheric pressure gave satisfactory analyses; m.p. 299° (dec.); water solubility at 25° > 20%. *Anal.* Calcd. for $C_7H_9Cl_2N_3$: Cl, 34.40. Found: Cl, 34.33, 34.63.

We wish to express our appreciation to Mr. Charles Chumley and Mr. Eddie Pace for the preparation of the 1,2-diamino-4,6-dinitrobenzene and 5-nitro-1,2,3-triaminobenzene used in these preparations and to Dr. Alfred Gellhorn of Columbia University College of Physicians and Surgeons for arranging to screen several of the products against tumors.

(6) G. M. van der Want, *Rec. trav. chim.*, **67**, 45 (1948).

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Bromomethylation; Preparation of 2,6-Bis-(bromomethyl)-4-alkyl Phenols

BY WILLARD M. BRIGHT[1] AND PETER CAMMARATA

This paper presents a direct method for the preparation of crystalline monomeric bromomethyl alkyl phenols. In it the phenol, dissolved in glacial acetic acid, is allowed to react with paraformaldehyde and anhydrous hydrogen bromide. The generality of the method is attested to by the simple preparations of 2,6-bis-(bromomethyl)-4-methylphenol,[2] 2,6-bis-(bromomethyl)-4-*t*-butylphenol, and 2,6-bis-(bromomethyl)-4-*t*-octylphenol.[3]

There seems to have been no direct bromomethylation procedure reported in the literature, although chloromethylation of non-phenolic materials is routine. In the latter connection, it has been noted that employing the usual procedures, phenols react so readily that the reaction goes too far, yielding polymeric material.[4] Buehler[5] has chloromethylated substituted phenols containing such strongly polar groups as $-NO_2$ and $-COOH$ which have been found to retard the undesirable resinification reaction leading to polymeric materials. He treated the phenol in concentrated hydrochloric acid with formalin in the presence of a strong acid catalyst, such as H_2SO_4. A patent[6] exists in which it is claimed that monomeric, crystalline 2,6-bis-(chloromethyl)-4-methylphenol was obtained as a result of reaction of aqueous formaldehyde, cresol and

(1) Address communications to: Clark Laboratory, The Kendall Company, Cambridge 39, Massachusetts.

(2) This compound has been previously prepared by reaction of 2,6-bis-(hydroxymethyl)-phenol. See K. von Auwers, *Ber.*, **40**, 2532 (1907), and F. Uhlman and K. Brittner, *ibid.*, **42**, 2540 (1909).

(3) Nomenclature for parent methylol phenol given variously as: (a) 2,6-bis-(hydroxymethyl)-4-*t*-octylphenol, (b) 2,6-bis-(hydroxymethyl)-4-diisobutylphenol, (c) α,α'-*m*-xylenediol-2-hydroxy-5-1,1,3,3-tetramethylbutyl.

(4) R. C. Fuson and C. H. McKeever, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 65.

(5) (a) C. A. Buehler, *J. Tennessee Acad. Sci.*, **22**, 303 (1947); (b) C. A. Buehler, F. K. Kirchner and C. F. Deebel, *Org. Syntheses*, **20**, 59 (1940).

(6) I. G. Farbenind. A.-G., British Patent 347,887 (1931).

concentrated hydrochloric acid. We were unable to confirm this claim, nor were we able to prepare the desired bromomethyl compound from aqueous systems.

The *t*-butyl and *t*-octyl compounds reported herein have not been described previously. They were characterized by direct comparison with samples prepared from 2,6-bis-(hydroxymethyl)-4-*t*-butylphenol[7] and 2,6-bis-(hydroxymethyl)-4-*t*-octylphenol,[8] by hydrogen bromide using the method of von Auwers.[2]

Experimental[9]

2,6-Bis-(bromomethyl)-4-methylphenol.—To 150 g. of glacial acetic acid was added 54 g. of *p*-cresol and 35 g. of paraformaldehyde. The flask containing the mixture was immersed in an ice-bath and anhydrous hydrogen bromide was passed into the reaction mixture. Heat was evolved and the admission of HBr was regulated in such a manner that the temperature of the mixture was never allowed to exceed 80°. Near the saturation point of HBr in acetic acid (evidenced by fuming at the mouth of the flask) the suspended paraformaldehyde disappeared and a clear solution was obtained. HBr addition was stopped when the solution was completely saturated and the *p*-cresol derivative precipitated immediately. After the solid product was filtered off, and recrystallized from heptane, approximately 60% yield was obtained; m.p. 115–117°.

Anal. Calcd. for $C_9H_{10}Br_2O$: C, 36.8; H, 3.4; Br, 54.4. Found: C, 36.7; H, 3.4; Br, 54.3.

Other Phenols.—2,6-Bis-(bromomethyl)-4-*t*-butylphenol was prepared in the same manner as the cresol derivative when 4-*t*-butylphenol was used; yield 50%, m.p. 92–93°.

Anal. Calcd. for $C_{12}H_{16}Br_2O$: C, 42.9; H, 4.8; Br, 47.6. Found: C, 42.6; H, 4.8; Br, 47.4.

2,6-Bis-(bromomethyl)-4-octylphenol was prepared similarly from the commercially available phenol, which was not further purified; yield 25%, m.p. 87–90°. Both the butyl and octyl derivatives required several hours of refrigeration to effect crystallization.

Anal. Calcd. for $C_{16}H_{24}Br_2O$: C, 49.0; H, 6.2; Br, 40.7. Found: C, 48.1; H, 6.3; Br, 40.0.

(7) F. Hanus, E. Fuchs and E. Ziegler, *J. prakt. Chem.*, **153**, 327 (1939).

(8) J. B. Niederl, *Ind. Eng. Chem.*, **30**, 1269 (1938).

(9) Analyses by Carol K. Fitz, 115 Lexington Ave., Needham Heights 94, Massachusetts.

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The Reaction between Niobium Pentachloride and Niobium Metal

BY C. H. BRUBAKER, JR., AND R. C. YOUNG

Recently Schäfer, Göser and Bayer[1] have shown niobium tetrachloride is produced, when niobium pentachloride and niobium metal (in a molar ratio greater than 4/1) are caused to react at 350°. Their results were in agreement with those obtained in our own rather extensive study of the reaction between niobium pentachloride and niobium. Presented here, however, are certain of our results and conclusions which were not covered in their paper.

Large needles (*ca.* 1 cm. long) are obtained directly, after removal of excess pentachloride by vacuum sublimation at 120°, when the penta-

(1) H. Schäfer, C. Göser and L. Bayer, *Z. anorg. allgem. Chem.*, **265**, 258 (1951).

chloride and metal are heated together at 350–400° for one week in a sealed, evacuated tube.

The results of the present investigation are summarized in Table I.

TABLE I

THE REACTION OF NIOBIUM PENTACHLORIDE WITH NIOBIUM

Approximately 0.6 g. of niobium metal powder was used in each experiment

Expt.	NbCl$_5$/ Nb	Temp., °C.	Products	Cl/Nb in products after removal of any excess NbCl$_5$
1	5/1	350	Lg. needles of NbCl$_4$ with NbCl$_5$	4.0/1
2	5/1	400	Lg. needles of NbCl$_4$ with NbCl$_5$	4.0/1
3	4/1	400	NbCl$_4$ needles with NbCl$_3$, some NbCl$_5$	3.6/1
4	2/1	450–500	Inert NbCl$_3$ and Nb	2.70/1
5	3/2	400–450	Inert NbCl$_3$ and Nb	2.71/1
6	1/1	475–500	Inert NbCl$_3$ and Nb	2.68/1

The tetrachloride is somewhat soluble in ethanol, methanol, champhor, diisobutyl ketone and acetone and sparingly soluble in ethyl ether. It is believed that the tetrachloride reacts with these solvents, because hydrogen chloride vapor could be detected coming from the solutions, even when the solvents were carefully dried. Niobium tetrachloride is also moderately soluble in the monomethyl ether of ethylene glycol: no hydrogen chloride could be detected above these violet solutions.

It is surprising that the products from the last three experiments cited in Table I had an almost constant composition (approximately Nb$_3$Cl$_8$) in view of the varying conditions employed and the different ratios of pentachloride to metal. However, X-ray analyses showed that the material was a mixture of trichloride and metal. Moreover, although the trichloride can be sublimed (in vacuo) at about 500°,[2] the trichloride could not be removed from these mixtures by vacuum sublimation. Rather, at about 600°, a black sublimate of niobium tetrachloride appeared on a cold-finger condenser in a sublimation apparatus. If no condenser is employed, the tetrachloride disproportionates immediately and gives the tri- and pentachlorides.

Therefore, one must assume that niobium trichloride and niobium react at elevated temperatures and form some lower chloride (perhaps Nb$_3$Cl$_8$), which disproportionates and forms the metal and tetrachloride near 600°.

Analyses of samples from experiments 1, 2 and 3 were carried out by hydrolysis of the product in dilute ammonia. These solutions were acidified with nitric acid in order to oxidize the niobium. The niobium pentoxide, thus formed, was precipitated with ammonia, filtered, ignited and weighed and the chlorine was determined as silver chloride in the acidified filtrate. Samples from experiments 4, 5 and 6 were fused with sodium carbonate

(2) C. H. Brubaker and R. C. Young, THIS JOURNAL, 73, 4179 (1951).

and the cooled melts were dissolved in water. These solutions were acidified with nitric acid, the pentoxide was precipitated with ammonia and chlorine was determined as silver chloride from the acidified filtrate.

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Dimethylcarbamyldimethylthiocarbamyl Disulfide

BY EARL C. GREGG, JR.

The novel method by which the subject compound may be prepared prompted this note.

The action of bromine on bis-(dimethylthiocarbamyl) sulfide is to precipitate the sulfide completely as a rust colored solid of unknown structure which is comprised of one mole of the sulfide and five gram-atoms of bromine as determined by the weight of the product. This rust colored solid reacts with cold water to form a relatively unstable, colorless solid (I), m.p. 108–110° (uncor.). Elemental analysis and molecular weight determination of I require an empirical formula C$_6$H$_{12}$N$_2$OS$_3$. A polarogram of I exhibits a well-defined reduction wave, Fig. 1, characteristic of bis-(diethylthiocarbamyl) disulfide.[1] The reduction potential and
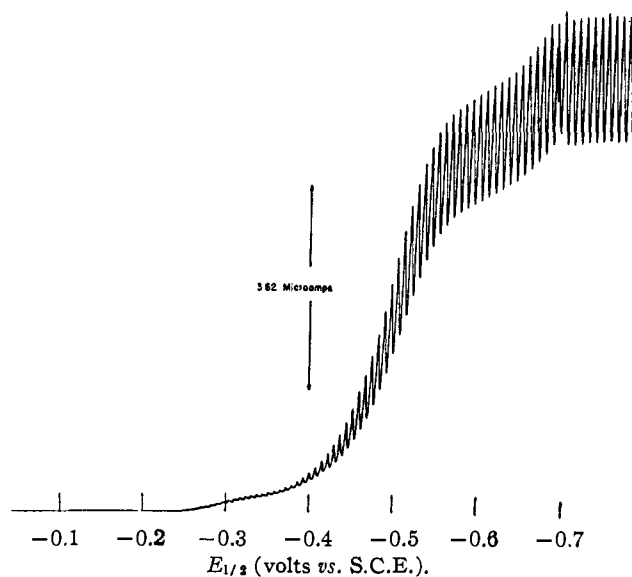

3.62 Microampa

-0.1 -0.2 -0.3 -0.4 -0.5 -0.6 -0.7
$E_{1/2}$ (volts vs. S.C.E.).

Fig. 1.

adsorption wave character suggest the presence of the >N—C—S—S—C—N< group.[1] However, an infrared spectrum of I, Fig. 2 center, exhibits both a carbonyl band at 5.94 μ and a thiocarbonyl band at 6.62μ.[2] To fit this evidence the above structural group may be modified to >N—C—S—S—C—N<.

The infrared spectrum of I has bands common to

(1) E. C. Gregg and W. P. Tyler, THIS JOURNAL, 72, 4561 (1950).

(2) Private communication. This assignment is in agreement with the extensive work not yet published on the thiocarbonyl absorption band by Mr. J. J. Shipman.
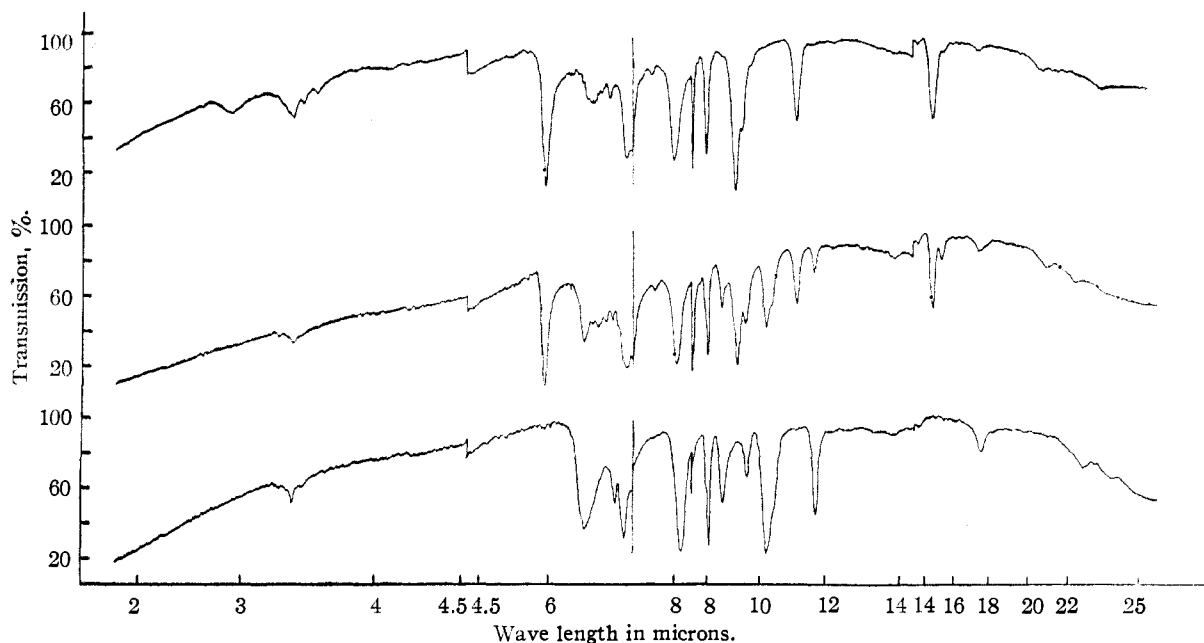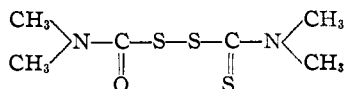
Fig. 2.—Top, dimethylcarbamyl disulfide (mull); center, dimethylcarbamyldimethylthiocarbamyl disulfide (mull); bottom, dimethylthiocarbamyl disulfide (mull); mull oils were Fluorolube from 2–7.4 μ and mineral oil from 7.4–25 μ.

the spectra of the related symmetrical disulfides, bis-(dimethylcarbamyl) disulfide (II), Fig. 2 top, and bis-(dimethylthiocarbamyl) disulfide (III), Fig. 2 bottom. A structure in agreement with all the above evidence is a mixed disulfide of a type which has not been reported, namely

$$CH_3 \diagdown N\text{—}C\text{—}S\text{—}S\text{—}C\text{—}N \diagup CH_3$$

with O under the first C and S under the second C.

That compound I is not an equimolar mixture of II and III may be demonstrated by the solubility of the compounds in various solvents. Compound II is soluble in water, methanol and benzene. Compound I is insoluble in water, but soluble in methanol and benzene. Compound III is insoluble in water and methanol, but soluble in benzene. If compound I were a mixture of II and III, complete solution in methanol could not be effected.

The sharp melting point of I suggests at once that I is not a double compound.

Compound I is an accelerator of rubber vulcanization and has an activity comparable to compound III, an ultra-accelerator. Compound II has no accelerator activity. Kawaoka[3] found that the zinc derivative of I, zinc dimethylcarbamate, had strong accelerator activity. Compound I is too unstable to be used as a practical rubber accelerator.

Experimental

Dimethylcarbamyldimethylthiocarbamyl Disulfide.—A sample of 20 g. (0.096 mole) of bis-(dimethylthiocarbamyl) sulfide[4] was dissolved in 200 ml. of benzene. To this solution at room temperature was added with stirring over a five-minute period a solution of 38.4 g. (0.48 gram-atom) of bromine in 100 ml. of carbon tetrachloride. A deep orange solid precipitated immediately. The stirring was continued until a uniform suspension was obtained. The insoluble orange colored precipitate was filtered off and washed with benzene, carbon tetrachloride and diethyl ether, respectively. The precipitate was added to 250 ml. of an ice-water mixture and the suspension stirred until all the orange solid had reacted. The temperature of the reaction mixture was not allowed to rise above 5°. A lemon-yellow solution formed and subsequently a colorless solid precipitated, m.p. 108–110° (uncor.) after one crystallization from methanol. Continued recrystallization to further purify the compound I resulted in decomposition. The weight of the colorless precipitate was 15.0 g. (0.059 mole) which is equivalent to 61% yield based on the assumption that one mole of compound I is theoretically available from one mole of bis-(dimethylthiocarbamyl) sulfide.

Anal. Calcd. for $C_6H_{12}N_2OS_2$: C, 32.12; H, 5.39; N, 12.49; O, 7.13; S, 42.87; mol. wt., 224.36. Found: C, 31.90, 32.03; H, 5.27, 5.36; N, 12.46, 12.48; S, 42.39, 42.25; O (difference), 7.92; mol. wt., 223, 224.

Bis-(dimethylcarbamyl) Disulfide.—A stream of carbonyl sulfide[5] was passed into 20 ml. of anhydrous dimethylamine in a flask immersed in melting ice until five grams had been absorbed. Colorless hygroscopic crystals of dimethylammonium dimethylthiocarbamate formed. The entire mixture was added to 50 ml. of petroleum ether and the solvent removed by decantation. The salt was dissolved in 20 ml. of water and an aqueous solution of iodine was added until the iodine color just persisted. The aqueous solution was extracted with benzene and the benzene layer evaporated. The residue consisted of colorless crystals of bis-(dimethylcarbamyl) disulfide. This compound is a powerful sternutator so that care should be taken not to allow fine particles of it to get suspended in the air. This disulfide may be crystallized from carbon tetrachloride with which it forms an addition compound of unknown composition. The addition compound decomposes when the crystals are allowed to air dry at room temperature to leave the pure disulfide, m.p. is 90–91° (uncor.). The disulfide will decompose after standing for two days at room temperature or three to four days under refrigeration. It may be kept pure indefinitely, however, if it is suspended in carbon tetrachloride where it exists as the stable addition compound. Whenever some of the compound is desired, the addition compound may be filtered off.

The polarogram was recorded on a Sargent model XX polarograph by the techniques described in reference 1. The infrared spectra were taken on the B. F. Goodrich infrared spectrometer described elsewhere.[6]

(3) Y. Kawaoka, *J. Soc. Rubber Ind. Japan*, **16**, 397 (1943).

(4) The compound was obtained from the Naugatuck Chemical Division of the U. S. Rubber Company.

(5) R. Fisher, *Biochem. Z.*, **125**, 12 (1921).

(6) Presented at the Symposium on Molecular Structure and Spectroscopy, The Ohio State University, Columbus, Ohio, June, 1951.

Acknowledgment,—The author wishes to express his gratitude to Mr. J. J. Shipman for obtaining the infrared spectra contained in this note.

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The Reaction of Nitrous Acid with Thiobenzamides

BY M. W. CRONYN AND T. W. NAKAGAWA

RECEIVED FEBRUARY 25, 1952

Since nitrous acid has been used to facilitate the conversion of amides to acids[1] the reaction of this reagent with thioamides has been investigated as a possible method for the preparation of thioacids. Thiobenzamide was treated with nitrous acid in concentrated sulfuric acid, acetic acid–water, dioxane–water and absolute ethanol. In each case the principal product isolated was 3,5-diphenyl-1,2,4-thiadiazole (I). The identity of the product was established by comparison with the thiadiazole resulting from the action of iodine in alcohol on thiobenzamide.[2]

$$C_6H_5CSNH_2 + HNO_2 \longrightarrow C_6H_5-C \underset{\underset{S-N}{}}{\overset{\overset{N-C-C_6H_5}{}}{<}}$$

I
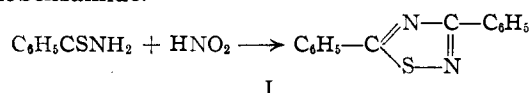
Experimental

The thiobenzamide, m.p. 115–116°, was prepared according to the method of Cahours.[3]

a. Acetic Acid–Water.—A cold solution of 5.0 g. of sodium nitrite in 50 ml. of water was added dropwise with stirring to a solution of 8.0 g. of thiobenzamide in 130 ml. of glacial acetic acid and 100 ml. of water cooled in an ice-bath. The mixture was diluted with water and 4 g. of a crude solid, m.p. 76–79°, was obtained. Solution of the crude material in 150 ml. of absolute ethanol gave 1.6 g. of a red insoluble solid; and, after treatment with Nuchar, there was obtained from the alcohol solution 2.4 g. (30%) of a product, m.p. 85–88° after crystallization from alcohol–water. Repeated recrystallization of a sample gave material with a m.p. of 89–90°. Analysis indicated a diphenylthiadiazole. By the action of iodine in ethanol on thiobenzamide 3,5-diphenyl-1,2,4-thiadiazole was prepared in 77% yield with a melting point of 87–88°.[2] A mixed melting point with the nitrous acid product was undepressed.

b. Dioxane–Water.—Using the same procedure in a mixture of dioxane and 2 N hydrochloric acid there was obtained 3 g. of a crude product; m.p. 78–82°, which gave 2.2 g. of purified material, m.p. 87–88°.

c. Butyl Nitrite in Ethanol.—To a cold solution of 2.0 g. of thiobenzamide and 0.43 g. of hydrogen chloride in 30 ml. of absolute ethanol there was added, dropwise with stirring, 1.5 g. of freshly distilled butyl nitrite. The reaction mixture was allowed to come to room temperature and was poured into water. After crystallization from ethanol there was obtained 1.5 g. (75%) of 3,5-diphenyl-1,2,4-thiadiazole; m.p. 86.5–87.5°.

d. Concentrated Sulfuric Acid.—The procedure of Sudborough[1] for the conversion of benzamide to the acid was applied. A crude yield of 2.7 g. was obtained from 5 g. of the thiobenzamide. The product was more impure than in the other cases but the principal constituent had a m.p. of 81–85° and its mixed melting point with 3,5-diphenyl-1,2,4-thiadiazole gave no depression.

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(1) L. Bouveault, *Bull. soc. chim.*, [3] **9**, 368 (1892); J. J. Sudborough, *J. Chem. Soc.*, **67**, 601 (1895).

(2) A. W. Hofmann and S. Gabriel, *Ber.*, **25**, 1578 (1892).

(3) Cahours, *Compt. rend.*, **27**, 239 (1848); S. Gabriel and P. Heymann, *Ber.*, **23**, 158 (1890).

The Reaction of Disubstituted Nitrosamines with Lithium Aluminum Hydride[1]

BY CALVIN HANNA AND F. W. SCHUELER

RECEIVED MARCH 3, 1952

Previously[2] we reported the preparation of unsymmetrical dimethylhydrazine by adding 1 mole of N-nitrosodimethylamine to 2 moles of lithium aluminum hydride in ether. Using similar conditions, 1 mole of N-nitrosodiphenylamine added to 4 moles of LiAlH₄ gave only diphenylamine. The compounds used in this study were the mixed alkylaryl nitrosamine, N-nitrosomethylaniline, the dicyclic substituted nitrosamine, N-nitrosodicyclohexylamine which was chosen as a dialkyl nitrosamine of dimensions comparable to nitrosodiphenylamine. Finally, N-nitrosopiperidine, as a heterocyclic alkyl type, completed the group studied. The nitroso compounds were prepared by method of Hartman and Roll[3] previously reported in the literature.

The above nitrosamines were reduced using lithium aluminum hydride to give 1-methyl-1-phenylhydrazine (77%), 1,1-dicyclohexylhydrazine (48%), and N,N-pentamethylenehydrazine (75%). The above results would indicate that dialkyl, alkylaryl, dicyclohexyl and cyclic nitrosamines may be satisfactorily reduced to the corresponding unsymmetrical hydrazine using lithium aluminum hydride. N-Nitrosodiphenylamine is reduced by a large excess of lithium aluminum hydride to diphenylamine.[2] Poirier and Benington[4] have demonstrated that under controlled conditions, by adding N-nitrosodiphenylamine to an equal molar quantity of lithium aluminum hydride or better yet through an "inverse" order of addition, unsymmetrical diphenylhydrazine may be obtained in yields up to 90%. Whether the reduction of nitrosamines, particularly diarylnitrosamines, stops at the hydrazine or proceeds to the amine depends greatly upon the quantity of lithium aluminum hydride. The N–O bond is much more polar than the N–N bond, consequently, it must be attacked first by lithium aluminum hydride. The polar character of the N–N bond is presumably enhanced by aromatic rings so that excess lithium aluminum hydride readily converts diarylnitrosamines directly to diarylamines.

Experimental

Reduction of Nitrosamines.—To 3.6 g. (0.1 mole) of lithium aluminum hydride in 150 ml. of tetrahydrofuran was slowly added a solution of 0.1 mole of the nitrosamine in 200 ml. of tetrahydrofuran. A colored complex forms. This is especially true with N-nitrosomethylaniline which yields a pink complex during the addition. This color should be discharged by vigorous stirring before more nitrosamine is added otherwise the reaction, once started, will react violently with much foaming. After the completion of the addition of the nitrosamine, the reaction mixture was stirred for an additional hour. Acetone (5 ml.) was used to decompose the excess reagent and to the resulting mixture 100 ml. of 30% sodium hydroxide was added with stirring.

(1) This work was aided by a grant from the U. S. Public Health Service.

(2) F. W. Schueler and Calvin Hanna, THIS JOURNAL, **73**, 4996 (1951).

(3) W. W. Hartman and L. V. Roll, "Organic Syntheses," Coll. Vol. II. John Wiley and Sons, Inc., New York, N. Y., 1943, p. 460.

(4) R. H. Poirier and F. Benington, THIS JOURNAL, **74**, 3192 (1952).

The tetrahydrofuran layer was separated and evaporated *in vacuo* to an oil. This oil was fractionally distilled, dissolved in abs. ether and dried over sodium hydroxide pellets. The pure hydrazine was obtained by fractionally distilling this ether solution.

N-Nitrosomethylaniline was reduced to 1-methyl-1-phenylhydrazine[5] in 77% yield which is an oil boiling at 106–109° (13 mm.).

N-Nitrosopiperidine was reduced to N,N-pentamethylenehydrazine[6] in 75% yield. It is an oil boiling at 146–148° (730 mm.).

N-Nitrosodicyclohexylamine was reduced to 1,1-dicyclohexylhydrazine in 48% yield. It is a white crystalline solid boiling at 95–98° (4 mm.) which sublimes above 162°. The hydrochloride forms white flaky crystals from ether, m.p. 238–240° (cor.). The methiodide forms small white plates from abs. ether, m.p. 250–252° (cor.). *Anal.* Calcd. for hydrochloride $C_{12}H_{25}N_2Cl$: Cl, 15.23. Found: Cl, 14.94. *Anal.* Calcd. for methiodide $C_{13}H_{27}N_2I$: I, 37.51. Found: I, 37.06.

Skita and Rolfes[7] attempted to prepare 1,1-dicyclohexylhydrazine by reducing N-nitrosodicyclohexylamine with zinc and hydrochloric acid and obtained dicyclohexylamine. When they used zinc in absolute alcohol with acetic acid no hydrazine could be isolated.

The 1,1-dicyclohexylhydrazine has a nauseating and irritating odor beyond that produced by high molecular weight amines. This compound in lethal doses in white mice produces convulsions characteristic of central nervous system stimulation. The LD_{50} dose in mice by the intraperitoneal route is 77 mg./kg.

(5) W. W. Hartman and L. V. Roll, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 418.

(6) Knorr, *Ann.*, **221**, 299 (1883).

(7) Skita and Rolfes, *Ber.*, **53**, 1251 (1920).

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Preparation of Telluric Acid

BY H. J. HORNER AND GUY WILLIAM LEONARD, JR.

RECEIVED MARCH 26, 1952

Several methods for the preparation of telluric acid have been reported in the literature and are listed by Gilbertson.[1] These methods either give an impure product or require large excesses of oxidizing agent and special preparation of the tellurium. The preparation as developed by Mathers and co-workers[2] is the most widely used. However, purification of the crude telluric acid thus obtained required repeated recrystallizations from concentrated nitric acid solutions.

Hydrogen peroxide is the ideal oxidizing agent, but when it is used alone or in the presence of an acid, a very large excess of peroxide is needed. In basic solutions the oxidation of tellurium dioxide by a slight excess of hydrogen peroxide proceeds nicely to completion. By using ammonia solutions, the by-products are readily separated from the telluric acid.

Experimental

The commercial grade tellurium dioxide (approximately 76% pure) was found to contain impurities which vigorously catalyzed the decomposition of hydrogen peroxide. The tellurium dioxide was purified by dissolving it in 5 N sodium hydroxide. After filtering, the tellurium dioxide was reprecipitated by adding 10 N nitric acid to the filtrate until the solution was acid to phenolphthalein. The supernatant

(1) L. I. Gilbertson, THIS JOURNAL, **55**, 1460 (1933).

(2) F. C. Mathers, C. M. Rice, H. Broderick and R. Torney, *Inorganic Syntheses*, **3**, 145 (1950).

liquid was then decanted and the precipitate washed five times with distilled water. The purified material was dried for 24 hours at 110°. This method produced a compound of about 98% purity. Subsequent repetition of the above procedure made no appreciable change in the purity, because of coprecipitation of sodium salts.

Preliminary determinations revealed no apparent reaction between pure tellurium dioxide and 30% hydrogen peroxide. However, in the presence of dilute ammonia solution some oxidation occurred with the formation of a gum which prevented further reaction. Nevertheless the reactions occurring in concentrated ammonium hydroxide produced a white crystalline precipitate of an ammonium tellurate which did not interfere with the oxidation of the tellurium dioxide.

Procedure.—A ten-gram sample of tellurium dioxide, purified and oven-dried, was placed in a 250-ml. erlenmeyer flask fitted with a rubber stopper. To the flask was added a mixed solution of 10 ml. of 30% hydrogen peroxide and 75 ml. of concentrated ammonium hydroxide. After the pressure generated by the initial reaction had subsided the flask was stoppered and set aside. During this period, the flask was frequently shaken. After 24 hours, the mixture was heated on a steam-bath until the vapors were free of ammonia, and the volume of solution had been reduced to 45 ml. Next, 10 ml. of concentrated nitric acid was added to the above solution. During the addition of the nitric acid, the ammonium tellurate dissolved. After 24 hours the supernatant liquid was removed from the crystals of telluric acid which had formed, and the liquid was further concentrated to 20 ml. Another 10 ml. of concentrated nitric acid was added and after an additional 24 hours the crops of crystals were combined. Further purification was accomplished by one recrystallization from distilled water. This method produces telluric acid of 99.99% purity and in yields of 75–80%. The telluric acid was analyzed by the method of Gooch and Howland.[3] The flame test and Nessler reagent showed that the telluric acid was not contaminated with either sodium or ammonium ions.

(3) F. A. Gooch and J. Howland, *Am. J. Sci.*, [3] **48**, 375 (1894).

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The Effect of Fluorine on Praseodymium Trifluoride

BY THEODORE P. PERROS AND CHARLES R. NAESER

RECEIVED MARCH 17, 1952

Since it has been shown that cerium tetrafluoride could be prepared quantitatively from cerous fluoride with fluorine at 500°,[1] it was thought to be of interest to determine what effect elemental fluorine would have on praseodymium trifluoride at this and other temperatures. Klemm[2] fluorinated praseodymium trichloride and obtained a mixture of the chloride and fluoride.

Experimental

Fluorine was prepared by the apparatus described by Von H. von Wartenberg.[1] A graphite anode was used. The rate of production of fluorine was about 35 ml. per minute.

A combustion boat was made from a fluorite cupel since most other substances which might be used for a boat are reacted upon by fluorine at temperatures above 500°.

A nickel tube 1/8″ in thickness, 7/8″ inside diameter and 14″ in length was used to house the combustion boat. The reaction tube was heated to the desired temperatures in an electric combustion furnace. The joints between the apparatus and the reaction tube were sealed with plaster of Paris. Before each run the system was dried by air.

Praseodymium trifluoride was prepared by the addition of hydrofluoric acid to a solution of the trichloride which had been warmed to 80°. The precipitate was filtered and

(1) Von H. von Wartenberg, *Z. anorg. allgem. Chem.*, **244**, 337 (1940).

(2) Klemm and Henkel, *ibid.*, **220**, 180 (1934).

washed with absolute alcohol. The precipitate was dried in an oven at 110°. Analysis indicated that the salt contained only a small amount of water (2–3%). About 0.7 g. of sample was used in each of the runs.

Table I contains a summary of the runs which were made.

TABLE I

	Temperature of reaction tube, °C.	Duration in hours of fluorination period
1	Room temperature	4.5
	Room temperature	7.5
2	300	4
	300	7
3	500	3
	500	8
4	625	3.75
	625	7.5
5	700	4
	700	7.5
6	800	4
	800	7.5

After each run, the sample was tested with hydriodic acid to determine whether any oxidation had occurred. In each instance, the results were negative. This confirms the work of Klemm.[2]

In the preliminary stages of this investigation when a platinum combustion boat was used, praseodymium(III) fluoplatinate was one of the products formed at temperatures above 500°. Detailed information on this and other fluoplatinates will be the subject of a paper now in preparation.

Acknowledgment.—Part of this work was supported by A. E. C. contract.

CONTRIBUTION FROM THE
CHEMISTRY DEPARTMENT OF THE
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Kinetics and Some Hydrogen Isotope Effects of the Reaction of Diphenyldiazomethane with Acetic Acid in Ethanol[1]

BY JOHN D. ROBERTS AND CLARE M. REGAN

As part of other investigations,[2,3] we have had occasion to study the kinetics and hydrogen isotope effects of the reaction of diphenyldiazomethane with acetic acid in ethanol using the techniques previously developed for other carboxylic acids.[2–5] As might be expected, the reaction of acetic acid with diphenyldiazomethane is very similar to that with benzoic acid in that it is accurately first order in acid as well as diazo compound and shows similar salt and medium effects (cf. Table I). All of the data are consistent with the hypothesis that acetic acid and benzoic acid react with diphenyldiazomethane by similar mechanisms involving rate-determining proton transfers from undissociated acid to diazo compound. Indeed, the only very striking difference between the behaviors of the

(1) Supported in part by the program of research of the United States Atomic Energy Commission.

(2) J. D. Roberts and C. M. Regan, Anal. Chem., **24**, 360 (1952).

(3) J. D. Roberts, W. Watanabe and R. E. McMahon, THIS JOURNAL, **73**, 760 (1951).

(4) (a) J. D. Roberts, E. A. McElhill and R. Armstrong, ibid., **71**, 2923 (1949); (b) J. D. Roberts and W. Watanabe, ibid., **72**, 4869 (1950).

(5) J. D. Roberts, C. M. Regan and I. Allen, ibid., **74**, 3679 (1952).

two acids is that a considerably higher fraction of benzhydryl acetate (87%) is formed with acetic acid than benzhydryl benzoate (55%) with benzoic acid[3] (Table II). This difference is likely to be due to steric hindrance since acetic acid with its small methyl group should be more reactive in a direct reaction[3] with diphenyldiazomethane than benzoic acid.

TABLE I

RATES OF REACTION OF DIPHENYLDIAZOMETHANE WITH ACETIC ACID IN ABSOLUTE ETHANOL AT 30.0°

Acetic acid, mole/l.	Diphenyl-diazo-methane, mole/l.	Salt, mole/l.	k_2, (moles/l.)$^{-1}$ min.$^{-1}$
0.0341	0.00218	....	0.562
.0683	.00328	....	.556
.1472	.00547	....	.578
.1472	.00547	0.033 LiClO₄	.624
.1472	.00547	.067 LiClO₄	.645
.1472	.00547	.100 LiClO₄	.692
.1472	.00547	.033 NaOAc	.523ᵃ
.1472	.00547	.067 NaOAc	.493ᵃ
.1472	.00547	.100 NaOAc	.462ᵃ
.1542ᵇ	.00526	....	2.12
.1542ᶜ	.00526	....	1.30
.1787ᵈ	.00947	....	0.166
.0953ᵉ	.00526	....	0.553
.0953ᵉ,ᵇ	.00526	....	2.12
.0953ᵉ,ᶜ	.00526	....	1.23
.1759ᵉ,ᵈ	.00947	....	0.151

ᵃ The same slowing of rate by carboxylate ion was observed with benzoic acid and admits of a similar explanation.[3] ᵇ Solvent was 82.5% ethanol–17.5% water (by volume). ᶜ Solvent was 82.5% ethanol–17.5% deuterium oxide (by volume), 38% calculated replacement of O–H groups by O–D groups. ᵈ Solvent was C₂H₅OD which was prepared as described previously.[5] ᵉ CD₃COOD used in place of CH₃COOH.

TABLE II

ACETIC ACID CONSUMPTION IN DIPHENYLDIAZOMETHANE REACTION AT 30.0° IN ABSOLUTE ETHANOL

Acetic acid, mole/l.	Diphenyldiazo-methane, mole/l.	Salt, mole/l.	Eq. acid consumed/ eq. of diphenyl-diazo-methaneᵃ
0.0440	.000915	....	0.88
.0440	.00915	....	.86
.0440	.00915	0.070 LiClO₄	.83
.0440	.00915	.070 LiClO₄	.82

ᵃ Determined by the procedure of ref. 3.

As part of our program of research on isotope effects,[3,5] several hydrogen isotope effects on the acetic acid–diphenyldiazomethane reaction were measured and are listed in Table I. Substitution of C₂H₅OD for ordinary ethanol as the solvent (with consequent replacement of O–H by O–D in the carboxyl group of the acetic acid) caused a very substantial decrease in the reaction rate (3.5-fold for acetic acid as compared with 3.6-fold for benzoic acid[5]) as expected for a rate-determining proton transfer. Similar replacement of 38% of the O–H bonds by O–D bonds in 82.5% ethanol–17.5% water brought about a 39% decrease in the reaction rate with acetic acid as compared with 38% with benzoic acid.[3] In a number of experiments

with CD₃COOD[6] in ordinary or deuterated ethanol, it was found that introduction of three deuteriums in the α-position does not alter the reactivity of acetic acid much beyond the experimental error.

In most cases the reactions were slower, but even the largest effect was under 10%. These results confirm the expectation that there should be no very significant difference in electrical or other effects between CH₃– and CD₃– groups on the carboxyl hydrogen.

(6) We are indebted to Dr. Donald J. Cram for the preparation of this material by the procedure of C. L. Wilson. *J. Chem. Soc.*, 492 (1935).

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Urea Derivatives Related to Procaine

BY NORMAN RABJOHN AND J. Z. SHAHABEDDIN[1]

RECEIVED MARCH 14, 1952

Numerous substituted ureas have been prepared and found to possess physiological properties; however, very few of these are of the diaryl type.

Accordingly, we have undertaken the syntheses of a number of diarylureas related to procaine by the reaction of the latter with various aryl isocyanates. The melting points, percentage yields, and analytical data for these compounds are recorded in Table I. As yet, they have not been tested for possible physiological properties.

Experimental[5]

Materials.—The aryl isocyanates were purchased from the Eastman Kodak Co. and were purified by distillation or crystallization immediately prior to use. The procaine base was prepared by treating the hydrochloride (Merck and Co., Inc.) with alkali, dissolving the resulting dihydrate in benzene and distilling the solution to a low volume. Upon cooling the residue, the desired base was obtained in almost quantitative yield; m.p. 58–59°.

Preparation of 4-(β-Diethylaminocarboethoxy)-carbanilide and its Hydrochloride.—This procedure is representative of the methods employed for the preparation of the compounds listed in Table I. To 11.8 g. (0.05 mole) of procaine base, dissolved in a mixture of 50 ml. of anhydrous benzene and 25 ml. of anhydrous toluene, was added 5.95 g. (0.05 mole) of phenyl isocyanate. The reaction mixture warmed spontaneously and was refluxed then for about 30 minutes. It was allowed to cool, and placed in a refrigerator until crystallization was completed. The white crystals were removed by filtration, washed with anhydrous ben

TABLE I

UREA DERIVATIVES OF PROCAINE, XC₆H₄NHCONHC₆H₄CO₂C₂H₄N(C₂H₅)₂

X	M.p., °C.	Yield, %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
			Bases				
H[a]	94–96	91	C₂₀H₂₅O₃N₃	67.58	67.67	7.09	7.14
2-CH₃[a]	87–89	96	C₂₁H₂₇O₃N₃	68.26	67.86	7.37	7.44
2-Cl[a]	86–88	87	C₂₀H₂₄O₃N₃Cl	61.61	61.68	6.20	6.44
3-Cl[a]	88–90	88	C₂₀H₂₄O₃N₃Cl	61.61	61.51	6.20	6.49
2,5-Cl[a]	155–156	89	C₂₀H₂₃O₃N₃Cl₂	56.61	56.39	5.46	5.53
4-Br[c]	174–176	87	C₂₀H₂₄O₃N₃Br	55.31	55.63	5.57	5.48
2-NO₂[c]	101–102	91	C₂₀H₂₄O₅N₄	59.99	60.30	6.04	6.26
4-NO₂[c]	156–158	84	C₂₀H₂₄O₅N₄	59.99	59.71	6.04	6.21
			Hydrochlorides				
H	202–204	97	C₂₀H₂₆O₃N₃Cl	61.29	61.26	6.68	6.88
2-CH₃[c]	174–175 (picrate)	92	C₂₇H₃₀O₁₀N₆	54.17	54.29	5.05	5.13
2-Cl	195–197	91	C₂₀H₂₅O₃N₃Cl₂	56.34	56.66	5.91	6.09
3-Cl	193–195	92	C₂₀H₂₅O₃N₃Cl₂	56.34	56.31	5.91	5.91
2,5-Cl	221–223	91	C₂₀H₂₄O₃N₃Cl₃	52.13	52.36	5.25	5.13
4-Br	215–217	86	C₂₀H₂₅O₃N₃ClBr	51.02	51.36	5.35	5.12
2-NO₂	202–203	97	C₂₀H₂₅O₅N₄Cl	54.98	55.11	5.77	6.09
4-NO₂	221–223	87	C₂₀H₂₅O₅N₄Cl	54.98	54.96	5.77	5.97

Crystallization solvents: [a] Ethyl acetate-petroleum ether (60–70°). [b] Ethyl acetate. [c] Absolute alcohol.

In connection with an investigation[2] of the effect of change in structure of the 4-amino group in procaine on its pharmacological activity, we prepared 4,4'-di-(β-diethylaminocarboethoxy)-carbanilide[3] and tests[4] indicated that it is relatively active as a local anesthetic.

(1) Abstracted in part from a thesis submitted by J. Z. Shahabeddin to the Graduate College of the University of Missouri, 1952, in partial fulfillment of the requirements for the degree of Master of Arts.

(2) N. Rabjohn, T. R. Hopkins and R. C. Nagler, THIS JOURNAL, **74**, 3215 (1952).

(3) U. N. Narayana Rao, B. H. Iyer and P. C. Guha, *Current Sci.* (*India*), **19**, 180 (1950); *C. A.*, **44**, 11025 (1950).

(4) The authors are indebted to the McNeil Laboratories for screening this compound.

zene and dried to give 16.2 g. (91%) of a product which melted at 90–94°. Four recrystallizations from a mixture of ethyl acetate and petroleum ether (60–70°) raised the melting point to 94–96°.

A sample (1.78 g.) of the purified substituted carbanilide was dissolved in 10 ml. of anhydrous ether and dry hydrogen chloride was passed through the solution. The precipitated hydrochloride was removed on a buchner funnel and dried over solid potassium hydroxide; wt. 1.94 g. (97%); m.p. 202–204°.

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(5) All melting points are uncorrected. The semimicro analyses were performed by Mr. P. D. Strickler.

Evidence for Interaction between Chloroform and Monoethylamine[1]

BY LEON SEGAL[2a] AND H. B. JONASSEN[2b]

RECEIVED JANUARY 10, 1952

Reagents are often removed from materials by washings with solvents, and often the solvent is reclaimed by some suitable process such as fractional distillation. In the decrystallization of cotton,[3] chloroform was used to remove anhydrous monoethylamine from the swollen fibers. The chloroform could be reclaimed easily by removing the ethylamine through neutralization with aqueous acid, but the recovery of the amine from the acidic solution was neither simple nor easy. Attempts to separate the amine and chloroform by distillation or by extraction with distilled water proved unexpectedly difficult, suggesting some type of interaction. The experiments to be reported were undertaken to explain these difficulties.

At first consideration no appreciable interaction between ethylamine and chloroform would be expected. A literature survey revealed little information on the system. Pauling[4] has pointed out that, from a consideration of the electronegativity scale, the C–H bond would not be attributed with sufficient ionic character to enter into hydrogen bonding to any degree. However, in hydrogen cyanide the electronegativity of the carbon atom is sufficiently enhanced by the attached electronegative nitrogen atom to permit the C–H ← N bond to form. In chloroform a similar effect might be expected due to the interaction of the three electro-negative halogen atoms attached to the carbon atom.[5]

There is evidence in the literature, based on azeotrope studies,[6] solubility studies,[7–9] infrared absorpton data,[10,11] and heats of mixing,[12–15] that chloroform is indeed capable of entering into hydrogen-bond formation with certain nitrogen- and oxygen-containing compounds. Since an effect of this nature seemed to be operating in the chloroform–ethylamine mixture, a brief investigation was made in which the behavior of chloroform–ethyl-

(1) Report of a study made under the Research and Marketing Act of 1946. Article not copyrighted.

(2) (a) Southern Regional Research Laboratory, one of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. (b) Tulane University.

(3) L. Segal, M. L. Nelson and C. M. Conrad, J. Phys. Chem., 55, 325 (1951).

(4) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 2nd Ed., 1940, pp. 294–295.

(5) M. L. Huggins, J. Org. Chem., 1, 407 (1936).

(6) R. N. Ewell and L. M. Welch, THIS JOURNAL, 63, 2475 (1941).

(7) M. J. Copley, E. Ginsberg, G. F. Zellhoefer and C. S. Marvel, ibid., 63, 254 (1941).

(8) M. J. Copley, G. F. Zellhoefer and C. S. Marvel, ibid., 60, 2666 (1938).

(9) G. F. Zellhoefer, M. J. Copley and C. S. Marvel, ibid., 60, 1337 (1938).

(10) W. Gordy, Nature, 142, 831 (1938); J. Chem. Phys., 7, 93 (1939); THIS JOURNAL, 60, 605 (1938).

(11) A. M. Buswell, W. H. Rodebush and M. F. Roy, ibid., 60, 2528 (1938).

(12) C. S. Marvel, M. J. Copley and E. Ginsberg, ibid., 62, 3109 (1940).

(13) D. B. McLeod and F. S. Wilson, Trans. Faraday Soc., 31, 596 (1935).

(14) R. W. Spence, J. Phys. Chem., 45, 304 (1941).

(15) G. F. Zellhoefer and M. J. Copley, THIS JOURNAL, 60, 1343 (1938).

amine and of hexane–ethylamine solutions was observed. In the latter system, no hydrogen bond formation would be expected.

Materials and Methods.—Gaseous monoethylamine (specified purity, 96% minimum) was drawn from a cylinder and condensed in all-glass apparatus cooled by circulating ice-water. It was collected and stored over potassium hydroxide pellets. Titration with standard acid indicated almost 100% purity.

Diethylamine (specified purity, 98% minimum) was stored over potassium hydroxide pellets before being distilled. The fraction distilling at 55° was collected and stored over potassium hydroxide. The boiling point of 55.5° indicated high purity.

Chloroform, U.S.P. grade, was washed, then dried over anhydrous calcium sulfate. The fraction distilling at 60–61° was collected and stored in brown glass bottles. The distilled solvent showed no test for acid.

The hexane used was a petroleum fraction distilling at 62–65°. It was collected and stored in brown glass bottles.

The amine concentrations in all the solutions were determined by rapid titration with 1.002 N hydrochloric acid. Samples, weighed or pipetted, were added to 100 ml. of chilled distilled water (4–10°), followed by 2 drops of methyl orange indicator. The flask was shaken and the acid was then led in rapidly until the end-point was approached. Only fair accuracy could be attained because of volatility of the amines.

One-liter solutions of ethylamine–chloroform and ethylamine–hexane were prepared by adding solvent to 200 ml. of anhydrous ethylamine. The concentrations of the solutions, determined by titration, were 128 g. per liter (approximately 2.8 molar). For distillation studies 700 ml. of solution was used, which if completely separated should give 140 ml. of ethylamine.

The distillations of the mixtures were carried out using an 11-section, bubble-cap, fractionating column, and condensers cooled by circulating ice-water. The amine concentrations of the solution and the distillate were determined after the distillation was stopped.

Boiling point diagrams were determined with the aid of an apparatus similar to that described by Daniels, et al.[16] Liquid temperatures were read from a tested Anschütz thermometer, totally enclosed in the system. Refluxing was permitted for at least 45 minutes in each determination. Fluctuations in barometric pressure never exceed 3 mm. In determining the compositions of the liquid and condensed vapor, the weighing bottles were emptied of the weighed samples under the surface of the chilled distilled water.

An Abbe-type refractometer was used to obtain the refractive indices, n^{20}D, of the solutions. Cooling water was maintained at 20 ± 0.2° at the instrument.

Extraction of the amine by water was performed in a separatory funnel by the successive addition and separation of 50-ml. portions of distilled water to 1 liter of the amine-solvent solution prepared as described above. After each addition the funnel was shaken and the layers allowed to separate. The amine concentration in the solvent layer, determined after each extraction, was plotted against the number of portions of water used.

The alkaline aqueous solution which was separated from the chloroform–ethylamine mixture gave off a strong odor of isocyanide which was probably formed by reaction between the dissolved amine and the small amount of dissolved chloroform (for aqueous ethylamine, $K_b = 5.6 \times 10^{-4}$).

Results and Discussion

When ethylamine and chloroform were first mixed in preparing the solution for separation by distillation, a noticeable increase in the temperature of the solution was evident. When the operation was repeated using equal volumes of the liquids, both at 5°, the maximum temperature observed after mixing was 28°, a rise of 23°. No temperature rise was found when ethylamine and hexane, also at 5°, were mixed.

(16) F. Daniels, J. H. Mathews and J. W. Williams, "Experimental Physical Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 2nd Ed., 1934, p. 66.

This observed rise should be related to the heat data on higher alkylamines reported by Spence[14] and by Marvel and co-workers.[12] According to these, heats of mixing of 700–800 cal. per mole of solution are found for solutions of chloroform with n-butyl, n-hexyl- and cyclohexylamines. All of these workers, on the basis of their data, assume that chloroform and the amines form equimolar complexes through the formation of C–H←N bonds. Following the Lewis concept, this heat given off on mixing could be conceived as being heat of neutralization of the basic amine and the weak acid $Cl_3C–H^+$.

Separation of ethylamine by distillation, at first consideration, should have been easily accomplished since the amine boils at 17°, whereas chloroform and hexane boil at around 60°. This was not true for the ethylamine–chloroform mixture. As the distillation proceeded, the vapor temperature at the top of the column rose steadily. After rising to 60° and after 400 ml. of distillate had been collected, the solution in the boiling flask was found to still have an amine content amounting to 14 g. per liter.

The ethylamine–hexane mixture on the other hand behaved more normally. A distillate of 160 ml. was collected with no increase over room temperature of the vapor temperature at the top of the column. A sample from the boiling flask showed upon titration an amine concentration of only 8 g. per liter. With the application of more heat, distillate was collected until the vapor temperature had risen to 39°. The amine concentration in the boiling flask was found to be only 2 g. per liter.

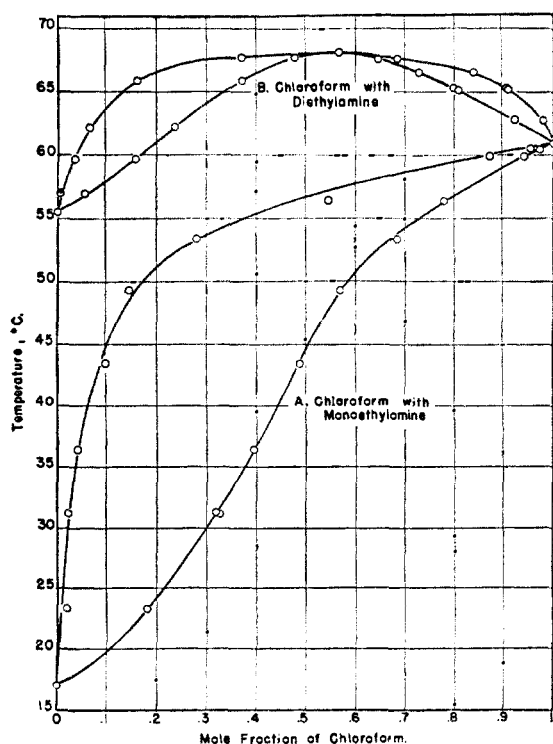The tenacious hold of chloroform for ethylamine, as evidenced in the distillation, might be explained by a change in association of the amine. Distribution measurements at different concentrations indicated that the abnormal behavior did not arise from such an effect, the distribution coefficient remained essentially constant at these concentrations.

The boiling point diagram for monoethylamine and chloroform, Fig. 1A was found to deviate considerably from Raoult's law, indicating an interaction. However, it did not show the azeotropic behavior which might be expected of an associated binary mixture. Ewell and Welch[6] found that triethylamine and chloroform also did not form an azeotrope. They concluded from their studies that maximum boiling mixtures result with donor liquids whose boiling points lie within a range centered about the boiling point of the given chloroparaffin. For chloroform this range was found to be 38°, the lower limit being 42.5°; the upper 80.5°. Monoethylamine (b.p. 17°), as well as triethylamine (b.p. 89°), lies outside this range and hence should not produce an azeotrope.

A prediction, based on Ewell and Welch's conclusion, that diethylamine (b.p. 55.5°) should form maximum boiling azeotrope was verified by experiment (B in Fig. 1). The maximum of 68.2° which occurs at a mole fraction of 0.57 chloroform suggests a possible association ratio of 1:1.

Since evidence for a 1:1 complex between chloroform and monoethylamine could not be obtained from the boiling point diagram, consideration that the refractive index might be effected by association resulted in the data presented in Fig. 2. The break in curve A occurring near mole fraction 0.5 chloroform seems to be indicative of 1:1 ratio.
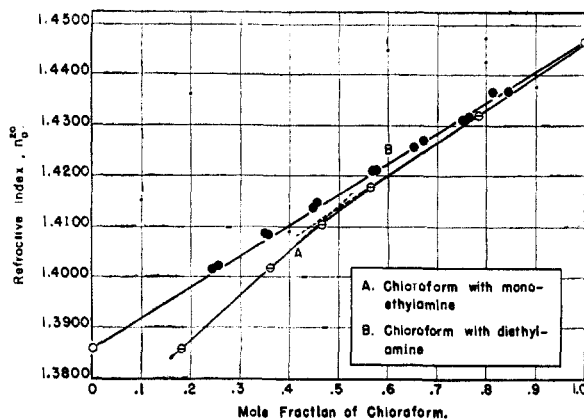

Fig. 1.

Fig. 2.

· When refractive index data for diethylamine and chloroform were plotted, the resulting curve B did not show any break. Whether this can be correlated with the findings of Ewell and Welch concerning the boiling point range and the appearance of the azeotrope in the boiling point diagram has not yet been established.

Further evidence for an associated binary mixture is shown by the effects observed when extraction of the amine with water was attempted (see Fig. 3). Here the curve for the chloroform solution indicates that the C–H←N bond which is believed to have been formed must be of consider-
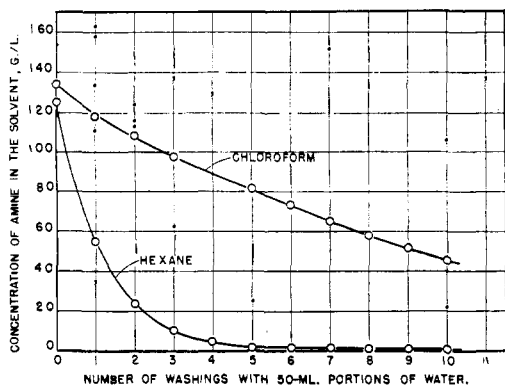
Fig. 3.

able strength, since the contacts with water were only partially effective in reducing the amine concentration in the solvent. This concept is supported, too, by the work of Smith[17] who determined the distribution coefficient for the system chloroform–water–ethylamine. Unfortunately, however, Smith's work dealt only with amine concentrations of the order of millimoles, whereas the present investigation is concerned with molar quantities.

On the other hand, the hexane–ethylamine solution, in which hydrogen bond formation can be ruled out, behaved differently toward water extraction. The curve shows that water was highly effective in reducing the amine concentration of the hexane. In fact, cold water was required for at least the first two extractions of the hexane solution, in order to reduce the vigor of the interaction between the water and the amine.

(17) H. O. Smith, J. Phys. Chem., 25, 204 (1921).

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Absorption Spectra of 8-Amino-6-quinolinol Types

BY EDGAR A. STECK AND FREDERICK C. NACHOD

Interest in 8-(3-dimethylamino-1-methylpropylamino)-6-quinolinol (SN-191,[1] Certuna, I) led us to compare its ultraviolet absorption spectra in neutral, acid, and alkaline media with those of 8-(4-diethylamino-1-methylbutylamino)-6-quinolinol (II), 8-amino-6-quinolinol (III) and 3-hydroxy-1-naphthylamine (IV).
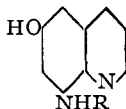
I, R = CH(CH₃)CH₂CH₂N(CH₃)₂
II, R = CH(CH₃)CH₂CH₂CH₂N(C₂H₅)₂
III, R = H

In Fig. 1 there are presented the absorption spectra of 8-amino-6-quinolinol (III) in acidic, basic and ethanolic solution. The comparison of

(1) All drugs identified by Survey Numbers (SN) in the files of the Antimalarial Survey have been tabulated, with antimalarial activities, in "Antimalarial Drugs, 1941–1945" (F. Y. Wiselogle, editor), Edwards Bros., Ann Arbor, Mich., 1946.
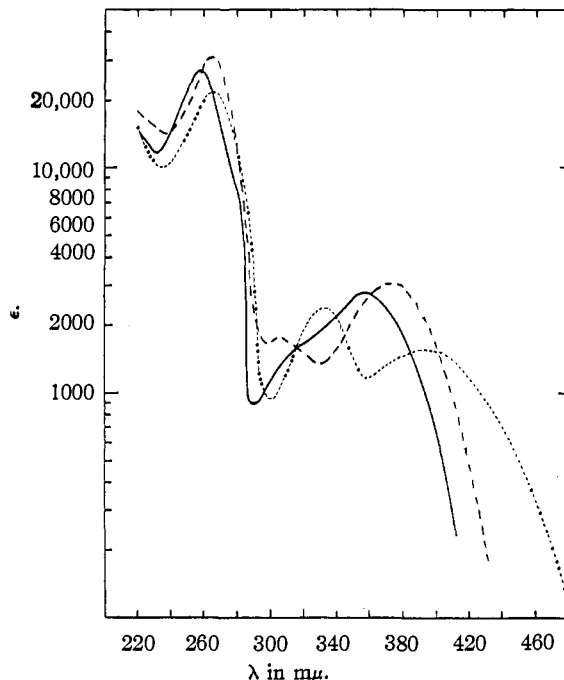

Fig. 1.—Spectra of 8-amino-6-quinolinol in: —, 95% EtOH; ------, 0.01 N HCl; – – –, 0.01 N NaOH.

these with corresponding ones of 6-quinolinol[2] shows that the 8-amino group has very little influence on the spectra. It may be noted that the spectra (Fig. 2) of 3-hydroxy-1-naphthylamine (IV), the naphthalene analog of (III), bear no simple relation to those of the contributing parents 2-naphthol[2] and 1-naphthylamine.[3] In acidic solution, the ionic contributions of (IV) cause it to be closely
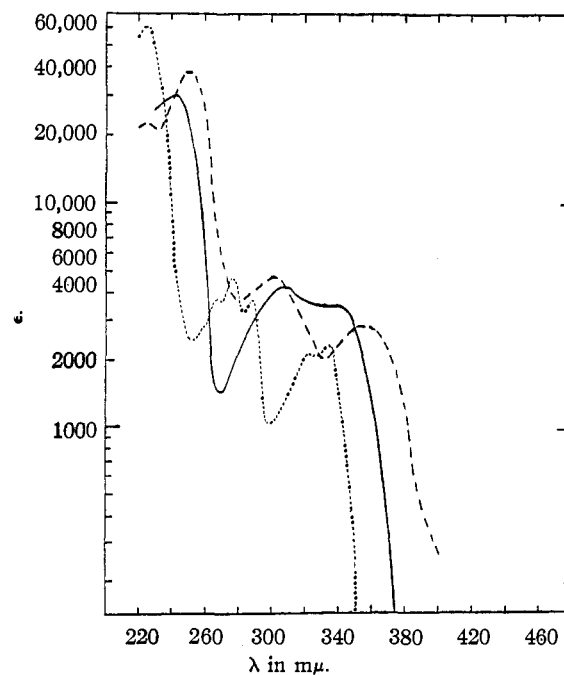

Fig. 2.—Spectra of 3-hydroxy-1-naphthylamine in: —, 95% EtOH; -----, 0.01 N HCl; – –, 0.01 N NaOH.

(2) G. W. Ewing and E. A. Steck, THIS JOURNAL, 68, 2181 (1946).
(3) E. A. Steck and G. W. Ewing, ibid., 70, 3397 (1948).

similar to 2-naphthol in form; however, in alkali some fine structure is lost, and in ethanol the interaction of influences of both functional groups results in an individual spectra pattern.

Spectra of 8-(4-diethylamino-1-methylbutylamino)-6-quinolinol (II) are shown in Fig. 3; the form of the absorption curve in the case of (II) follows the general aspects of that of the parent type (Fig. 1) with variations induced by the contributions of the side-chain. The inflection in the 300–320 mμ range in ethanol for (III) is lost in (II), and the minor maximum at 308 mμ for (III) in base is de-emphasized in (II) to become an inflection. Further, there is a bifurcation of the maximum at 270 mμ shown by (III) in acid, producing twin peaks at 265 and 278 mμ in (II). All spectral curves in Fig. 3 show hypsochromic displacement when compared with those in Fig. 1. This indicates hindered resonance in (II), as expected, due to the dialkylaminoalkyl substituent on the amino group.
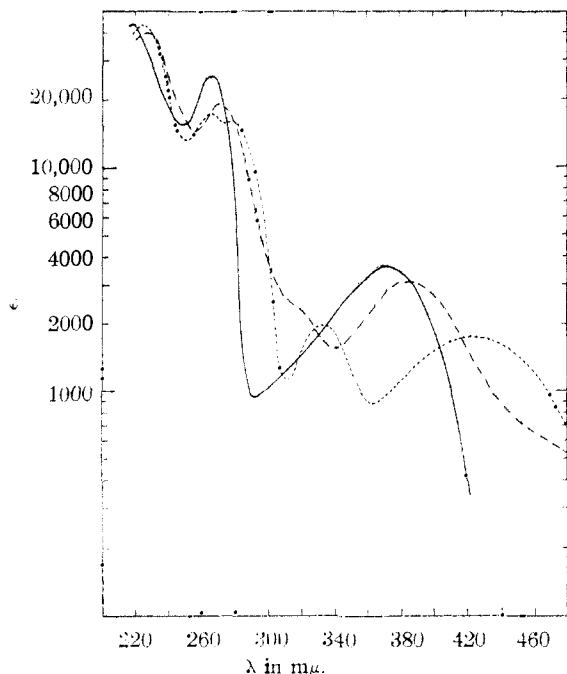

Fig. 3.—Spectra of 8-(4-diethylamino-1-methylbutylamino)-6-quinolinol in: ---, 95% EtOH; -----, 0.01 N HCl; - -, 0.01 N NaOH.

The absorption spectra of Certuna (I) in Fig. 4, while related in shape, present a rather different picture when compared with Figs. 1 and 3. Despite close similarity of the side-chains attached to the amino groups in (I) and (II), the spectral patterns are less related than 4-amino-7-chloroquinolines bearing more variations in character as well as length of chain.[4] This is the result of differences in ease of interaction of forces in the 8-aminoquinolines with respect to the ring nitrogen. While most features of the spectrum of (I) in ethanol resemble those of (II), in the short-wave region it follows (III) in character and the sloping shoulder at ca. 280–300 mμ in the case of (I) may have a kindred feature in the 270–290 mμ region of (III).

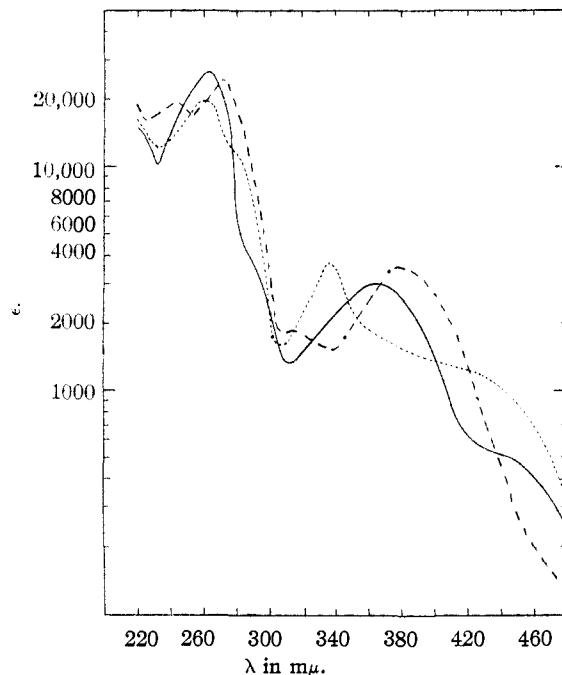(4) E. A. Steck, G. W. Ewing and F. C. Nachod, THIS JOURNAL, 70, 3110 (1948).

Fig. 4.—Spectra of 8-(3-dimethylamino-1-methylpropylamino)-6-quinolinol in: —, 95% EtOH; -----, 0.01 N HCl; - -, 0.01 N NaOH.

In acid solution, (I) loses much of the character shown by (II); the doublet at 265 and 278 mμ is reduced to a maximum and an inflection, and the broad maximum at 420 mμ is diminished to a mere inflection in the case of (I). While these features prevail, the maximum at 300 mμ in (II) and (III) is displaced batho- and hyperchromically in (I). Solution in alkali leads to formation of sodium salts, and while the general patterns of the spectra are more related, Certuna shows an hyperchromic displacement of the maxima in the 270 and 380 mμ regions in (II), and the maximum at 244 mμ in (I) is probably the result of bathochromic shifting of a band at shorter wave length in (II) and (III).

Experimental[5]

3-Hydroxy-1-naphthylamine.—4-Nitro-2-naphthol was prepared from 1-naphthylacetamide by the method of Morgan and Evens.[6,7] It was reduced in ethanol with 10% platinum–charcoal catalyst at 3 atm. to give 88% of 3-hydroxy-1-naphthylamine, m.p. 203.5–205° dec. The compound was sublimed twice (170°, 0.1 mm.) and then crystallized from 85% ethanol (containing traces of sodium dithionite). The white needles melted at 208.5–209°, cor. (evacuated capillary); literature,[7] m.p. 198° dec.

Anal. Calcd. for $C_{10}H_9NO$: N, 8.80. Found: N, 8.89.

8-Amino-6-quinolinol.—The demethylation of 8-amino-6-methoxyquinoline, carried out as described in the patent literature,[8] gave 8-amino-6-quinolinol (m.p. 170–172° dec.) in 85% yield. A sample was crystallized twice from ethyl acetate–hexane and then from water (containing traces of sodium dithionite) to produce the compound as pale yellow needles, m.p. 177–177.5°, dec. (lit.[8,9] 177 and 188°).

Anal. Calcd. for $C_9H_8N_2O$: N, 17.49. Found: N, 17.34.

8-(3-Dimethylamino-1-methylpropylamino)-6-quinolinol was prepared[10] from 8-(3-dimethylamino-1-methylpropyl-

(5) Analyses by Mr. K. D. Fleischer and staff of the Microanalytical Laboratories of this Institute.

(6) G. T. Morgan and E. D. Evens, *J. Chem. Soc.*, 115, 1132 (1919).

(7) W. A. P. Challenor and C. K. Ingold, *ibid.*, 123, 2080 (1923).

(8) F. Mietzsch and H. Klös, U. S. Patent 1,903,407.

(9) J. Mathéus, *Ber.*, 21, 1645 (1888).

(10) E. A. Steck and W. Boehme, to be published.

amino)-6-methoxyquinoline (*cf.* ref. 11) by refluxing with hydrobromic acid.[12] The compound was used as the sulfate trihydrate, m.p. 118–120°.[10]

8-(4-Diethylamino-1-methylbutylamino)-6-quinolinol.[13]— Pamaquine base was demethylated with hydriodic acid and the product characterized[10] as the dihydroiodide (m.p. 162–164°) and the methylene 1,1'-bis-(2-hydroxy-3-naphthoate) (m.p. > 250°).

The spectra were determined with a Cary recording spectrophotometer, using a dynode voltage of 4, a slit schedule of 20, and 1-cm. quartz cells. The concentrations of the solutions ranged from 0.01 to 0.200 g./l. and their spectral behavior conformed with Beer's law in all instances. The assistance of Mrs. M. Becker is gratefully acknowledged.

(11) E. C. Kleiderer, J. B. Rice and V. Conquest, Office of Publication Board, Dept. of Commerce, Washington, D. C., 1945, Report 248, p. 32.

(12) W. Kikuth, U. S. Patent 2,291,235.

(13) Swiss Patent 129,425 (to I. G. Farbenindustrie).

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Observations on Curium Valence States; A Rapid Separation of Americium and Curium[1]

BY S. E. STEPHANOU AND R. A. PENNEMAN

A search for oxidation states higher than Cm(III) in aqueous solution has been made using macro amounts of curium (up to 238 μg. per experiment). Since Cm[242] has a specific activity of *ca.* 7×10^9 α/min./microgram,[2] it was anticipated that production of hydrogen peroxide or other reducing materials might be a limiting factor in the oxidation. Consequently, americium, which does exhibit higher oxidation states (V)[3a] and (VI)[3b] in solution, was used as an internal check for oxidation. It was found that Am(III) was not oxidized to Am(VI) in the presence of curium concentrations of *ca.* 500 μg./ml. However, the oxidation of Am(III) to Am(VI) is complete at curium concentrations of *ca.* 160 μg./ml., or lower. The effect of curium α-radiation on the solution would presumably be the same for higher oxidation states of both curium and americium, and therefore could not be the limiting factor in the curium oxidation within the concentration ranges studied.

Experimental

The chemicals used were all reagent grade. The isotopes employed were Cm[242] and Am[241], α-emitters of 162 day[2] and 475 year[4] half-lives, respectively.

Oxidation in Acid.—Experiments were performed with 0.1–0.3 *f* HNO_3 or $HClO_4$ solutions containing americium and curium in various weight ratios. These solutions were treated with solid ammonium peroxydisulfate and heated 1–2 hours in a water-bath at 85°. The oxidation of Am(III) to Am(VI) in the presence of curium was achieved best when the hydroxides were freshly precipitated with gaseous ammonia, dissolved in acid to give a solution of 0.1 *f* in hydrogen ion, and immediately oxidized with peroxydisulfate. Dilute acid solutions of americium and curium which had been left to stand for several hours or longer were not readily oxidized. Immediately following the oxidation, the solution was made 3–4 *f* in HF to precipitate CmF_3 and any

(1) Work done under the auspices of the AEC.

(2) G. C. Hanna, B. G. Harvey and N. Moss, *Phys. Rev.*, **78**, 617 (1950).

(3) (a) L. B. Werner and I. Perlman, THIS JOURNAL, **73**, 495 (1951); (b) L. B. Asprey, S. E. Stephanou and R. A. Penneman, *ibid.*, **73**, 5715 (1951).

(4) B. B. Cunningham, S. G. Thompson and H. Lohr, unpublished work (1949).

americium still in the (III) state. (The 27 *f* HF used was pretreated with solid ammonium peroxydisulfate.) The fluoride precipitate was separated by centrifugation and washed with hot ammonium peroxydisulfate solution, 0.1 *f* in $HClO_4$ and 3 *f* in HF. The supernatant and wash were combined.

The fluoride precipitate was dissolved in 1 *f* HNO_3, saturated with H_3BO_3. Mixed $Cm(OH)_3$ and $Am(OH)_3$ were precipitated from the resulting solution with gaseous ammonia. The precipitate was dissolved in 0.2 *f* perchloric acid; Am(III) was determined in the Beckman DU spectrophotometer by observation of the 503 mμ peak (molecular extinction coefficient of 360 in 0.1 *f* $HClO_4$). Curium was determined by a total α-count after correction for the americium alphas present.

The fluoride supernatant was treated with hydrogen peroxide to reduce Am(VI) to Am(III) with consequent precipitation of AmF_3. The precipitate was dissolved as described above and americium(III) determined spectrophotometrically.

Experiments were performed with and without lanthanum as carrier for the curium. Typical results of this separation method are shown in Table I.

TYPICAL RESULTS FOR THE PEROXYDISULFATE SEPARATION METHOD (ONE CYCLE)

Cm	μg./ml. Am	La	Wt. fraction Cm:Am Before oxidation	Cm:Am After oxidation (CmF₃)
3.7	1060	350	0.0035	0.11
82	210	800	0.39	10.0
85	28	215	3.0	19.0
160[a]	270	0	0.59	15.7
540	39[b]	0	14.0	15.8

[a] At this concentration, without lanthanum carrier, the solubility of CmF_3 limits the yield of curium in the precipitate to *ca.* 90%. [b] In the absence of curium, Am(III) is completely oxidized to Am(VI) at concentrations even as low as 11 μg./ml.

Curium was not oxidized to a fluoride-soluble state, since it was possible to precipitate CmF_3 and leave *ca.* 95% of the Am(VI) in solution. This eliminates the possibility that Cm(VI) was formed, but does not rule out the possibility of Cm(IV), which would also have an insoluble fluoride. Consequently, four experiments were performed using Zr(IV) phosphate; Cm(III) was treated with ammonium peroxydisulfate, both with and without silver catalyst, in 0.1–1 *f* acid and Zr(IV) phosphate precipitated. Since only 2–10% of the curium present was carried by zirconium phosphate, it seems evident that no Cm(IV) is formed under these conditions. (At these low acidities, the gelatinous precipitate would be expected to carry some Cm(III).)

Alkaline Oxidation.—Experiments were performed to attempt to form Cm(V) by peroxydisulfate oxidation in 2 *f*, 3 *f* and saturated K_2CO_3 solution, and to demonstrate its existence by co-precipitation with Am(V). The Am(V) precipitate contained only 0.5–2% of the curium. Concentrations ranged from 5 to 320 μg. of curium per ml. with 13 to 500 μg. of americium per ml. In this last experiment, only 2% of the curium was found in the Am(V) precipitate. It was concluded that curium is not oxidized to Cm(V) under conditions in which Am(III) is quantitatively oxidized to Am(V). Spectrophotometric examination of the carbonate supernatant was made to look for Cm(IV) or Cm(VI); only the absorption spectrum of Cm(III) was found.

The possibility of a slow step in the curium oxidation cannot be ruled out. However, the oxidation of very dilute americium solutions ($4.5 \times 10^{-5} f$) is complete in less than an hour (Am(III) → Am(VI), 0.1 *f* H^{+}, peroxydisulfate). Inasmuch as Am(VI) and Am(V) undergo auto-reduction at the rate of a few per cent. an hour, due to the products of americium α-radiation,[5] and the specific activity of Cm[242] is 1000 times that of Am[241], it seems likely that a sufficient concentration of reduction materials would be produced to prevent complete oxidation of americium when sufficient curium is present. However, the effect should *not* limit the

(5) L. B. Asprey and S. E. Stephanou, AECU-924, November 10, 1950.

oxidation of curium only, while allowing *ca.* 100% oxidation of americium in the same solution.

No evidence for the existence of Cm(IV), -(V) or -(VI) was found in the oxidation of Cm(III)–Am(III) mixtures in either acid or alkaline media under conditions where Am(III) yielded Am(VI) or Am(V), quantitatively. Consequently, the potential of Cm(III) to Cm(IV), (V), or Cm(VI) is at least more negative than the corresponding americium couples. The Cm(III)–(VI) couple is probably more negative than −2 volts (the peroxydisulfate–argentic couple).

A rapid separation method based on the precipitation of CmF_3 from Am(VI) was developed. For macro amounts of curium, CmF_3 is precipitated without carrier, leaving Am(VI) in the supernatant; for amounts of curium where the solubility of CmF_3 is a limiting factor, lanthanum fluoride carrier is used. Where lanthanum is introduced as carrier for CmF_3, a later purification from this element must be performed. This is readily accomplished by means of a column elution using 13 *f* HCl.[6] Where no lanthanum carrier was used, the solubility of CmF_3 was found to be *ca.* 12 μg./ml.

(6) K. Street, Jr., and G. T. Seaborg. THIS JOURNAL, **72**, 2790 (1950).

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Toluene-Soluble Copper and Silver Fluoborates. Decomposition of Diazonium Fluoborates[1]

BY JAMES C. WARF

During the course of some investigations concerning copper hydrides, a variety of copper compounds was treated with lithium aluminum hydride under various conditions. Compounds of copper soluble in organic media (solvents stable toward lithium aluminum hydride) were sought, and phenylcopper seemed a promising material. Phenylcopper was prepared by Reich[2] *via* the action of Grignard reagents on copper(I) iodide at 0°, as a reactive and unstable substance. Gilman and Straley[3] also prepared phenylcopper and related compounds by Reich's method. Bolth, Whaley and Starkey,[4] and later Whaley and Starkey,[5] decomposed aromatic diazonium fluoborates in the presence of copper and boiling benzene or toluene, and observed that some of the copper was dissolved. They attributed this to the formation of arylcopper compounds, largely on the basis of examination of derivatives with pyridine and other materials. Thus they claimed the identification of the phenylcopper–pyridine derivative as $C_6H_5Cu\cdot3C_5H_5N$, a blue, water-soluble compound.

Phenylcopper *via* Grignard and Diazonium Reagents.—The above preparative methods both were repeated, but gave products widely different, especially in stability and in behavior toward pyridine. Phenylcopper prepared by Reich's method decomposed in toluene solution slowly at 0°, more rapidly at room temperature, forming a copper mirror on the walls of the vessel; further it gave no blue coloration with pyridine. Neither Reich nor Gilman and Straley had noted coloration on dissolving phenylcopper in pyridine. On the other hand, toluene solutions prepared

(1) Presented at the XII International Congress of Pure and Applied Chemistry, New York, N. Y., September, 1951.

(2) R. Reich, *Compt. rend.*, **177**, 322 (1923).

(3) H. Gilman and J. M. Straley, *Rec. trav. chim.*, **55**, 821 (1936).

(4) F. A. Bolth, W. M. Whaley and E. B. Starkey, THIS JOURNAL, **65**, 1456 (1943).

(5) W. M. Whaley and E. B. Starkey, *ibid.*, **68**, 793 (1946).

using benzenediazonium fluoborate and copper, according to Whaley, *et al.*, deposited no copper even on boiling, and with pyridine (and air) yielded blue crystals. Work was, therefore, undertaken to clarify this discrepancy, and possibly employ both types of copper compounds in the copper hydride studies.

The general techniques of Whaley, *et al.*, were followed in work with the diazonium compounds. The principal deviation from their procedure was the use of an all-glass apparatus designed to permit refluxing, stirring, filtration and introduction of pyridine in a strictly air-free system. Pyridine was distilled from aluminum chloride directly into the filtrate. Nitrogen, freed of oxygen by passage through activated cobalt(II) oxide[6] was employed to exclude air and to pressure the solutions through sintered glass disks. Benzene- and *p*-nitrobenzenediazonium fluoborates were prepared using fluoboric acid according to Roe,[7] and dried over sulfuric acid in vacuum desiccators. These compounds, especially the *p*-nitro derivative, were observed to decompose slowly, and preparations two or more weeks old gave some tarry products.

Toluene solutions of phenylcopper were prepared by Gilman and Straley's method; substitution of phenyllithium for phenylmagnesium iodide was found to be advantageous.

Treatment of the filtrate from the benzenediazonium fluoborate–copper reaction with pyridine under air-free conditions caused precipitation of a pale yellow material, and no blue color developed until the mixture was aerated. The yellow and blue substances thus appeared to be copper(1) and copper(II) compounds, respectively. Whaley, *et al.*, supposed the blue material to be formed without air oxidation, and to be $C_6H_5Cu\cdot3C_5H_5N$.

Tetrapyridinecopper(II) Fluoborate.—The blue crystals (A) from benzenediazonium fluoborate were recrystallized from ethanol. *p*-Nitrobenzenediazonium fluoborate, when decomposed similarly in boiling toluene in the presence of copper, gave two reaction products with pyridine and air. Treatment with hot ethanol yielded blue crystals (B) from the soluble portion, and a green residue (C). Substance C was insoluble in the common solvents except glacial acetic acid, which on cooling deposited blue-green crystals (D). Qualitative analysis of A and B disclosed the presence of fluoborate ion, and analysis identified both as tetrapyridine-copper(II) fluoborate, $Cu(C_5H_5N)_4(BF_4)_2$, a substance previously prepared by Lange[8] and by Wilke-Dörfurt and Balz.[9]

The blue crystals were prepared in quantity by dissolving basic copper(II) carbonate in fluoboric acid and adding pyridine, and recrystallizing from ethanol. This preparation (E) was shown by analysis to have the same composition as A and B. Substance C was evidently impure copper(II) hydroxide, and D a partially hydrated copper(II) acetate.

Carbon, hydrogen and nitrogen analyses were made[10] using standard methods. Copper determinations were made iodometrically employing the blue crystals directly, or after successive digestions with alkali and nitric acid, both methods giving identical results. Fluoborate analyses were made gravimetrically by precipitating nitron fluoborate.[8,9,11]

Anal. Calcd. for $Cu(C_5H_5N)_4(BF_4)_2$: Cu, 11.48; C, 43.39; H, 3.64; N, 10.12; BF_4, 31.37. Found for A: Cu, 11.7; C, 43.5; H, 4.1; N, 9.71; BF_4, 31.1. For B: Cu, 11.5; C, 43.5; H, 4.5; N, 8.4; BF_4, 31.5. For E: Cu, 11.5; C, 43.4; H, 4.5; N, 9.0; BF_4, 31.8.

Anal. Calcd. for $Cu(OH)_2\cdot0.5H_2O$: Cu, 59.5; H, 2.8. Found for C: Cu, 60.0; C, 0.0; H, 3.5.

Anal. Calcd. for $Cu(C_2H_3O_2)_2\cdot0.63H_2O$: Cu, 32.9; C, 24.8; H, 3.8. Found for D: Cu, 32.9; C, 25.0; H, 4.5.

Hydrogen analyses of the fluoborates were high, probably on account of partial absorption of boron trifluoride in the weighing tubes. Nitrogen analyses were somewhat low and variable, probably owing to partial loss of pyridine during recrystallization and drying; a portion of A, freshly recrystallized from alcohol–pyridine mixtures, had a nitrogen content of 10.48%.

(6) H. A. Pagel and E. D. Frank, *ibid.*, **63**, 1468 (1941).

(7) A. Roe, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 193 ff.

(8) W. Lange, *Ber.*, **59**, 2107 (1926).

(9) E. Wilke-Dörfurt and G. Balz, *Z. anorg. allgem. Chem.*, **159**, 197 (1927).

(10) Microanalyses were carried out by Mr. J. Piric.

(11) V. L. Berkovich and Y. V. Kulyashev, *J. Applied Chem.* (*U.S.S.R.*), **10**, 192 (1937).

That A, B and E were identical was confirmed through X-ray diffraction patterns made using powdered specimens. The three materials gave patterns identical in every respect. While no structure determination was made, the material had a low order of symmetry, being orthorhombic, monoclinic or triclinic. According to the conclusions of Whaley, et al., substances A and B should be different, namely, C_6H_5·Cu·$3C_5H_5N$ and p-$NO_2C_6H_4Cu$·$3C_5H_5N$, and it now seems certain that these compositions are erroneous.

Copper(I) Fluoborate via Diazonium Fluoborates.—Identification of the blue crystals as a derivative of copper(II) fluoborate suggested that the intermediate, toluene-soluble copper(I) compound, formed through the attack of copper metal during decomposition of the diazonium fluoborates, was copper(I) fluoborate. This idea was supported by consideration of the well-known solubility of silver perchlorate in aromatic hydrocarbons, the comparable size of copper(I) and silver(I) ions and the similarity of their compounds, the structural resemblance of the fluoborate and the perchlorate ions, and the failure of the copper compound to form when non-aromatic solvents are substituted.[5] Accordingly, the proposed reaction, in the case of the unsubstituted diazonium fluoborate, is

$$2C_6H_5N_2BF_4 + 2Cu \longrightarrow 2CuBF_4 + 2N_2 + (C_6H_5)_2$$
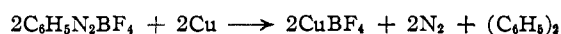
Treatment of toluene filtrates from p-nitrobenzenediazonium fluoborate–copper reaction mixtures with water or very dilute sulfuric acid gave a green copper(II) solution and metallic copper, corresponding to the disproportionation of the copper(I) ion. Moreover, the p,p'-dinitrobiphenyl was isolated and identified as follows. The toluene was steam distilled and the resulting tarry residue recrystallized from alcohol several times. This gave yellow crystals of p,p'-dinitrobiphenyl, m.p. 231–233° (literature, 233°). A portion was reduced to benzidine, which was converted to p,p'-bis-(p-tolylsulfonamido)-biphenyl, m.p. 241–243° (literature, 243°); a mixed melting point of this derivative with an authentic specimen showed no depression.[12]

Silver Fluoborate.—Silver powder was substituted for copper in the decomposition of p-nitrobenzenediazonium fluoborate in boiling toluene, and small but unmistakable quantities of silver as a toluene-soluble substance were detected in the filtrate. The concentration of silver was so low, however, that attempts were made to prepare silver fluoborate in quantity by other means, and investigate its behavior toward toluene.

Silver fluoborate monohydrate was prepared by a slight modification of the procedure of Wilke-Dörfurt and Balz.[9] The evaporation and final drying, which was carried out in vacuum over anhydrous magnesium perchlorate, requiring about five weeks at room temperature, yielded white flakes assaying approximately 93% $AgBF_4$·H_2O. This material was found to dissolve abundantly in toluene with slight evolution of heat, forming a viscous solution. Using the phase data of Hill and Miller[13] on the silver perchlorate–toluene–water system as a guide, it was predicted that addition of water to a toluene solution of the fluoborate should cause it to separate first into two and then into three liquid phases. Accordingly, water was slowly added (temperature 25°) to a toluene solution which was 3.61% H_2O and 39.4% $AgBF_4$ (all percentages by weight). When the water content reached 6.22% (38.4% $AgBF_4$), a second liquid phase began to separate. When the water content reached 9.47% (37.0% $AgBF_4$), a third liquid phase began to separate. More water was added, the three phases separated, and each analyzed. The lower layer was 69.3% $AgBF_4$; the middle layer was 50.0% $AgBF_4$; and the top layer was 0.56% $AgBF_4$, and approximately 91% toluene. These data differ somewhat quantitatively from those of the silver perchlorate system, but are very similar qualitatively.

It was believed profitable to examine the anhydrous system, and accordingly the synthesis was attempted by the action of boron trifluoride on silver fluoride suspended in boiling toluene. Anhydrous silver fluoride was prepared by the method of Moles and Batuecas,[14] modified in that the final dehydration was carried out at 70–75° under vacuum using a large iron vessel. The silver fluoride (0.30 mole) was transferred to the all-glass system employed in the diazonium fluoborate decomposition work, covered with 300

ml. of toluene, stirred vigorously, and boiled under reflux. Boron trifluoride from a tank of compressed gas was bubbled into the suspension for 14 hours. Filtration was effected by nitrogen pressure; essentially all of the silver fluoride had dissolved. The filtrate consisted of two layers, the volume of the upper phase being roughly three times that of the lower.

The existence of a two-liquid phase system was ascribed to adventitious introduction of moisture during transfer of the extremely hygroscopic silver fluoride into the system or to incomplete dehydration of the original material. Relatively little water is required to split either the silver perchlorate–toluene or silver fluoborate–toluene system into two liquid phases. Analysis of each layer showed Ag:BF_4 ratios of 1.12:1 for the lower phase, indicating some excess silver fluoride, and 1.01:1 for the upper phase. The concentrations were 119 and 16.5 mg. of silver per gram for the lower and upper phases, respectively.

Copper(I) Fluoborate via Boron Trifluoride.—It also proved possible to prepare a toluene solution of copper(I) fluoborate through the use of boron trifluoride. Since copper(I) fluoride does not exist at room temperature,[15] a stoichiometric mixture of copper metal and copper(II) fluoride was used instead. The latter compound was prepared by hydrofluorinating basic copper carbonate at 500°. Employing the same apparatus and technique as in the case of the silver compound, the boron trifluoride treatment was carried out for 2.5 hours. The toluene filtrate was treated with very dilute sulfuric acid, when metallic copper and a green copper(II) solution resulted from disproportionation of the copper(I) fluoborate. The copper in each state was determined; the copper(II) constituted slightly more than half of the total. The original toluene filtrate contained 0.382 mg. of Cu per gram of solution.

Attempted Preparation of Copper(I) and Silver Fluoborates via Metathesis.—Stoichiometric quantities of ammonium fluoborate with copper(I) chloride on the one hand and with silver sulfate on the other were refluxed with toluene 24 and 6 hours, respectively. In neither case, however, did detectable amounts of the metal enter the hydrocarbon phase.

Discussion.—If it is supposed that the constitution of silver fluoborate in toluene resembles that of the perchlorate,[16] i.e., ion pairs in dilute solutions, molecular aggregates in more concentrated solution, the existence of solid compounds such as $AgBF_4$·$C_6H_5CH_3$ is predicted. This behavior may be regarded as another manifestation of the resemblance of fluoborate and perchlorate ions, which, as pointed out by Wilke-Dörfurt,[17] have similar structures, size (Cl–O = 1.63 Å., B–F = 1.53 Å.) and crystal packing behavior. The interaction of silver ions with aromatic hydrocarbons evidently plays the deciding role in the solubility of the perchlorate and fluoborate, and stabilizes the latter; evidently pure silver fluoborate is incapable of existence, except possibly at low temperatures and high boron trifluoride pressure. Apparently a similar situation exists in the case of copper(I) fluoborate. The single bond covalent radii of copper and silver,[18] 1.17 and 1.34 Å., respectively, are not widely different. The subtle factors influencing solubilities of these and related compounds in aromatic hydrocarbons are illustrated by the insolubility of thallium(I) perchlorate, thallium(I) fluoborate,[19] and silver permanganate in toluene, and the moderate solubility of silver trifluoroacetate in benzene.[20]

(12) This part was done by N. Schwartz.

(13) A. E. Hill and F. W. Miller, This Journal, **47**, 2702 (1925).

(14) B. Moles and T. Batuecas, J. chim. phys., **17**, 537 (1919).

(15) H. von Wartenberg, Z. anorg. allgem. Chem., **241**, 381 (1939).

(16) A. E. Hill, This Journal, **43**, 254 (1921); **44**, 1163 (1922).

(17) E. Wilke-Dörfurt, Z. angew. Chem., **37**, 712 (1924).

(18) L. Pauling, This Journal, **69**, 542 (1947).

(19) Prepared by vacuum dehydration of $TlBF_4$·H_2O at 108°; H. Funk and F. Binder, Z. anorg. allgem. Chem., **159**, 121 (1927).

(20) F. Swarts, Bull. soc. chim. Belg., **48**, 176 (1939).

From molecular weight determinations using benzene solutions, Hill[15] concluded that at higher concentrations, two or even three ion pairs of silver perchlorate associated into clusters. Estimations of the size of the solute particle by Luder, et al.,[21] also indicate dimerization. It may prove possible to determine the solute particle geometry by an

(21) W. L. Luder, P. B. Kraus, C. A. Kraus and R. M. Fuoss. THIS JOURNAL, **58**, 255 (1936).

X-ray diffraction technique, using concentrated solutions of silver perchlorate or fluoborate in toluene, such as was carried out by Vaughan, et al.,[22] with complex ions of certain heavy metals.

(22) P. A. Vaughan, J. H. Sturdivant and L. Pauling, ibid., **72**, 5477 (1950).

DEPARTMENT OF CHEMISTRY
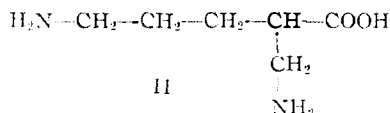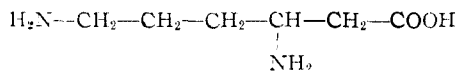UNIVERSITY OF SOUTHERN CALIFORNIA
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COMMUNICATIONS TO THE EDITOR

STRUCTURE OF THE DIAMINOHEXANOIC ACID FROM STREPTOTHRICIN[1]

Sir:

Previously we have reported that streptothricin on hydrolysis yields three ninhydrin-positive products, one of which, the fastest-moving on papergrams, was characterized as a diaminohexanoic acid.[2,3] The same amino acid has been isolated from viomycin[3,4,5] and appears to be present also in streptolin.[3,6]

Possible structures for this substance were limited to isomers I and II on the basis of the following data[2,3]: negative Kuhn–Roth, negative

$$H_2N—CH_2—CH_2—CH_2—CH—CH_2—COOH$$
$$\overset{|}{NH_2}$$
I

$$H_2N—CH_2—CH_2—CH_2—CH—COOH$$
$$\overset{|}{CH_2}$$
II
$$\overset{|}{NH_2}$$

periodate, and negative α-amino acid tests; degradation via the Curtius reaction to a triaminopentane which reacted with periodate (one mole) yielding ammonia and formaldehyde.

Since further degradation studies were unproductive, the synthesis of isomers I and II was undertaken. I was obtained from α-N-phthalyl-δ-N-benzoyl-L-ornithine by application of the Arndt-Eistert reaction in a manner similar to that described by Balenović, et al.,[7] for derivatives of tyrosine. The resulting β,ε-diamino-n-caproic acid

(1) Supported by a grant from the Abbott Laboratories, Eli Lilly and Company, and the Upjohn Company.

(2) H. E. Carter, W. R. Hearn and W. R. Taylor. "Abstracts of Papers." 119th Meeting. American Chemical Society. Cleveland, Ohio. April, 1951, p. 25A.

(3) H. E. Carter, W. R. Hearn and W. R. Taylor, "Abstracts of Papers" 120th Meeting, American Chemical Society. New York. N. Y., September, 1951, p. 3L.

(4) T. H. Haskell, S. A. Fusari, R. P. Frohardt and Q. R. Bartz. THIS JOURNAL, **74**, 599 (1952).

(5) We are indebted to Parke, Davis and Company for a generous supply of viomycin.

(6) E. E. Smissman, R. W. Sharpe and E. E. van Tamelen. "Abstracts of Papers" 121st Meeting, American Chemical Society, Milwaukee, Wisconsin, April, 1952, p. 80.

(7) von K. Balenović, V. Thaller and I. Filipović, Helv. Chim. Acta, **34**, 744 (1951).

was optically active ([α]²³D +24°, c 1.1 in 1 N hydrochloric acid), and yielded the following derivatives: p-hydroxyazobenzene-p'-sulfonate, m.p. 246–249°; N,N-dibenzoyl acid, m.p. 113–116° (found: C, 67.94; H, 6.30; N, 7.73); N,N-dibenzoyl methyl ester, m.p. 147–150° (found: C, 68.47; H, 6.42; N, 7.77). The corresponding derivatives of the natural substance ([α]²³D +25°, c 1.1 in 1 N hydrochloric acid) melted at 224–246° (found: C, 51.52; H, 4.44; N, 12.23; S, 9.30), 113–116° (found: C, 68.02; H, 5.73; N, 7.93), and 148–150° (found: C, 68.63; H, 6.22; N, 7.86), respectively. The infrared spectra of the N,N-dibenzoyl acids and esters of the synthetic and natural substances were respectively identical. Moreover, crystallization from ethanol of the crude benzoylation products of both the synthetic and natural substances yielded neutral dibenzoyl derivatives (synthetic, m.p. 143–146°, found: C, 68.95; H, 6.77; N, 7.43; natural, m.p. 146–148°, found: C, 68.71; H, 6.97; N, 7.89) having superimposable infrared spectra.

Isomer II was prepared in racemic form by reduction of ethyl α,γ-dicyanobutyrate in a glacial acetic–sulfuric acid mixture with platinum oxide as catalyst. The racemic N,N-dibenzoyl acid (m.p. 156–158°, found: C, 68.13; H, 5.92; N, 7.66) and N,N-dibenzoyl methyl ester (m.p. 119–122°) of II gave infrared spectra differing significantly from those of the corresponding derivatives of the natural substance.

These data establish conclusively that the diaminohexanoic acid from streptothricin and viomycin has structure I (β,ε-diamino-n-caproic acid). It is suggested that the trivial name β-lysine be assigned to this compound.

Structural studies upon streptothricin and its hydrolytic products will be reported later in more detail.

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