trous acid removed with urea. The diazonium solution was then buffered at a *p*H of about 6 by the addition of 50 g. of sodium acetate and 15 cc. of glacial acetic acid in 50 cc. of water.[13] The diazonium solution was then added dropwise with stirring at 0° during a 2-hr. period to a solution of 4 g. of β-mercaptopropionic acid and 10 g. of sodium acetate in 50 cc. of water. There was an immediate formation of a yellow-white solid and an evolution of gas during the addition. The best method of working up the product was to collect it and recrystallize it once from aqueous alcohol. The product was then allowed to stand in aqueous acetone with some concd. hydrochloric acid for 3 days at room temperature, following the hydrolysis procedure described above for the ester XI. The solution was extracted with ether, the extracts were washed with sodium carbonate, and the desired acid VI was obtained by acidification of the carbonate solution; it weighed 4.7 g. (36%) and melted at 135–137°. The ether extract yielded an appreciable amount of neutral crystalline material, m.p. 82–82.5°, shown to be 4-methoxybiphenyl by a mixed m.p.

5-Phenyl-8-methoxythiochromanone (V).—The only way found for the cyclization of VI to V was the following. The acid VI (1 g.) was treated in a platinum dish with 20–30 g. of anhydrous hydrogen fluoride. The dish was placed in a paraffin-coated desiccator over calcium chloride and allowed to stand overnight. The viscous oil in the dish was dissolved in benzene, with warming on a steam-bath, and was extracted with sodium carbonate; the residue in the dish was also extracted by sodium carbonate; usually about 0.6 g. of the starting acid VI was recovered by acidification of the carbonate extracts. The benzene solution was washed with water, dried, and chromatographed on alumina, using dry benzene as the eluent. The benzene yielded a dark oil, from which was obtained crystalline material, which, after two crystallizations from methanol, weighed 0.2 g. (50%, based on unrecovered starting material) and melted at 124–125°.

Anal. Calcd. for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22. Found: C, 71.02; H, 5.43.

The dinitrophenylhydrazine melted, after two recrystallizations from chloroform–ethanol, at 253–256°.

Anal. Calcd. for $C_{22}H_{18}N_4O_5S$: C, 58.65; H, 4.02. Found: C, 58.70; H, 4.39.

β-(2-Naphthyl)-mercaptopropionic Acid.—This compound was not obtained by the action of diazotized β-naphthylamine on β-mercaptopropionic acid, using either an acetate buffer or an acid solution; tar and naphthalene were the products. It was readily prepared by heating 4 g. of β-thionaphthol with 10 g. of methyl acrylate and a few drops of piperidine for 6 hr. The volatile material was then removed *in vacuo*, the residue was dissolved in acetone, concd. hydrochloric acid was added until a precipitate appeared, and additional acetone was added to clear the solution. After standing for 4 days, the mixture was worked up as described above, and 4.5 g. (77%) of the desired acid was obtained, m.p. 102–103°, after crystallization from benzene.[14]

5,6-Benzothiochromanone (XII).[14]—This compound was prepared in 60% yield by the cyclization with anhydrous hydrogen fluoride, by essentially the procedure described above for V. The same yield was obtained by the use of sulfuric acid (as in ref. 14) but the product from the hydrogen fluoride was easier to work up.

5,6-Benzothiochromanone Sulfone (XIII).—The thiochromanone (1 g.) was refluxed 1 hr. with 10 g. of 30% hydrogen peroxide in glacial acetic acid, and the excess peroxide was decomposed by addition of manganese dioxide. The solution was filtered, was diluted with water and the resulting precipitate was isolated. After three crystallizations from ethanol, 0.79 g. (69%) of sulfone, m.p. 150–151°, was obtained.

Anal. Calcd. for $C_{13}H_{10}O_3S$: C, 63.45; H, 4.06. Found: C, 63.57; H, 4.10.

ROCHESTER, N. Y.

---

[13] The reaction did not take place in an unbuffered solution of low *p*H; *cf.* D. S. Tarbell, E. G. Lindstrom, *et al.*, THIS JOURNAL, **70**, 1381 (1948).

[14] The m.p. reported for the acid (F. Krollpfeiffer and H. Schultze, *Ber.*, **56**, 1819 (1923)) prepared by the action of β-bromopropionic acid on β-thionaphthol, is 104–105°.

NOTES

Preparation of β-Hydroxydialkyl Peroxides

BY M. R. BARUSCH AND J. Q. PAYNE

RECEIVED DECEMBER 12, 1952

Three β-hydroxydialkyl peroxides were prepared by a reaction of *t*-butylhydroperoxide with epoxides. The compounds synthesized were β-hydroxyethyl-*t*-butyl peroxide, β-hydroxypropyl-*t*-butyl peroxide and β-hydroxyisobutyl-*t*-butyl peroxide. Yields obtained ranged from 33–43%. No effort was made to develop optimum conditions to improve these yields. 3,5-Dinitrobenzoates of two of the hydroxy peroxides were prepared. It seems likely that reactions of this type could be used as a general preparative method for β-hydroxydialkyl peroxides or hydroperoxides.

β-Hydroxyethyl-*t*-butyl Peroxide.—A 500-ml. round-bottom flask fitted with a mercury-sealed stirrer, dropping funnel, condenser and thermometer, was immersed in an ice–salt-bath. Forty-four grams (1.0 mole) of ethylene oxide and 150 ml. of ethyl ether were introduced. Maintaining the temperature below 3°, 15 ml. of 40% potassium hydroxide was added over a 30-minute period. Forty-seven grams (0.33 mole) of 63% *t*-butyl hydroperoxide obtained from the Union Bay State Company was added dropwise over a 1.5-hr. interval, maintaining the temperature below 5°. The mixture was allowed to come to room temperature and stirring continued for four hours. The aqueous layer was discarded. Light ends were removed from the organic phase by distillation at atmospheric pressure followed by vacuum distillation to 30° (20 mm.) head temperature. From the bottoms 14.6 g. (33% yield) of crude product was recovered, b.p. 35° at 35 mm. to 34° at 1.5 mm. Redistillation of this material produced 11.5 g. of product, b.p. 37–38° at 2 mm., n^{20}_D 1.4249, d^{20}_4 0.9561.

Anal.[1] Calcd. for $C_6H_{14}O_3$: C, 53.71; H, 10.51. Found: C, 53.79; H, 10.49.

The 3,5-dinitrobenzoate of this compound was prepared by the method of Malone and Reid.[2] The derivative was recrystallized several times from aqueous ethanol and finally from absolute ethanol. It had a melting point of 63–63.6°.

Anal. Calcd. for $C_{13}H_{16}O_8N_2$: C, 47.56; H, 4.91; N, 8.53. Found: C, 47.32; H, 4.99; N, 8.67.

β-Hydroxypropyl-*t*-butyl Peroxide.—In similar manner to the above, but in the absence of the ether, 39 g. (0.67 mole) of 1,2-propene oxide, 10 ml. of 40% potassium hydroxide and 24 g. (0.17 mole) of 63% *t*-butyl hydroperoxide were agitated. After the addition of the hydroperoxide was complete, the mixture was allowed to come to room temperature and then was heated to 40° for two hours. The

---

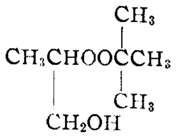
[1] Microanalyses were made by Microchemical Specialties, Berkeley, California.

[2] G. B. Malone and E. E. Reid, THIS JOURNAL, **51**, 3424 (1929).

yield of crude product on distillation of the organic layer was 11 g. (44%). Pure material was obtained on redistillation; b.p. 36.6–37.1° at 2.5 mm., n^{20}_D 1.4184, d^{20}_4 0.9296.

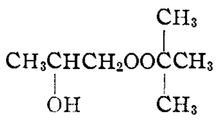
Anal. Calcd. for $C_7H_{16}O_3$: C, 56.73; H, 10.88. Found: C, 57.55; H, 10.75.

From the condensation reaction of 1,2-propene oxide with *t*-butyl hydroperoxide, two isomeric β-hydroxy peroxides are possible: a primary alcohol represented below by formula I and a secondary alcohol, formula II.



$$\begin{array}{l} CH_3 \\ CH_3CHOOCCH_3 \\ |CH_3 \\ CH_2OH \end{array}$$

I



$$\begin{array}{l} CH_3 \\ CH_3CHCH_2OOCCH_3 \\ OHCH_3 \end{array}$$

II

Stephan[3] showed that primary and secondary alcohols could be separated by boiling in benzene with phthalic anhydride. Under such conditions the primary alcohol rapidly esterifies while the secondary reacts very slowly. Cox, Nelson and Cretcher[4] separated the isomeric *n*-propyl ethers of 1,2-propylene glycol by this method. An indication that the compound isolated from the reaction of *t*-butyl hydroperoxide with 1,2-propene oxide was the secondary alcohol was obtained by this procedure as follows:

To 25 ml. of benzene, 3.7 g. of reaction product and 4.5 g. of phthalic anhydride were added. The mixture was refluxed for one hour, allowed to cool, and filtered. On distillation *in vacuo*, 3.4 g. (89%) of the starting material was recovered.

The 3,5-dinitrobenzoate of the β-hydroxypropyl-*t*-butyl peroxide was prepared in the same way as the dinitrobenzoate of β-hydroxypropyl-*t*-butyl peroxide. The derivative was recrystallized twice from ethyl ether and had a melting point of 88–89°.

Anal. Calcd. for $C_{14}H_{18}O_8N_2$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.44; H, 5.21; N, 8.26.

β-Hydroxyisobutyl-*t*-butyl Peroxide.—As above, the reaction of 72 g. (1.0 mole) of 1,2-isobutene oxide with 60 g. (0.42 mole) of 63% *t*-butyl hydroperoxide in the presence of 20 ml. of 40% potassium hydroxide was carried out. After the peroxide addition was complete the mixture was permitted to come to room temperature and then was heated with stirring to 55–60° for two hours. Distillation of the organic phase produced 25 g. (37%) of crude product, b.p. b.p. 45–48° at 5–6 mm. Pure material was obtained by redistillation, b.p. 37–37.5° at 4 mm., n^{20}_D 1.4165, d^{20}_4 0.9085.

Anal. Calcd. for $C_8H_{18}O_3$: C, 59.23; H, 11.18. Found: C, 59.60; H, 11.25.

RICHMOND LABORATORIES
CALIFORNIA RESEARCH CORPORATION
RICHMOND, CALIFORNIA

The Synthesis of 2,4,6-Trinitrostyrene and Some Intermediates

BY C. F. BJORK, W. A. GEY, J. H. ROBSON AND R. W. VAN DOLAH

RECEIVED DECEMBER 20, 1952

Preparation of 2,4,6-trinitrostyrene polymer was attempted in the hope that it might combine the explosive properties of 2,4,6-trinitrotoluene with the flexibility in the control of mechanical properties characteristic of polymers. Concurrent investigations of a similar nature have already been described by Wiley and Behr,[1] who reported the successful synthesis of 2,4,6-trinitrostyrene and the failure of the monomer to undergo polymerization. The present report is concerned, therefore, only with those phases of our study which extend the work of these authors or involve different preparative methods.

Attempted preparation of 2,4,6-trinitrostyrene by dehydration of 2-(2,4,6-trinitrophenyl)-ethyl alcohol was unsuccessful due to the failure of the alcohol to lose water when heated with concentrated sulfuric acid, with a mixture of sirupy phosphoric acid and phosphoric anhydride or with aluminum chloride in benzene. The olefin was obtained conveniently, however, by conversion of the alcohol to the corresponding chloride which, with pyridine, gave 2-(2,4,6-trinitrophenyl)-ethylpyridinium chloride, whose degradation with sodium carbonate proceeded facilely. Attempts to prepare the olefin by direct dehydrohalogenation of the chloride with alcoholic potassium hydroxide, pyridine or aqueous carbonate led to the formation of unidentifiable resinous materials. Dehydrohalogenation could be accomplished by mild heating of the chloride but only dark resinous products which could not be adequately characterized were obtained.

Trinitrostyrene was also obtained by the general procedure of Wiley and Behr.[1] The Mannich condensation of dimethylamine with 2,4,6-trinitrotoluene was accomplished by the method of Bruson and Butler.[2] The resulting 2-(2,4,6-trinitrophenyl)-ethyldimethylamine was isolated as the hydrochloride and then directly converted to the quaternary iodide in good yield. This latter was degraded to trinitrostyrene by heating with dilute aqueous sodium carbonate.

As reported, 2,4,6-trinitrostyrene could not be polymerized by catalysis by peroxides or boron trifluoride. Other Friedel–Crafts catalysts and basic catalysts, such as sodium and sodium amide, also failed to yield polymers. The olefin was unreactive toward bromine in either water or carbon tetrachloride solution, but reacted readily with ammonia in anhydrous ether to form bis-(2,4,6-trinitrophenylethyl)-amine. This behavior is in accord with the strong electrophilic character of 2,4,6-trinitrostyrene. Similar reactions between ammonia and 3-nitro-6-bromo-β-nitrostyrene[3] and β-nitrostyrene[4] have been reported.

Experimental

Attempted Dehydration of 2-(2,4,6-Trinitrophenyl)-ethyl Alcohol.—2-(2,4,6-Trinitrophenyl)-ethyl alcohol[5] was heated directly with sirupy phosphoric acid at 150° and recovered unchanged. At 200° considerable charring occurred and neither the residue nor the supernatant liquid decolorized alkaline permanganate. Similar attempts at heating with concd. sulfuric acid or a mixture of phosphoric anhydride and phosphoric acid failed to yield the desired product.

2-(2,4,6-Trinitrophenyl)-ethyl alcohol was suspended in benzene and anhydrous aluminum chloride was added. The bright orange precipitate, which was immediately formed, reacted readily with moisture in the air to give aluminum hydroxide and an unidentified material which did not decolorize alkaline permanganate.

Dehydrohalogenation of 2-(2,4,6-Trinitrophenyl)-ethyl Chloride.—2-(2,4,6-Trinitrophenyl)-ethyl chloride[6] was heated with pyridine for various lengths of times to yield py-

---

(3) K. Stephan, *J. prakt. Chem.*, [2] **60**, 248 (1899).

(4) H. L. Cox, W. L. Nelson and L. H. Cretcher, THIS JOURNAL, **49**, 1080 (1927).

(1) R. H. Wiley and L. C. Behr, THIS JOURNAL, **72**, 1822 (1950).

(2) H. A. Bruson and G. B. Butler, *ibid.*, **68**, 2348 (1946).

(3) D. E. Worrall and J. Finkel, *ibid.*, **61**, 2969 (1939).

(4) D. E. Worrall, *ibid.*, **49**, 1598 (1927).

(5) V. Vender, *Gazz. chim. ital.*, **45**, II, 97 (1915).

(6) F. Challenger and P. H. Clapham, *J. Chem. Soc.*, 1612 (1948).

ridine hydrochloride and products varying from dark resins to brown, infusible materials, depending on length of heating. One such resin analyzed correctly (17.48%) for nitrogen (theory for trinitrostyrene, 17.58%) but was not otherwise characterized.

Dehydrohalogenation could be accomplished by heating the chloride at 85–90° until the evolution of HCl was completed as evidenced by testing with moist litmus paper. The products were brittle, resinous substances with a softening temperature of 50–60° which did not change on further heating.

2-(2,4,6-Trinitrophenyl)-ethylpyridinium Chloride.—2-(2,4,6-Trinitrophenyl)-ethyl chloride, 27.6 g. (0.1 mole), was added to 23.7 g. (0.3 mole) of pyridine. After the entire mass had solidified (about 20 minutes) the excess pyridine was extracted with low-boiling petroleum ether. Recrystallization of the residue from a methanol–methyl ethyl ketone mixture gave 17.7 g. (50%) of light yellow to colorless 2-(2,4,6-trinitrophenyl)-ethylpyridinium chloride, m.p. 132.0–134.2°.

Anal. Calcd. for $C_{13}H_{11}O_6N_4Cl$: N, 15.80; Cl, 10.00. Found: N, 15.90; Cl, 9.94.

On dilution of the pyridine extract with water, colorless platelets were deposited which on recrystallization from carbon tetrachloride melted at 63–64°. These were shown, by mixed melting point with an authentic sample, to be 2,4,6-trinitrostyrene.

Preparation of 2,4,6-Trinitrostyrene from 2-(2,4,6-Trinitrophenyl)-ethylpyridinium Chloride.—To a mixture of 5 g. (0.014 mole) of 2-(2,4,6-trinitrophenyl)-ethylpyridinium chloride and 100 ml. of water, 0.75 g. (0.007 mole) of sodium carbonate was added with shaking, forming a cherry-red solution, which gradually turned darker. Pyridine was evolved and a brown precipitate settled. After 20 minutes, the solution was neutralized with dilute hydrochloric acid. Extractions of the precipitate with carbon tetrachloride yielded a solution from which was isolated 1.0 g. (29%) of trinitrostyrene, m.p. 63–64°, which failed to add bromine but did decolorize alkaline permanganate.

Anal. Calcd. for $C_8H_5N_3O_6$: C, 40.18; H, 2.11; N, 17.57. Found: C, 40.44; H, 2.22; N, 17.54.

2-(2,4,6-Trinitrophenyl)-ethyltrimethylammonium Iodide.—To a warm solution of 12.8 g. (0.04 mole) of 2-(2,4,6-trinitrophenyl)-ethyldimethylamine hydrochloride[1] in 80 g. (2.5 moles) of methanol, 9.9 g. (0.07 mole) of methyl iodide and 2.7 g. (0.048) mole of potassium hydroxide pellets were added with vigorous shaking. The brick-red precipitate which began to form in about 20 minutes was promptly separated by decanting and was recrystallized from methanol to give 12.7 g. (75%) of 2-(2,4,6-trinitrophenyl)-ethyltrimethylammonium iodide, m.p. 139–141°.

Addition of Ammonia to 2,4,6-Trinitrostyrene.—To a solution of 0.69 g. of the olefin in 25 ml. of anhydrous ether, 0.5 ml. of anhydrous ammonia was added. On partial evaporation of the solvent, 0.5 g. (70%) of yellow bis-(2,4,6-trinitrophenylethyl)-amine, m.p. 129.5–130.5° after repeated washing with dry ether, separated.

Anal. Calcd. for $C_{16}H_{13}O_{12}N_7$: N, 19.80. Found: N, 19.61.

ORGANIC CHEMISTRY BRANCH
U. S. NAVAL ORDNANCE TEST STATION
INYOKERN, CHINA LAKE, CALIF.

The Dichlorination of o-Xylene[1]

BY CARL BOYARS[2]

RECEIVED NOVEMBER 3, 1952

Hinkel and co-workers[3,4] reported that the low temperature, iron-catalyzed dichlorination of o-xylene with chlorine gas yielded only the 4,5- and 3,4-dichloro-isomers. The absence of substantial quantities of 3,5-dichloro-o-xylene would, of course, be expected because of the ortho–para directive power of the chlorine atom, but the failure of these workers to obtain 3,6-dichloro-o-xylene is puzzling in view of the tendency of catalyzed chlorination to occur predominantly in the position para to chlorine already present.[5] In addition, White, Biggs and Morgan[6] reported that 5-nitro-3,4-dichloro-o-xylene which was prepared according to the method of Hinkel and co-workers had a melting point higher than the one given by the original authors. White and co-workers attributed the higher melting point to contamination of their product with 3-nitro-4,5-dichloro-o-xylene in solid solution.

In the present work a low temperature, iron-catalyzed dichlorination of o-xylene was carried out and the products fractionated. 4,5-Dichloro-o-xylene was identified by its melting point and the melting point of the mononitro derivative. The distillation fractions in which 3,4-dichloro-o-xylene would be expected on the basis of the previous work were found to have melting points substantially higher than that of the pure compound (8–9°[3,4]). Recrystallization of these fractions yielded a compound which melted at the same temperature as that recorded for 3,6-dichloro-o-xylene (29°[4]). The infrared spectrum of the compound shows a strong absorption band at 8.03 cm.$^{-1}$, a frequency which is characteristic of 1,2,3,4-tetrasubstituted benzenes.[7] The mononitro derivative prepared from these fractions was found, after purification, to have the melting point recorded for 4-nitro-3,6-dichloro-o-xylene (84°[4]) rather than that for 5-nitro-3,4-dichloro-o-xylene (78°[3]). To confirm the conclusion that 3,6-dichloro-o-xylene was formed in the chlorination, a dinitro-derivative was prepared from one of these fractions. This compound had a melting point closer to the recorded value for 4,5-dinitro-3,6-dichloro-o-xylene (174°[4]) than that for 5,6-dinitro-3,4-dichloro-o-xylene (172°[3,4]).

No attempt was made to isolate 3,4-dichloro-o-xylene which was probably present as a minor constituent in the fractions containing 3,6-dichloro-o-xylene. These two isomers have the same boiling point (234°[3,4]). The melting points of the distillation fractions (Table I, below) indicate that the major constituent of fractions 6, 7 and 8 is the 3,6-dichloro-isomer. The decreasing melting points of the later fractions are probably due to the presence of increasing amounts of 4,5-dichloro-o-xylene as a contaminant.

Experimental

Five moles of o-xylene (City Chemical Corporation, b.p. 143.5–144.5°, n^{20}_D 1.5047) with 5.5 g. of iron filings was chlorinated at −10 to 0° using chlorine dried with concentrated sulfuric acid. A total of 32 hours was required for the reaction mixture to gain the weight corresponding to dichlorination. This weight increase was determined after aspirating the reaction product. The chlorinated product was washed with water, refluxed one hour with 10% sodium

---

[1] Abstracted mainly from a portion of a thesis on "The Dielectric Properties of Solid Nitrodichloro-o-xylenes" directed by Dr. Reuben E. Wood and submitted in partial fulfillment of the requirements for the M.S. degree at The George Washington University, May, 1952.

[2] Research and Development Department, Naval Powder Factory, Indian Head, Md.

[3] L. E. Hinkel, E. E. Ayling and L. C. Bevan, *J. Chem. Soc.*, 1874 (1923).

[4] L. E. Hinkel, E. E. Ayling and T. M. Walters, *ibid.*, 1946 (1934).

[5] H. J. Lucas, "Organic Chemistry," American Book Company, New York, N. Y., 1935, p. 360.

[6] A. H. White, B. S. Biggs and S. O. Morgan, THIS JOURNAL, 62, 16 (1940). 3,4-Dichloro-o-xylene is erroneously referred to as 4,5-dichloro-o-xylene on p. 17 of this article.

[7] P. J. Launer and D. A. McCaulay, *Anal. Chem.*, 23, 1875 (1951).

hydroxide solution, separated, washed, and dried with anhydrous calcium chloride. The crude material (810 g.) was placed in a flask and about half of it distilled through a 22-plate column. Melting points and boiling ranges of the fractions are shown in Table I. The distillation was stopped when the change in boiling point indicated that 4,5-dichloro-*o*-xylene was beginning to distil; this compound was isolated by chilling the residue and then recrystallizing the solid portion from methanol.

A 1.3-g. sample from fraction 7 was twice recrystallized from chilled methanol yielding fine white crystals of m.p. 29.1–29.3°.[8] The infrared spectrum of the crystals which had been melted by crushing between salt plates was obtained using the Naval Powder Factory's Perkin-Elmer 12-C spectrometer. Using the method of Hinkel and coworkers, a mononitro derivative was prepared from a 16-g. mixture of equal portions of fractions 6, 7 and 8. The product, after recrystallization once from ethanol and twice from petroleum ether (b.p. 35–65°), melted at 84.0–84.1°. The dinitro derivative prepared from 1 g. of fraction 7 by the method of Hinkel and co-workers and recrystallized twice from ethanol melted at 175.1–175.1°.

TABLE I

DISTILLATE FRACTIONS FROM CRUDE DICHLORO-*o*-XYLENE

Fraction	B. range, °C.	*P*, mm.	Wt., g.	Wt. %	M.p., °C.
1	55.0–90.2	27.5	41.8	5.16	Below −15
2	90.0–90.2	27.5	45.4	5.60	−7.2 to −6.5
3	90.0–90.2	27.5			
	73.5–74.0	9	32.1	3.96	−6.2 to −5.2
4	74.0–94.5	9	20.1	2.48	Below −15
5	94.5–96.0	9	19.8	2.44	9.7 to 12.0
6	95.8–96.5	9	46.9	5.79	16.0 to 17.0
7	96.3–96.3	9	52.2	6.44	16.8 to 17.8
8	96.3–96.8	9	40.5	5.00	16.2 to 17.3
9	96.6–96.9	9	45.4	5.60	13.5 to 14.2
10	96.7–97.6	9	28.5	3.52	9.0 to 10.8
11	97.7–99.0	9	35.1	4.33	1.5 to 3.2

Acknowledgment.—Discussions of synthetic methods with Dr. S. N. Wrenn are gratefully acknowledged.

[8] All melting points were determined using a calibrated, partial immersion thermometer.

DEPARTMENT OF CHEMISTRY
THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, D. C.

The Reaction of Silver Cyclobutanecarboxylate with Bromine[1]

BY E. R. BUCHMAN AND J. C. CONLY

RECEIVED DECEMBER 12, 1952

The production of cyclobutyl bromide by the action of bromine on silver cyclobutanecarboxylate has been demonstrated by Cason and Way.[2,3] There are also formed in this reaction a $C_9H_{14}O_2$ ester mixture[3] and a tribromide $C_4H_7Br_3$.

The nature of this tribromide has now been elucidated. It is 1,2,4-tribromobutane[4] formed by a theoretically interesting cleavage of the cyclobutane ring under the conditions of the Hunsdiecker degradation.

Experimental[5]

Reaction of Silver Cyclobutanecarboxylate wth Bromine.—The techniques employed have been described previously[2,6]; *ca.* 0.2 mole of silver cyclobutanecarboxylate was used in each experiment.

When silver salt was added during 2.5 hours to excess of bromine in carbon tetrachloride at 10–12°, cyclobutyl bromide, b.p. 106–108°, b.p. 46–48° at 100 mm., n^{25}D 1.4768, d^{24}_{4} 1.43, was obtained in 44% yield; also produced in this reaction were ester (*ca.* 6%) and tribromide (*ca.* 10%).

Bromine was added dropwise (until color persisted) to silver salt in carbon tetrachloride at 25°. No monobromide was noted: the yield of ester[7] was 60%, that of tribromide 5%. A high-boiling fraction, b.p. *ca.* 125° at 2 mm., n^{25}D *ca.* 1.516, d^{25}_{4} *ca.* 1.60, was obtained, probably formed (in 8% yield) by addition of bromine to allylcarbinyl cyclobutanecarboxylate.[3]

Silver salt was added (1.5 hours) to a refluxing solution of excess bromine in carbon tetrachloride. The only identified product was tribromide, yield 60%, b.p. 72–74° at 3 mm., n^{25}D 1.5661–1.5679, d^{25}_{4} 2.21, m.p. −20 to −15°. A portion was recrystallized from ether at −80° and redistilled, n^{25}D 1.5683, m.p. unaltered.

Anal. Calcd. for $C_4H_7Br_3$: C, 16.3; H, 2.4. Found: C, 16.1: H, 2.5.

Identification of Tribromide.—A portion of the above tribromide was treated with maguesium in ether and the product carbonated.[8] The resulting allylacetic acid was converted to the *p*-bromophenacyl ester, m.p. 58.5–59.5°, not depressed when mixed with authentic material, m.p. 59.5–60°.[9]

3,4-Dibromobutanol-1,[10] was treated with a saturated solution of hydrogen bromide in glacial acetic acid at 0°; the temperature was raised slowly (20 hours) to 100° and was maintained there for two hours. The yield of 1,2,4-tribromobutane, b.p. 56–59° at 1 mm., n^{25}D 1.5588, was 82%. Another sample of tribromide was available,[6] obtained by Hunsdiecker degradation of 1,2,4-butanetricarboxylic acid. A comparison of the infrared spectra[11] of the three tribromide specimens establishes that the tribromide from silver cyclobutanecarboxylate (all the evidence indicates a high degree of purity for this material) has the same structure as the other two.

---

[1] Research supported by the Research Corporation and by the Office of Naval Research.

[2] J. Cason and R. L. Way, *J. Org. Chem.*, **14**, 31 (1949).

[3] *Cf.* J. D. Roberts and H. E. Simmons, Jr., THIS JOURNAL, **73**, 5487 (1951).

[4] We are indebted to Dr. Saul Winstein who originally suggested this structure for the tribromide.

[5] Microanalyses by Dr. A. Elek, Los Angeles.

[6] J. C. Conly, THIS JOURNAL, **75**, 1148 (1953).

[7] The n^{25}D 1.4528 of a portion indicates[3] slight contamination. Equivalents of cyclobutyl bromide and silver cyclobutanecarboxylate in carbon tetrachloride, after standing at room temperature for twelve days, gave[3] a 75% yield of ester mixture, n^{25}D 1.4496.

[8] J. von Braun and H. Deutsch, *Ber.*, **44**, 3699 (1911).

[9] L. I. Smith and S. McKenzie, Jr., *J. Org. Chem.*, **15**, 74 (1950).

[10] Formed in 60% yield from allyl carbinol, H. Pariselle, *Ann. chim.*, [8] **24**, 317 (1911).

[11] Spectra reproduced in the Ph.D. thesis of J. C. Conly, California Institute of Technology, 1950.

GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA 4, CALIFORNIA

The Addition of Water to Diphenylacetylene-1,2-C_1^{14}[1]

BY JOHN G. BURR, JR.

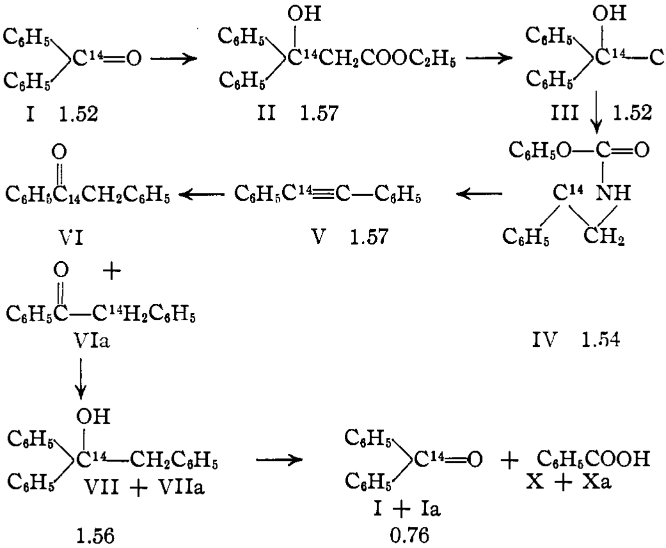
RECEIVED NOVEMBER 3, 1952

During the course of another investigation, a sample of diphenylacetylene-1,2-C^{14} was prepared by the series of reactions recently described by Newman and Kutner.[2] It appeared of interest to explore the possibly unsymmetrical addition of the

---

[1] This document is based upon work performed under Contract Number W-7405-eng. 26 for the Atomic Energy Commission at the Oak Ridge National Laboratory.

[2] M. S. Newman and A. Kutner, THIS JOURNAL, **73**, 4199 (1951). The writer is indebted to Professor Newman for suggesting the investigation of this hydration, for providing in advance of publication a copy of his and Dr. Kutner's manuscript, and for friendly advice.



elements of water across the C^{12}–C^{14} triple bond (*i.e.*, the isotope effect),[3] of this substance.

This has now been done. The series of reactions employed is shown in the scheme above. The arabic numerals represent the radioactivities in microcuries per millimole. The average of ten determinations upon the compounds I through VII was 1.55 ± 0.02 μc. of C^{14}/mmole (average derivation). When this is compared with the value of 1.52 ± 0.01 μc. of C^{14}/mmole which is twice the observed activity of the degradation product, I + Ia, it is apparent that any isotope effect in the hydration of diphenylacetylene must be less than 1–2%. The results of the assays upon the other degradation product, benzoic acid (X), could not be applied to this study, since the low value obtained, 0.66 μc. of C^{14}/mmole, indicates that the benzoic acid obtained must have been diluted during the oxidation of VII + VIIa with benzoic acid from some inactive source.

Experimental[4]

Diphenyl Ketone-C^{14}.—Thirty-five grams of aluminum chloride was added portionwise to a mixture of 56 g. of benzene, 60 ml. of carbon disulfide, 28.1 g. of benzoyl chloride and 50.1 mg. of benzoic acid containing about 1 mc. of carbon-14. After stirring overnight, the mixture was hydrolyzed, the product processed and then distilled. The distillate was 26.34 g. (72%); the still was chased with 21.33 g. of inactive benzophenone, of which 19.70 g. was recovered in the distillate, making a total of 46.04 g. (253 mmoles) of crystalline benzophenone. A portion of this was converted to the oxime, m.p. 141°, which was recrystallized for assay. The assay showed 1.50, 1.53 μc. of C^{14}/mmole.

Ethyl 3-Hydroxy-3,3-diphenylpropionate-3-C^{14}.—This was prepared by the procedure of Rupe and Busolt,[5] in essentially quantitative yield as a solid, which, after crystallization, melted at 85–86°. It contained 1.56, 1.58 μc. of C^{14}/mmole.

3-Hydroxy-3,3-diphenylpropionic Acid-3-C^{14} Hydrazide.—This was prepared by refluxing the above ester, 13.5 g., with a mixture of 10 ml. of 95% hydrazine hydrate and 25 ml. of ethanol for three hours. The yield was 16 g. of colorless solid which after crystallization from benzene melted at 130° and contained 1.52 μc. of C^{14}/mmole.

5,5-Diphenyl-2-oxazolidone-4-C^{14}.—A solution of the hydrazide (7.2 g.) in 60 ml. of acetic acid and 6 ml. of 6 *N* hydrochloric acid was treated, with stirring, with a solution of 2.1 g. of sodium nitrite in 15 ml. of water. The suspension of white solid which formed was heated on the steam-bath until cessation of gas evolution and the resulting clear yellow solution cooled and diluted with water. The pale yellow crystalline solid which formed was filtered (4.1 g.), m.p. 196–198°, and crystallized from ethanol to give colorless crystals melting at 200°, and containing 1.56, 1.52 μc. of C^{14}/mmole.

Diphenyl-(acetylene-1-C_1^{14}).—The above oxazolidone was converted through the nitroso compound to the acetylene by the procedure described by Newman and Kutner.[3] The acetylene was obtained in 60% yield as a pale cream solid, m.p. 52–55°. Recrystallization from alcohol–water gave colorless needles melting at 56–57° and containing 1.59, 1.56 μc. of C^{14}/mmole.

Benzyl Phenyl Ketone-C^{14}.—A portion of the above acetylene (0.50 g.) was warmed with a mixture of 5 ml. of concentrated sulfuric acid and 15 ml. of acetic acid until a clear solution resulted (about one hour), then a few crystals of mercuric chloride was added and warming continued for a few minutes. The solution was poured into water, and the pale yellow precipitate filtered and air-dried. It weighed 500 mg. and melted at 51–52°. The mixture melting point of this with authentic desoxybenzoin (m.p. 51–52°) showed no depression but the mixture melting point with diphenylacetylene (m.p. 56–57°) was 35–45°.

Benzyldiphenyl-(carbinol-C^{14}).—The above product was added to the Grignard solution prepared from 3 g. of bromobenzene and 0.5 g. of magnesium, and the resulting turbid suspension stirred overnight. Hydrolysis and crystallization of the product from hexane gave 480 mg. of nearly colorless needles which melted at 88° and contained 1.56 μc. of C^{14}/mmole.

Oxidation of Benzyldiphenylcarbinol-C^{14}.—After about 100 mg. of the above material had been reserved for analysis, the residual product was heated for one hour on the steam-bath with a solution of 0.5 g. of chromic oxide in 10 ml. of acetic acid. The dark green solution was poured into water, and the water solution was ether extracted. This ether extract was shaken with 1 *N* sodium hydroxide and water, then dried and evaporated. The residual darkish oil was heated with hydroxylamine hydrochloride, pyridine and ethanol to give after crystallization from dilute ethanol, 150 mg. of benzophenone oxime, whose melting point and mixture melting point with authentic oxime (m.p. 141°) was 141°. It contained 0.756, 0.758 and 0.763 μc. of C^{14}/mmole. The alkaline extract obtained above was acidified and ether extracted. The darkish oil obtained from the ether was treated with a large excess of thionyl chloride and the solution heated under vacuum to remove excess thionyl chloride and any acetyl chloride. The residue from this was dissolved in benzene and treated with excess aniline. The benzene solution after washing with water and drying was evaporated, and the residual solid crystallized from benzene. The benzanilide was so obtained as colorless plates which melted at 161° and contained 0.690, 0.656, 0.660 and 0.676 μc of C^{14}/mmole.

CHEMISTRY DIVISION
OAK RIDGE NATIONAL LABORATORY
OAK RIDGE, TENNESSEE

---

(3) *Cf.* G. A. Ropp and O. K. Neville. *Nucleonics*, 9, 22 (1951). for a general review of the isotope effect.

(4) C-14 assays were accomplished by wet combustion of the compounds and ionization chamber counting of the evolved carbon dioxide on a vibrating reed electrometer. Melting points were taken upon a Kofler hot-stage.

(5) H. Rupe and E. Busolt, *Ber.*, 40, 4537,

Dielectric Constant for the Dioxane–Water System from 20 to 35°

BY FRANK E. CRITCHFIELD, JOHN A. GIBSON, JR., AND JAMES L. HALL[1]

RECEIVED DECEMBER 24, 1952

This paper is a report of the dielectric constants of dioxane–water mixtures over the range of tem-

---

(1) Address communications to James L. Hall.

perature 20 to 35°. In performing some studies of conductance at high frequencies it was necessary to have solutions of accurately known dielectric constant. Dioxane–water mixtures have been used for this purpose, but our attempts to verify previously published data[2] for certain mixtures were not successful and so the entire system was redetermined. The data reported here enable use of dielectric constant to determine accurately the composition of dioxane–water mixtures.

Experimental

Materials.—The water used in these measurements was prepared by three distillations. Tap water was ordinarily distilled using a Barnstead still. The distillate was distilled in Pyrex equipment from an alkaline solution of permanganate. The middle third fraction from the second distillation was again distilled in Pyrex equipment retaining the middle third fraction which had a specific conductance of 1×10^{-6} ohms^{-1} cm.$^{-1}$.

Dioxane from the Carbide and Carbon Chemical Corporation was purified according to the method of Hess and Frahm[3] except the recrystallization was omitted. Time–temperature cooling curves were then run on the purified dioxane, employing an N.B.S. calibrated resistance thermometer and a Leeds and Northrup Co. Mueller Bridge. The freezing point was found to be 11.73° and the purity, as determined from the shape of the curves by the method of Rossini,[4] was not less than 99.95%.

Method.—For measurements of the dielectric constant of the various mixtures a General Radio Co. Twin-T Impedance Measuring Circuit was used.[5] A General Radio Co. Type 805-C Standard Signal Generator served as the frequency source. The detector unit consisted of a Hallicrafters SX-42 Receiver with a Du Mont Type 208-B Oscillograph for visual indication of the null point. All measurements were made at a frequency of one megacycle.

A new non-inductive type cell was constructed which is somewhat similar in design to one described by Ferry and Oncley,[6] and modified by Conner, Clarke and Smyth.[7] This cell is improved, as compared with previous ones of similar design, by the use of Teflon as the insulation material. Further, the lower Teflon plug and the inner electrode were threaded so as to permit complete dismantling of the cell. Several sizes of the central electrode were made to provide a range of capacitance. The metal parts of the cell were heavily nickel plated brass. At temperatures varying greatly from that of the room, temperature control within this water-jacketed cell may be not quite as precise as if the cell were in a thermostat, but this slight disadvantage is more than compensated for by the elimination of large lead corrections. Throughout all the measurements the temperature remained constant well within ±0.05°. The thermometer used was compared with an N.B.S. calibrated thermometer.

In the calibration of the cell, the dielectric constant of water was assumed to be 78.48 at 25° as reported by Albright.[8] All readings of capacitance from the Twin-T Circuit were corrected for drum variance using the manufacturer's calibration. The cell capacitance, $d\epsilon/dC$ was 1.83 μμf. and the lead capacitance was 1.4 μμf. To verify the method and to check the properties of the cell over a range of dielectric constant, the methanol-water system was studied at 25°. For this temperature the results of Albright and Gosting[9] were duplicated within one part in 1000.

Results

The values shown in Table I were obtained for the system dioxane–water at the temperatures shown.

TABLE I

DIELECTRIC CONSTANT FOR THE DIOXANE–WATER SYSTEM

Weight % dioxane	Temperature, °C. 20	25	30	35
0.00	80.38	78.48	76.72	74.97
10.00	72.02	70.33	68.74	67.10
20.00	63.50	61.86	60.38	58.96
30.00	54.81	53.28	51.91	50.60
40.00	45.96	44.54	43.33	42.24
50.00	36.89	35.85	34.81	33.88
60.00	28.09	27.21	26.45	25.74
70.00	19.73	19.07	18.58	18.07
80.00	12.19	11.86	11.58	11.26
90.00	6.23	6.07	5.96	5.85
95.00	3.99	3.89	3.83	3.76
100.00	2.24	2.21	2.20	2.19

Due to the low capacitance of the measuring cell the results in the low range of dielectric constant are limited to an accuracy of about one part in 200. The accuracy of the data at the higher dielectric constants listed is believed to be about one part in 2000. The value of the dielectric constant of pure dioxane at 25° is in excellent agreement with the value, 2.213, reported by Conner, Clarke and Smyth.[7] The value for pure dioxane differs from that given by Åkerlöf and Short[2] by one part in 20. In the low range our values for the mixtures differ from those of Åkerlöf and Short[2] by as much as 12%. The percentage difference decreases with increasing dielectric constant.

Acknowledgment.—This work was in part a joint undertaking of the Department of Chemistry of West Virginia University and the Office of Ordnance Research. Appreciation is expressed to James B. Hickman for assistance in determination and analysis of the time–temperature cooling curves and to H. N. Critchfield for assistance in construction of the cell.

DEPARTMENT OF CHEMISTRY
WEST VIRGINIA UNIVERSITY
MORGANTOWN, W. VA.

---

[2] G. Åkerlöf and O. A. Short, THIS JOURNAL, **58**, 1241 (1936).

[3] K. Hess and H. Frahm, *Ber.*, **71B**, 2627 (1938).

[4] B. J. Mair, A. R. Glasgow and F. D. Rossini, *J. Research Natl. Bur. Standards*, **26**, 591 (1941).

[5] D. B. Sinclair, *Proc. Inst. Radio Engrs.*, **28**, 310 (1940).

[6] J. D. Ferry and J. L. Oncley, THIS JOURNAL, **63**, 272 (1941).

[7] W. P. Conner, R. P. Clarke and C. P. Smyth, *ibid.*, **64**, 1379 (1942).

[8] P. S. Albright, *ibid.*, **59**, 2098 (1937).

[9] P. S. Albright and L. J. Gosting, *ibid.*, **68**, 1061 (1946).

The Introduction of Isotopic Hydrogen into Purine Ring Systems by Catalytic Exchange[1]

BY MAXWELL LEIGH EIDINOFF AND JOSEPH E. KNOLL

RECEIVED NOVEMBER 19, 1952

Tritium or deuterium can be introduced by isotopic exchange in the presence of reduced platinum catalyst into atomic positions in adenine and guanine that do not exchange isotopic hydrogen under the usual conditions of aqueous acid or alkali. The presence of such non-labile atomic positions has been demonstrated in this Laboratory for adenine, guanine, cytosine and uracil using a biosynthetic procedure.[2] The catalytic exchange procedure described below makes it possible to prepare labeled products of tritium or deuterium content equal in order of magnitude to that of the aqueous medium used. The isotopic content of the products, relative to that of the reaction media,

---

[1] This work was supported in part by grants-in-aid from the Atomic Energy Commission #AT(30-1)-910.

[2] M. L. Eidinoff, H. C. Reilly, J. E. Knoll and D. H. Marrian, *J. Biol. Chem.*, **199**, 511 (1952).

was used to calculate the extent of isotopic label incorporated (column 4, Table I). It is seen from the result of experiments 1–4 that catalytic isotopic exchange at 100° takes place in acidic medium or in an aqueous solution of the purine base. The recognized lability[3] of H in $-NH_2$ and $=NH$ leaves only the 8-position in guanine as the site of the isotopic label. The result in column 4 (expt. 5) indicates that the isotopic exchange did not go to completion under the experimental conditions. In adenine, the 2 and 8 positions may be sites for non-labile hydrogen. The isotopic content of the product is equivalent to slightly less than one equivalent atom position (method of calculation described below). The results (0.8–0.9) can signify either (a) substantially complete exchange at either the 2- or 8-positions or (b) partial exchange at both the 2- or 8-positions. Either possibility does not decrease the usefulness of the product for analyses using isotopic dilution techniques and for studies in which the adenine is not transformed into other compounds. Its usefulness in tracer metabolism studies depends on the location of the hydrogen isotope label. This method has been utilized to prepare adenine with tritium activity equal to 0.5 mc. per millimole using the conditions stated in experiment 3. The catalytic procedure described above will probably be useful for introducing isotopic hydrogen into other compounds having purine ring structures.

TABLE I

EXTENT OF ISOTOPIC EXCHANGE IN PREPARATION OF LABELLED ADENINE AND GUANINE[a]

Expt.	Compound	Medium	Equivalent no. of labeled atom positions
1	Adenine	70% AcOH + AcOT (no catalyst)	0
2	Adenine	70% AcOH + AcOT	0.8 ± 0.1
3	Adenine	H_2O + HTO	.85 ± .02
4	Adenine	D_2O	.91 ± .02
5	Guanine	H_2O + HTO 0.1 *N* HCl	.6 ± .1

[a] 18 hours at 100° for each run. Pt catalyst in all media except expt. no. 1.

Experimental

The platinum catalyst (250 mg.) was reduced in the reaction medium (Table I) with ordinary hydrogen gas at room temperature. The reaction mixture contained the reduced catalyst and 500 mg. of adenine or guanine in a total volume of 25 ml. After the contents had been frozen, the reaction tube was sealed off under vacuum. The tube was agitated at 100° for 18 hours. In experiment 4, the catalyst was reduced with 99.7% D_2 in 99.8% D_2O. The water used to prepare the media in experiments 1, 2, 3 and 5 had a tritium atom fraction of approximately 10^{-9}. The tritium was obtained from the Isotopes Division, U. S. Atomic Energy Commission.

The product in experiment 2, after heating with *N* sodium hydroxide for several minutes, was precipitated from hot solution as the hydrochloride. The products in experiments 3 and 4 were purified by recrystallization of the free base from ordinary water. The tritium content of the adenine was unchanged after standing in 0.01 *N* HCl solution for two days at room temperature and after boiling in *N* NaOH for five minutes. The product in experiment 5 was dissolved in hot *N* sodium hydroxide and precipitated as the sulfate. Deuterium or tritium bonded to nitrogen and oxygen would be replaced by ordinary hydrogen during the above purification steps. The purity of the products was checked by ultraviolet spectrophotometry (Beckman model DU instrument) using transmittance ratios at 250, 280 and 290 relative to 260 mμ. The infrared spectrum of the adenine prepared in experiment 1 was compared with that of a purified stock sample using a Model C Perkin–Elmer infrared spectrometer and rock-salt prism. The samples were prepared as a Nujol mull on a rock-salt window. The spectra were identical.

Isotopic Analyses.—The dried adenine and guanine samples were burned in a combustion train in which nitrogen oxides were reduced to nitrogen gas over copper at approximately 500°. The water was converted to hydrogen gas over zinc at 420°. Deuterium measurements were made using a dual collector Nier-type hydrogen mass spectrometer. Tritium measurements were made using a hydrogen–methane gas mixture in the proportional region as previously described by the authors.[4] The numerical values in column 4, Table I are equal to nf where n is the number of hydrogen atom positions undergoing exchange and f is the ratio of the D or T isotopic abundance in the n-positions to that in the aqueous exchange medium. For example, in experiment number 3, the tritium abundance in the medium was expressed as 9.6×10^6 counts per minute per standard volume of hydrogen gas, while the tritium abundance in the adenine prepared was 1.64×10^6 counts per minute per standard volume of hydrogen gas obtained from the combustion of the product. Taking the 5 hydrogen atoms into account $(9.6 \times 10^6)\, nf/5 = 1.64 \times 10^6$ and $nf = 0.85$. The result may be interpreted as showing the presence of one atom position undergoing catalytic exchange with $f = 0.85$ or possibly two exchangeable atom positions with average $f = 0.42$. Degradation studies would be required to resolve this question.

---

(3) M. Kamen, "Radioactive Tracers in Biology," 2nd ed., Academic Press, Inc., New York, N. Y., Chap. VII, 1951.

(4) M. L. Eidinoff, J. E. Knoll, D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **74**, 5280 (1952).

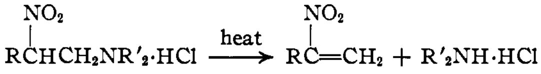
DIVISION OF PHYSICS AND BIOPHYSICS
SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
NEW YORK, N. Y.

Low Temperature Pyrolysis of Boron Trifluoride–Mannich Base Complexes. 2-Nitro-1-alkenes[1]

BY WILLIAM D. EMMONS, WILLIAM N. CANNON, JOHN W. DAWSON AND ROBERT M. ROSS

RECEIVED DECEMBER 20, 1952

Recently Blomquist and Shelley[2] have demonstrated that Mannich base hydrochlorides derived from nitroalkanes undergo thermal decomposition[3] to yield the corresponding 2-nitro-1-alkenes. These investigators carried out the pyrolysis reaction at relatively high temperatures and this is certainly disadvantageous when heat-labile intermediates or



$$\overset{NO_2}{\underset{|}{R\!-\!CH}}CH_2NR'_2\cdot HCl \xrightarrow{\text{heat}} \overset{NO_2}{\underset{|}{RC}}{=}CH_2 + R'_2NH\cdot HCl$$

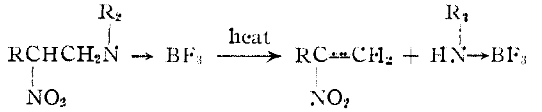
unstable products are present in the reaction mixture. We have established that the use of boron trifluoride complexes of these Mannich bases effectively reduces the temperature necessary for carrying out the reaction by as much as 100°. This is in agreement with electronic theory which predicts that the carbon–nitrogen bond in this system will be weaker than in the corresponding hydrochloride. Furthermore the yields of nitroölefins obtained (80–90%) were as good as and in most

---

(1) This work was carried out under Army Ordnance Contract W-01-021-ORD-334.

(2) A. T. Blomquist and T. H. Shelley, Jr., THIS JOURNAL, **70**, 147 (1948).

(3) H. R. Snyder and W. E. Hamlin (*ibid.*, **72**, 5072 (1950)) utilized similar Mannich bases as nitroalkene precursors for alkylating nitroparaffins.



$$\underset{NO_2}{RCH}CH_2\overset{R_2}{N} \rightarrow BF_3 \xrightarrow{heat} \underset{NO_2}{RC}{=}CH_2 + H\overset{R_1}{N}\rightarrow BF_3$$

cases better than those reported with the Mannich base hydrochlorides.

In the initial experiments the boron trifluoride complexes were prepared from gaseous boron trifluoride and isolated prior to their pyrolysis (Experimental procedure B). It was found, however, that these complexes were not very stable and frequently decomposed on standing. Accordingly the boron fluoride adducts were prepared *in situ* by addition of an equivalent amount of boron trifluoride etherate to a solution of the Mannich base in an inert solvent. The resulting mixture was then heated under reduced pressure until pyrolysis was complete and the nitroölefin was removed by distillation as it was formed. The yields obtained with this procedure (procedure A) were much better and more reproducible than those obtained using procedure B. The nitroalkenes were identified by determination of physical constants, examination of infrared spectra, and conversion to the *p*-toluidine derivatives.

Experimental[4,5]

Mannich Bases of Nitroalkanes.—The Mannich bases were all prepared according to the directions of Blomquist and Shelley.[2] The physical constants of N-(2-nitropropyl)-piperidine (b.p. 87° (1 mm.), $n^{20}D$ 1.4469) which were determined and reported by these investigators were not confirmed in this Laboratory. Our values for this compound are: b.p. 67–68° (1–1.5 mm.), $n^{20}D$ 1.4650. This nitroamine was also converted to the picrate, m.p. 127–127.5° (recryst. from ethanol).

Anal. Calcd. for $C_{14}H_{19}N_5O_9$: C, 41.89; H, 4.74; N, 17.45. Found: C, 41.68; H, 4.99; N, 17.47.

2-Nitro-1-alkenes.—A summary of the pyrolysis experiments performed by both procedure A (use of inert diluent without isolation of the boron trifluoride complex) and procedure B (pyrolysis of the isolated boron trifluoride complex) is presented in Table I. The preparations of 2-nitropropene by procedure A and 2-nitro-1-butene by procedure B are described in detail. The nitroölefins obtained directly from the pyrolysis reactions were sufficiently pure for most purposes.

2-Nitropropene (Procedure A).—To a stirred solution of 17.2 g. (0.1 mole) of freshly distilled N-(2-nitropropyl)-piperidine in 150 ml. of di-2-ethylhexyl phthalate was added 15.6 g. (0.105 mole) of boron trifluoride etherate. A viscous white liquid separated out on the walls of the flask immediately. The ethyl ether formed in this reaction was removed under reduced pressure at room temperature. The mixture was then heated to 85° at a pressure of 1 mm. with continuous stirring. At this temperature the solution darkened and the 2-nitropropene began to form. The nitroolefin was distilled into a Dry Ice–acetone-cooled receiver as fast as it was formed. The solution was heated to 105° and was maintained at this temperature for one hour. There was obtained in the distillate receiver 6.7 g. (77%) of light green solid which melted on warming to room temperature, $n^{20}D$ 1.4296 (lit.[6] $n^{23}D$ 1.4292). The *p*-toluidine derivative of this nitroölefin was prepared and melted at 81–82° (lit.[2] 81.5–82.5°). The infrared spectrum of 2-nitropropene showed a conjugated nitro band at 1525 cm.$^{-1}$.

2-Nitro-1-butene (Procedure B).—A solution of 34.8 g. (0.2 mole) of freshly distilled N-(2-nitrobutyl)-diethylamine in 150 ml. of dry petroleum ether was saturated with gaseous boron trifluoride at 0–5°. The solid which separated was collected on a filter and washed with petroleum ether. It was then dried in a vacuum desiccator; yield 46.5 g. (96%) of slightly yellow solid, m.p. 50–53°. The boron trifluoride adduct (24.2 g., 0.1 mole) was then heated under a pressure of 1 mm. in a distillation apparatus with a distillate receiver packed in Dry Ice–acetone. Decomposition was observed at 35°. The distillation pot was slowly heated to 60° and was maintained at this temperature for one hour. There was obtained in the receiver 6.3 g. (63%) of 2-nitro-1-butene, $n^{20}D$ 1.4258 (lit.[2] $n^{20}D$ 1.4256). The *p*-toluidine adduct of this nitroölefin was prepared and melted at 68.5–69.5° (lit.[2] m.p. 67.5–68.5°). The infrared spectrum of 2-nitro-1-butene showed a conjugated nitro band at 1522 cm.$^{-1}$.

TABLE I

PYROLYSIS OF MANNICH BASE-BORON TRIFLUORIDE COMPLEXES

Boron trifluoride complex	Nitroolefin, 2-nitro-	Procedure A Yield, %	Procedure A Pyrolysis temp., °C.	Procedure B Yield, %	Procedure B Pyrolysis temp., °C.
N-(2-Nitropropyl)-piperidine	Propene	77	105	48	70
N-(2-Nitrobutyl)-diethylamine	1-Butene	78	100	62	60
N-(2-Nitrobutyl)-dimethylamine	1-Butene	86	100	72	90
N-(2-Nitropentyl)-diethylamine	1-Pentene	90	110	40	80

ROHM AND HAAS COMPANY
JOSIAH GORGAS LABORATORY
REDSTONE ARSENAL RESEARCH DIVISION
HUNTSVILLE, ALABAMA

Optical Enantiomorphs of α-Aminoadipic Acid

BY JESSE P. GREENSTEIN, SANFORD M. BIRNBAUM AND M. CLYDE OTEY

RECEIVED DECEMBER 15, 1952

A resolution of racemic α-aminoadipic acid into its optical enantiomorphs has not been recorded. Borsook, *et al.*, reported a preparation of L-α-aminoadipic acid with $[\alpha]^{25}D$ +33.9° for a 5.49% solution in 6 *N* HCl by treating carbobenzoxy-DL-α-aminoadipic acid with aniline and papain, followed by hydrolysis of the anilide and removal of the carbobenzoxy group from the separated L-enantiomorph.[1] No mention was made of the D-enantiomorph.

We have resolved the racemic aminodicarboxylic acid into its optical enantiomorphs by the acylase procedure developed in this Laboratory.[2,3] Chloroacetyl-DL-α-aminoadipic acid was prepared and subjected at *p*H 7.0 to the asymmetric action of hog kidney acylase I to yield L-α-aminoadipic acid and chloroacetyl-D-α-aminoadipic acid. The latter compound yielded D-α-aminoadipic acid after HCl hydrolysis followed by adjustment to *p*H 3.2. For 2% solutions in 5 *N* HCl the $[\alpha]^{25}D$ for the L-isomer was +25.0°, and for the D-isomer −25.0°. The $[\alpha]^{25}D$ for a 6% solution of the D-isomer in 6 *N* HCl was −24.9°. L-α-Aminoadipic acid was

---

[4] All melting and boiling points are uncorrected.

[5] We are indebted to Dr. Keith S. McCallum and Mr. Al Kennedy for infrared interpretations and microcombustion data. The Commercial Solvents Corporation generously supplied us with a sample of 1-nitrobutane.

[6] A. T. Blomquist, W. J. Tapp and J. R. Johnson, THIS JOURNAL, 67, 1519 (1945).

[1] H. Borsook, C. L. Deasy, A. J. Haagen-Smit, G. Keighley and P. H. Lowy, *J. Biol. Chem.*, **176**, 1383 (1948).

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

[3] J. P. Greenstein, S. M. Birnbaum and L. Levintow, in "Biochemical Preparations," Vol. III, in press.

found to be oxidized by relatively large amounts of *Crotalus adamanteus* L-amino acid oxidase and the optical purity of the D-isomer could be readily determined by the procedure now routine in this Laboratory.[4,5] The D-α-aminoadipic acid was found to contain less than 1 part in 1,000 of the L-isomer. Furthermore, the L-isomer was quantitatively oxidized by the oxidase, thus excluding any appreciable contamination by piperidonecarboxylic acid. We have no explanation for the discrepancy between our rotation values and that of Borsook, *et al.*

Experimental Part

N-Chloroacetyl-DL-α-aminoadipic Acid.—One hundred and sixty-eight grams of aminoadipic acid[6] was treated with chloroacetyl chloride and chilled NaOH in the usual manner. The reaction mixture was acidified to a *p*H of about 0.5 with concd. HCl and extracted several times with ethyl acetate. The combined extracts were dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residual sirup was dissolved in dry ether from which crystals separated on chilling. The yield of N-chloroacetyl-DL-α-aminoadipic acid was 74 g., m.p. 127° (cor.). After recrystallization from ethyl acetate the m.p. was 129° (cor.). The yield was 31%, but from the aqueous layer 46 g. of unaltered DL-α-aminoadipic acid (N, calcd. 8.7, found 8.6) could be recovered.

Anal.[7] Calcd. for $C_8H_{12}O_5NCl$: N, 5.9; Cl, 14.9. Found: N, 5.8; Cl, 14.6.

Enzymatic Resolution of Chloroacetyl-DL-α-aminoadipic Acid.—Eighty-six and a half grams of chloroacetyl-DL-α-aminoadipic acid was suspended in 2 liters of water and brought into solution at *p*H 7.0 by addition of 2 *N* LiOH. Water was added to bring the final volume to 3,640 cc. (0.1 *M*) and 2.8 g. of acylase I powder was dissolved in the solution. The latter was brought back to *p*H 7.0 by addition of a few drops of LiOH, and placed in a water-bath at 38°.[8] After 10 hours of incubation, manometric ninhydrin analyses on an aliquot of the digest revealed 50% hydrolysis of the racemate. Further incubation of the digest up to 24 hours did not result in a change of this figure. Accordingly, acetic acid was added to *p*H 5, and the protein filtered off with the aid of Norit. The filtrate was evaporated to about 400 cc. *in vacuo*, and the small amount of protein which flocculated was again removed by filtration. The filtrate was treated dropwise with concd. HCl to *p*H 3.2. A copious crystallization of L-α-aminoadipic acid quickly ensued. Twice the volume of absolute ethanol was added, and the mixture chilled at 5° for several hours. The L-isomer was filtered and washed with ethanol, and the mother liquor and washings combined and set aside for the preparation of the D-isomer. The yield of L-α-aminoadipic acid was 27 g. or 93%; $[\alpha]^{25}\text{D}$ +24.6° (2% in 5 *N* HCl). It was recrystallized by adding sufficient boiling water to dissolve the solid, filtering rapidly through a heated filter, and chilling quickly in a −20° alcohol-water-bath to 5°. The final yield of pure L-α-aminoadipic acid was 22 g. or 76%; $[\alpha]^{25}\text{D}$ +25.0° (2% in 5 *N* HCl).

Anal. Calcd. for $C_6H_{11}NO_4$: C, 44.7; H, 6.9; N, 8.7. Found: C, 44.8; H, 6.9; N, 8.7.

The combined alcoholic mother liquor and washings contained chloroacetic acid, chloroacetyl-D-α-aminoadipic acid, and traces of unprecipitated L-α-aminoadipic acid. It was evaporated *in vacuo* nearly to dryness, concd. HCl was added with careful cooling to a *p*H of about 0.5, and the acid solution extracted several times with ethyl acetate. The combined extracts were dried over Na_2SO_4 and evaporated *in vacuo* to a residual oil. The oil was taken up in a liter of dry acetone, filtered, the acetone removed by a stream of air, and the residue dissolved in 500 cc. of 2 *N* HCl. The solution was refluxed for 2 hours, decolorized with a little Norit, and evaporated *in vacuo* to a thick sirup. The sirup was dissolved in 400 cc. of H_2O, and the solution treated dropwise with pyridine to *p*H 3.2. The D-α-aminoadipic acid which appeared was recrystallized from water as described for the L-isomer. Yield of pure product was 12 g. or 42%; $[\alpha]^{25}\text{D}$ was −25.0° for a 2% solution, and −24.9° for a 6% solution, in 6 *N* HCl.

Anal. Found: C, 44.5; H, 7.0; N, 8.7.

Optical Purity of D-α-Aminoadipic Acid.—One thousand micromoles of D-α-aminoadipic acid at *p*H 7.2, and in the presence of catalase, was practically inert to 30 mg. of *Crotalus adamanteus* venom. When, under the same conditions, 1 micromole of the L-isomer was mixed at the beginning of the run with the 1,000 micromoles of the D-isomer, there was an oxygen consumption equivalent to that of the 1 micromole of L-isomer added. The reaction reached completion in about 1 hour. There was evidently less than 1 part of the L-isomer present in 1,000 parts of the D. Ten micromoles of the L-isomer alone in the presence of large amounts of the venom and catalase, also consumed close to the theoretical amount of oxygen. The D-isomer itself was completely inert to hog kidney D-amino acid oxidase, and therefore the optical purity of the L-isomer could not be determined in this fashion.[4]

D-Piperidonecarboxylic Acid.—A solution of 2 g. of D-α-aminoadipic acid in 100 cc. of H_2O was refluxed, and aliquots removed at intervals for manometric ninhydrin analyses. After two hours an equilibrium value was established of 73% piperidonecarboxylic acid and 27% aminodicarboxylic acid. The *p*H of the solution was 3.2. On chilling, about half of the aminoadipic acid crystallized. It was filtered off, and the mother liquor evaporated to dryness. The residue was extracted several times with hot alcohol, the extracts were combined, filtered and evaporated to a low bulk from which the D-piperidonecarboxylic acid crystallized as large prisms. The yield was 80%; $[\alpha]^{25}\text{D}$ − 16.5° (2% in H_2O) and −41.5° (2% in 6 *N* HCl).

Anal. Calcd. for $C_6H_9O_3N$: C, 50.4; H, 6.3; N, 9.8. Found: C, 50.3; H, 6.3; N, 9.8.

No racemization of the piperidonecarboxylic acid occurred for when 250 mg. was refluxed for 2 hours with 25 cc. of 2 *N* HCl, and the resulting D-α-aminoadipic acid isolated by treatment with pyridine to *p*H 3.2 (yield 230 mg.), the latter possessed $[\alpha]^{25}\text{D}$ − 25.1° (2% in 6 *N* HCl).

Anal. Found: C, 44.5; H, 7.0; N, 8.7.

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

---

[4] A. Meister, L. Levintow, R. B. Kingsley and J. P. Greenstein, *J. Biol. Chem.*, **192**, 535 (1952).

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

[6] Donated by Dr. Alton Meister.

[7] Analyses by R. J. Koegel and staff of this Laboratory.

[8] At *p*H 7.0 and 38°, the rate of hydrolysis of this substrate by crude hog kidney aqueous homogenate is 1.5 micromoles per hour per mg. N; with acylase I this rate is 45. Since the reaction is zero order, the amount of acylase added to the solution should be sufficient to hydrolyze the L-component of the racemate in about 8 hours.

C^{14} Tracer Studies in the Rearrangements of Unsymmetrical α-Diketones. III. *p*-Methoxybenzylideneacetophenone Oxide[1]

BY EDWARD C. HENDLEY[2a] AND O. KENTON NEVILLE[2b]

RECEIVED JUNE 16, 1952

Benzylideneacetophenone oxide, labeled with carbon-14 in the carbonyl group was found to rearrange in alkaline medium to 2-hydroxy-2,3-diphenylpropionic acid, labeled exclusively in the carbinol group.[3] These results if interpreted as due to a benzilic acid type of rearrangement of intermediate benzyl phenyl diketone suggest either a very

---

[1] This paper is based upon work performed under contract Number W-7405-eng-26 for the Atomic Energy Commission at Oak Ridge National Laboratory.

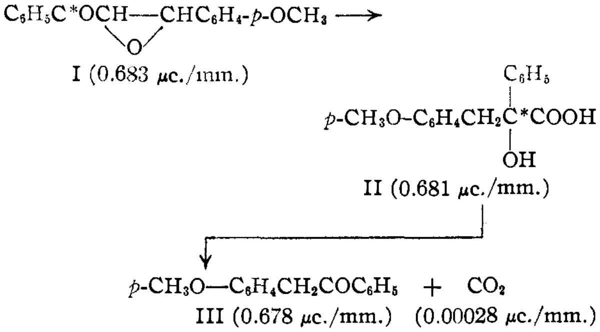
[2] (a) Member of the Research Participation Program sponsored jointly by the Oak Ridge National Laboratory and the Oak Ridge Institute of Nuclear Studies; permanent address, Dept. of Chemistry, Mississippi State College, State College, Miss. (b) Nuclear Instrument and Chemical Corp., Chicago, Ill.

[3] C. J. Collins and O. K. Neville, THIS JOURNAL, **73**, 2471 (1951).

high migratory aptitude for the benzyl group in this rearrangement, or a great difference in the reactivities of the carbonyl groups.

When *p*-methoxybenzylidene-(aceto-1-C^{14})-phenone was prepared as an intermediate in another synthesis, it was of interest to determine its mode of reaction in the base-catalyzed rearrangement.

p-Methoxybenzylidene-(aceto-1-C^{14})-phenone oxide (I) was prepared by condensation of anisaldehyde with (aceto-1-C^{14})-phenone and treatment of the resulting *p*-methoxybenzylidene-(aceto-1-C^{14})-phenone with hydrogen peroxide. Rearrangement of the resulting oxide gave 2-hydroxy-2-phenyl-3-(*p*-methoxyphenyl)-propionic acid, labeled exclusively in the carbinol group, thus demonstrating no phenyl group migration. The radioactivities, reported as microcuries per millimole (µc./mm.) are shown in the reaction scheme below. Degradations and assays were carried out as described previously.[3] The reported radioactivities are subject to an error of ±1%.



Although the *p*-methoxyphenyl group has been shown to migrate less than phenyl in the benzilic acid rearrangement,[4] presumably because of their relative effects on the carbonyl group reactivities, the substitution of a *p*-methoxy group on the potential benzyl group ring of benzylideneacetophenone oxide does not promote phenyl group migration to a discernible level. Although the carbon dioxide obtained in the oxidation of the acid product in the present case contained slightly less radioactivity than did that previously reported, it seems unwise to attach significance to these small numbers.

Experimental

***p*-Methoxybenzylidene-(aceto-1-C^{14})-phenone.**—A 4.05-g. portion of (aceto-1-C^{14})-phenone was condensed with 5.11 g. of anisaldeyde in the presence of ethanolic alkali[3,5] to yield 7.00 g. (87%) of *p*-methoxybenzylidene-(aceto-1-C^{14})-phenone, m.p. 132–134°.

***p*-Methoxybenzylidene-(aceto-1-C^{14})-phenone Oxide (I).**—A 6.7-g. portion of *p*-methoxybenzylidene-(aceto-1-C^{14})-phenone was treated with alkaline hydrogen peroxide[3,6] to obtain 3.58 g. (50%) of I, m.p. 82–83°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.50; H, 5.55. Found: C, 75.37; H, 5.60.

Radioanal: 0.0276 microcurie C^{14} per 10.26-mg. sample.

2-Hydroxy-2-phenyl-3-(*p*-methoxyphenyl)-propionic Acid (II).—A 3.33-g. sample of I was rearranged by the previously described method to give 1.56 g. (44%) of II, m.p. 192.5–193.0°.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.52; H, 5.92. Found: C, 70.50; H, 5.98.

Radioanal: 0.0527 microcurie C^{14} per 21.37-mg. sample.

***p*-Methoxyphenyl(aceto-1-C^{14})-phenone (III).**—A 0.5-g. sample of II was oxidized as previously described[3] to give 0.358 g. (86%) of *p*-methoxyphenyl-(aceto-1-C^{14})-phenone (III), m.p. 96°, and 0.354 g. (96%) of barium carbonate.

Radioanal: II: 0.0430 microcurie C^{14} per 14.32-mg. sample. $BaCO_3$: 0.00098 microcurie C^{14} per 70-mg. sample.

CHEMISTRY DIVISION, OAK RIDGE NATIONAL LABORATORY
OAK RIDGE, TENNESSEE

---

(4) J. D. Roberts, D. M. Smith and C. C. Lee, THIS JOURNAL, **73**, 618 (1951).

(5) E. P. Kohler and H. M. Chadwell, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, pp. 78–80.

(6) E. Weitz and A. Scheffer, *Ber.*, **54**, 2338 (1921).

Carveol and Carveol Acetate

BY ROBERT H. REITSEMA

RECEIVED OCTOBER 31, 1952

Two important constituents of spearmint oil, carveol and carveol acetate have been prepared by a convenient method. The reduction of carvone to carveol using aluminum isopropoxide has been reported several times.[1-3] It seemed of interest to investigate this reduction using lithium aluminum hydride as the reducing agent to compare yields and the nature of the isomers obtained.

The yield of crude carveol, $[\alpha]_D$ −36.2°, obtained was 92.8% of the theoretical amount. Reduction with aluminum isopropoxide has been reported to give carveol mixtures with rotations of 100.9–108.2°[2] and −109.0°[3] from *d*-carvone and *l*-carvone, respectively. This would indicate that nearly equal amounts of the *cis* and *trans* isomers formed since *d*-carvone leads to *d-cis*-carveol, $[\alpha]_D$ 23.9°, and *d-trans*-carveol, $[\alpha]_D$ 213.1°. Lithium aluminum hydride gives predominantly the *cis* configuration as can be seen from the rotation of the crude mixture which is $[\alpha]_D$ −36.2°. This would be the most favored configuration assuming that attack takes place at the less hindered side of the carbonyl group. The mixture was investigated by isolation of *l-cis*-carveol 3,5-dinitrobenzoate and by separation of the *p*-nitrobenzoate into the *cis* and *trans* isomers.

Experimental

Carvone was isolated from spearmint oil with sodium bisulfite and redistilled giving a product boiling 103–104.5° (11 mm.), α_D −59.55°. To 3.1 g. (0.33 equiv.) of lithium aluminum hydride in 75 ml. of anhydrous ether was added dropwise 45.0 g. (0.3 mole) of this carvone in 75 ml. of anhydrous ether. After all the carvone had been added, the mixture was boiled under reflux for an additional hour. About 15 ml. of water was added cautiously, followed by 200 ml. of 10% hydrochloric acid. The ether layer was separated and the aqueous extracts were dried over anhydrous sodium sulfate. Ether was evaporated leaving 43.9 g. (96%) oil, $[\alpha]_D$ −33.1°, n^{24}_D 1.4922. Distillation of the oil gave 92.9% of the theoretical amount of carveol, b.p. 109–111° (12 mm.), $[\alpha]_D$ −36.2°, n^{20}_D 1.4955, d^{25}_{25} 0.9527. This compares with *l-cis*-carveol, b.p. 101° (10 mm.), $[\alpha]_D$ 23.9°, n^{25}_D 1.4959, d^{25}_4 0.9521.[2]

To 1.0 g. of the product in 3 ml. of dry pyridine was added 1.7 g. of 3,5-dinitrobenzoyl chloride. The mixture was stirred thoroughly, allowed to cool to room temperature and poured into 1.5 ml. of water. The resulting oil was slurried with 10 ml. of 5% sodium carbonate giving a white solid which was washed with water and recrystallized from ethanol three times giving 0.68 g., m.p. 91–92.5°, $[\alpha]_D$ 45.0° ($CHCl_3$, *c* 3). This compares with the report[2] for

---

(1) W. Ponndorf, *Z. angew. Chem.*, **39**, 138 (1926).

(2) R. G. Johnson and J. Read, *J. Chem. Soc.*, 233 (1934).

(3) T. Nagasawa, *Repts. Osaka Imp. Ind. Research Inst.*, **19**, No. 4 (1938); *C. A.*, **34**, 219[9] (1940).

the *d-cis*-carveol derivative, m.p. 92.5°, $[\alpha]_D$ 44.2° ($CHCl_3$, *c* 2).

In a similar manner the *p*-nitrobenzoate was prepared giving a mixture melting mainly at 27–28° and completely melted at 70–72°. Recrystallization gave a mixture of transparent plates, m.p. 26–28°, and a powder, m.p. 75–78°, after mechanical separation. This compares with the report[3] of the *d-cis* derivative m.p. 26.5–28° and the *d-trans* derivative, m.p. 77°.

Boiling 10.78 g. of the carveol mixture with 10 ml. of acetic anhydride and 1.0 g. of anhydrous sodium acetate for two hours gave on distillation 9.56 g. of carveol acetate, b.p. 110–113° (12 mm.), $n^{20}D$ 1.4760, αD −33.2°.

Oxidation of 6.0 g. of the carveol mixture in 12.5 ml. of glacial acetic acid with 5.4 g. of chromic anhydride in 12.5 ml. of acetic anhydride at 13–17° gave carvone, αD −54.6°, $n^{20}D$ 1.4959. This indicates that little isomerization of the ring structure occurred during the reduction and subsequent oxidation.[4,5]

---

[4] This reaction was carried out by Mr. V. J. Baarman.

[5] Unless otherwise indicated all notations taken on homogeneous materials.

RESEARCH LABORATORY
A. M. TODD COMPANY
KALAMAZOO, MICHIGAN

The Vapor Pressures of Some Substituted Benzotrifluorides[1]

BY SAMUEL KARDON AND JOHN H. SAYLOR

RECEIVED JANUARY 16, 1953

The measurements reported in this note resulted from a continuation of a general program in this Laboratory concerning the solubility and other physical properties of organic fluorine compounds.

TABLE I

PHYSICAL CONSTANTS AND CONSTANTS OF THE VAPOR PRESSURE EQUATION

Benzotrifluoride	B.p., °C. Calcd.	F.p., °C. Obsd.	F.p., °C. Dep.	$\eta^{20°}D$	$\eta^{30°}D$	$\epsilon^{30°}$	*A*	*B*	*C*
m-Nitro	202.75	−1.32	0.06	1.4719	1.4675	17	7.18025	1710.60	195.12
m-Amino	191.13	5.65	.01	1.4788	1.4750		7.17030	1650.21	193.58
3-Nitro-4-chloro	222.58	−2.54	.04	1.4895	1.4853	12.8	7.15778	1738.71	183.95
2-Chloro-5-nitro	231.88	21.7	.5		1.5043	9.8	7.15409	1779.91	184.64

Experimental

Materials.—The compounds were supplied by the Hooker Electrochemical Company and were further purified by distillation at reduced pressure (controlled to ±0.1 mm.) in a silvered vacuum-jacketed glass column packed with $^1/_8''$ glass helices. The fractions used were characterized by measuring refractive indices, dielectric constants and freezing points. The dielectric constants were measured by the heterodyne beat method. The apparatus was calibrated with benzene and chlorobenzene and has been found to give good results in measuring dielectric constants of highly purified materials with values up to approximately 15. The freezing points were determined as previously described.[2]

Vapor Pressures.—The apparatus which was previously used by Potter[2] was employed. It was a modification of the boiling point apparatus described by Rossini and coworkers.[3]

Results

Fifteen to twenty individual measurements were made on each compound from approximately 5 to 740 mm. The data were fitted by the method of least squares to the equation

$$\log p = \frac{-B}{t + C} + A$$

where p is the pressure in mm. and t is the temperature in degrees centigrade.

The standard deviation between the observed pressures and those calculated from the equation ranged from 0.09 to 0.11 mm.

Table I gives the boiling points calculated from the vapor pressure equation, the freezing points, the freezing point depressions, the refractive indices (η), the dielectric constants (ϵ) and the values of the three constants in the above equation. The value given for the dielectric constant of *m*-nitrobenzotrifluoride is not considered as reliable as those for the other compounds.

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, NORTH CAROLINA

---

[1] Part of the work reported was carried out under Contract N6ori-107, T. O. II with the Office of Naval Research. Taken from the thesis submitted by Samuel Kardon to the Graduate School of Duke University in partial fulfillment of the requirements for the degree of Master of Arts, June 1952.

[2] J. C. Potter and J. H. Saylor, THIS JOURNAL, **73**, 90 (1951).

[3] C. B. Willingham, W. J. Taylor, J. M. Pignocco and F. D. Rossini, *J. Research Natl. Bur. Standards*, **35**, 219 (1945).

Polyalkylene Sulfides. XII.[1] Termination by Disulfide Formation[2]

BY C. S. MARVEL, C. W. HINMAN AND H. K. INSKIP

RECEIVED DECEMBER 18, 1952

It has been observed[3] that 96–98% of the thiol groups have reacted in 8 to 16 minutes when hexamethylenedithiol and biallyl polymerize in a persulfate initiated reaction at 30°. The complete disappearance of thiol groups occurs only after many hours. The polymer formed in the first few minutes has an inherent viscosity of 0.4 to 0.7 and that obtained after a much longer reaction time has an inherent viscosity of about 1.0. Other dithiols and diolefins show a similar behavior. This has suggested to us that the slow reaction may be an oxidation of terminal thiol groups in the polymers first formed, to yield a disulfide which thus terminates further polymerization.

Evidence of the presence of disulfide links in the polymers of higher inherent viscosity produced in the above reaction has now been obtained. If one of the polymers produced in the long reaction time is reduced by amalgamated zinc and hydrochloric acid in hot xylene solution, it is cleaved to a polymer of lower inherent viscosity. This reduction product can be reoxidized with iodine to produce a poly-

---

[1] For the eleventh communication on this topic, see C. S. Marvel and H. N. Cripps, *J. Polymer Sci.*, **9**, 53 (1952).

[2] The work discussed herein was performed as a part of the research project sponsored by the Reconstruction Finance Corporation, Office of Synthetic Rubber, in connection with the Government Synthetic Rubber Program.

[3] C. S. Marvel and A. H. Markhart, Jr., THIS JOURNAL, **73**, 1064 (1951).

mer of approximately the same inherent viscosity as that before the reduction.

A polymer which is produced in the first rapid reaction between hexamethylenedithiol and biallyl (inherent viscosity 0.472) has been isolated and oxidized with iodine to produce a product with a higher viscosity which resembles in all ways a product formed by the usual long polymerization process. Moreover, this polymer can be again reduced to give a product of lower inherent viscosity.

It is a significant fact that reduction of the higher molecular weight product does not reduce the viscosity enough to indicate that all material present after reduction is half of the original molecular weight. Neither does oxidation of a low viscosity polymer double the molecular weight, as a rule. This would suggest that not all the high molecular weight polyalkylene sulfide molecules contain a central disulfide linkage. Some termination of the polymerization reaction may involve dimerization of carbon free radical intermediates as was suggested earlier.[3]

Polyhexamethylene sulfides were also prepared from hexamethylenedithiol and biallyl with azo-bis-isobutyronitrile as the initiator. In 18 hours at 50° these polymers grew to an inherent viscosity of 0.5 to 0.65. These polymers could be oxidized with iodine to give polymers with an inherent viscosity of over 1.0. The unoxidized polymers were not reduced in viscosity when treated with zinc and acid in xylene solution. Hence they apparently still retain the mercaptan end groups.

Experimental

All inherent viscosities were determined on solutions of 0.20 g. of polymer in 50 ml. of chloroform at 25°.

Preparation of Polymers.—Polyhexamethylene sulfide polymers (inherent viscosity of 0.8 to 0.9) were prepared as described earlier[4] and also by initiating the reaction with azo-bis-isobutyronitrile. This initiator was used in the standard acetate buffered emulsions at *p*H 3.5 and the mixture tumbled at 50° for 18 hours. The ammonium persulfate, sodium bisulfite, cupric sulfate and *p*-*t*-butylcatechol used in the standard method were omitted and 0.03 g. of azo-bis-isobutyronitrile was introduced. The polymers were isolated as before. Polymers were obtained in 94-99% yield which had inherent viscosities of 0.5 to 0.65.

Reduction of High Molecular Weight Polyhexamethylene Sulfide Polymers.—One gram of persulfate initiated polymer (inherent viscosity 0.829) was dissolved in 150 ml. of xylene. Amalgamated zinc (about 30 g.) was added, stirring was started, the temperature was raised to 80° and then over a period of 12 to 18 hours 30 ml. of aqueous hydrochloric acid (one part of sp. gr. 1.19 hydrochloric acid to one part of water) was added at the rate of three to five drops per minute. After that time the mixture was cooled, filtered and poured into a large excess of cold methanol. The polymer isolated had an inherent viscosity of 0.537. Analytically its composition was unchanged. The melting point and appearance of the polymer was also essentially unchanged.

Oxidation of Low Molecular Weight Polyhexamethylene Sulfide Polymers.—One gram of persulfate initiated polymer (produced in the first five to eight minutes of reaction, inherent viscosity 0.472) was dissolved in 50 ml. of chloroform and to the solution was added about 0.2 g. of iodine. The solution was tumbled at 50° for about 24 hours, much of the solvent evaporated and the polymer isolated by pouring the residue into methanol. The product isolated had an inherent viscosity of 1.013 and in all respects appeared to be identical with a polymer produced in the usual long time polymerization.

Other Oxidation and Reduction Experiments.—In the following tables are collected the results of a number of oxidation and reduction experiments on a variety of polyhexamethylene sulfides.

TABLE I

REDUCTION AND REOXIDATION OF PERSULFATE INITIATED POLYHEXAMETHYLENE SULFIDES

Experiment no.	Inherent viscosity Of original polymer	After zinc reduction	After reoxidation with I_2
3–4[a]	0.691	0.514	...
7–5	.801	.633	0.815
7–4	.829	.537	0.780
6–2	.921	.849	1.039

[a] The polymer used in experiment 3–4 had the following analysis: C, 62.31; H, 10.26; S, 27.67. After reduction with zinc the analysis was: C, 61.89; H, 10.13; S, 27.22. The calculated values of $[C_6H_{12}S]_x$ are C, 62.00; H, 10.41; S, 27.59.

TABLE II

AZO-BIS-ISOBUTYRONITRILE INITIATED POLYHEXAMETHYLENE SULFIDES

Experiment no.	Original inherent viscosity	Inherent viscosity After oxidation with I_2	After subsequent reduction
12–9	0.617	...	0.605[a]
6–6	.657	0.812	.664
12–7	.507	1.295	.703
12–8	.507	1.194	....
6–7	.478	0.650	....

[a] This sample was reduced without intermediate oxidation.

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILL.

---

[4] C. S. Marvel and G. Nowlin, THIS JOURNAL, **72**, 5026 (1950).

Some Xanthineacetic Acid Derivatives

BY FREEMAN H. MCMILLAN AND H. M. WUEST

RECEIVED DECEMBER 8, 1952

In continuation of our program in the search for new analeptic drugs[1] it was decided to prepare N,N-diethyltheophylline-7-acetamide and N,N-diethyltheobromine-1-acetamide. The preparation of these and some closely related compounds together with some observations concerning their chemical properties constitute the subject matter of this paper.

Theophylline-7-acetic acid was prepared as described in the literature.[2] This acid was converted by usual methods to the ethyl ester in 83% yield and to the acid chloride in 36% yield. Theophylline-7-acetamide was prepared by shaking a benzene solution of theophylline-7-acetyl chloride with ice and excess ammonium hydroxide. N,N-Diethyltheophylline-7-acetamide was not obtained by treatment of theophylline-7-acetyl chloride with excess diethylamine in benzene; this was prepared, however, by treatment of theophylline with N,N-diethylchloroacetamide in aqueous sodium hydroxide solution or, in better yield, in ethanolic sodium hydroxide solution.

As in the case of 2-(3-pyridazonyl)-acetic acid,[3] theophylline-7-acetic acid when refluxed with acetic anhydride and pyridine, gave off carbon dioxide

---

[1] For the previous paper on this topic see F. H. McMillan and J. A. King, THIS JOURNAL, **73**, 3165 (1951).

[2] E. Merck, O. Wolfes and E. Kornick, German Patent 352,980, March 20, 1922.

[3] J. A. King and F. H. McMillan, THIS JOURNAL, **74**, 3222 (1952).

and 7-acetonyltheophylline was isolated in 36% yield; this compound was characterized as a ketone by semicarbazone formation.

Theobromine-1-acetic acid was prepared by the same method[2] as was used to prepare theophylline-7-acetic acid, *viz.*, alkylation of the parent xanthine with sodium chloroacetate in aqueous sodium hydroxide although considerable unalkylated theobromine was recovered from this reaction and the yield was only 25%. In contrast to theophylline-7-acetic acid, theobromine-1-acetic acid did not give a readily isolatable acid chloride when treated with thionyl chloride; the ethyl ester, however, was formed in moderate yield in ethanol containing a little sulfuric acid.

Ethyl theobromine-1-acetate was treated with excess cold concentrated ammonium hydroxide; after three days of standing, however, no amide was formed and the ester was recovered almost quantitatively. Theobromine-1-acetamide was prepared in 34% yield by bubbling ammonia through molten theobromine-1-acetic acid at 280–290°. When this same technique was applied in an attempt to prepare N,N-diethyltheobromine-1-acetamide no reaction took place. Attempted alkylation of theobromine with N,N-diethylchloroacetamide in aqueous sodium hydroxide gave no homogeneous product; N,N-diethyltheobromine-1-acetamide was obtained, however, in poor yield (12%) by using absolute ethanol as the solvent and sodium ethoxide as the base.

When theobromine-1-acetic acid was refluxed with acetic anhydride and pyridine no carbon dioxide was evolved and the acid was recovered unchanged.

The more satisfactory alkylation of theophylline is in agreement with the conclusions of Biltz and Beck,[4] who stated that in xanthines the order of decreasing ease of alkylation of the nitrogens is 3 > 7 > 1. If one agrees with the above authors' conclusions that this sequence is also that of decreasing acidity of the hydrogen atoms, one has an explanation for the more ready reactivity of theophylline-7-acetic acid with acetic anhydride and pyridine. That nitrogen atom possessing the more labile hydrogen atom will also more easily facilitate carbanion formation on the methylene group of a corresponding acetic acid residue; it has been previously demonstrated[5] that ease of carbanion formation of the carbon adjacent to the carboxyl group is a controlling factor in the course of the decarboxylative acylation of carboxylic acids.

Preliminary pharmacological evaluation of these substances indicates that they do exhibit some central nervous stimulant activity.

Experimental[6,7]

Theophylline-7-acetyl Chloride.—A mixture of theophylline-7-acetic acid[2] (12.0 g., 0.05 mole) and thionyl chloride (100 ml.) was refluxed for one hour; the excess thionyl chloride was evaporated under vacuum leaving a reddish-brown residue which on crystallization from benzene (100 ml.) gave 4.7 g. (36%) of yellowish crystals which melted at 150–154° (dec.).

Anal. Calcd. for $C_9H_9N_4O_3Cl$: N, 21.83. Found: N, 21.64.

Theophylline-7-acetamide.—Crude theophylline-7-acetyl chloride (2 g., 0.008 mole) in benzene (80 ml.) was shaken with concentrated ammonium hydroxide (15 ml.) and ice for 15 minutes. Crystalline material separated from the mixture which after four crystallizations from water weighed 1.1 g. (58%) and melted at 272–273°.

Anal. Calcd. for $C_9H_{11}N_5O_3$: C, 45.56; H, 4.67; N, 29.53. Found: C, 45.71; H, 4.74; N, 29.27.

Ethyl Theophylline-7-acetate.—A mixture of theophylline-7-acetic acid (6.0 g., 0.025 mole) and absolute ethanol (100 ml.) containing a few drops of sulfuric acid was refluxed for 3.5 hours. The hot mixture was filtered to remove a little undissolved material; chilling the filtrate gave 5.5 g. (83%) of crystals melting at 138–139°. An analytical sample, after three crystallizations from water, melted at 143–144°.

Anal. Calcd. for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.06. Found: C, 49.89; H, 5.02; N, 21.12.

N,N-Diethyltheophylline-7-acetamide.—Theophylline (11.9 g., 0.06 mole) was added to a solution of sodium hydroxide (2.4 g., 0.06 mole) in water (280 ml.); this mixture was cooled to 5° and N,N-diethylchloroacetamide (9.0 g., 0.06 mole) was added dropwise, over a period of 15 minutes, with vigorous stirring. The temperature of the mixture was allowed to come to 25° and then the mixture was heated at reflux for two hours. On standing overnight at room temperature there were deposited crystals which, after two crystallizations from water, weighed 1.5 g. (9%) and melted at 186–187°.

Anal. Calcd. for $C_{13}H_{19}N_5O_3$: C, 53.23; H, 6.53; N, 23.90. Found: C, 53.49; H, 6.31; N, 23.94.

When this reaction was repeated in ethanol the yield was 5.0 g. (29%) melting at 182–183°.

7-Acetonyltheophylline.—A mixture of theophylline-7-acetic acid (7.1 g., 0.03 mole), acetic anhydride (30 ml.) and pyridine (30 ml.) was refluxed for one hour during which about 200 ml. of carbon dioxide was collected. The solution was evaporated to dryness under vacuum; the residue after two crystallizations from ethanol (50 ml.) gave 2.5 g. (36%) of crystals melting at 160–161°.

Anal. Calcd. for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.75. Found: C. 50.96; H, 4.93; N, 23.54.

A small sample of this ketone gave a semicarbazone which after crystallization from ethanol melted at 247–248° (dec.).

Anal. Calcd. for $C_{11}H_{15}N_7O_3$: N, 33.06. Found: N, 33.47.

Ethyl Theobromine-1-acetate.—A mixture of theobromine-1-acetic acid[2] (6.0 g., 0.025 mole) and absolute ethanol (100 ml.) containing a few drops of sulfuric acid was refluxed for 3.5 hours. The hot mixture was filtered to remove a little undissolved material; the filtrate on cooling deposited crystals which melted at 154–157° to an opaque melt. This material was suspended in water (25 ml.) and 2 *N* sodium hydroxide was added until the solution was distinctly alkaline; the resulting suspension was heated to boiling and water added (85–90 ml.) until everything dissolved. Chilling gave 3.3 g. (50%) of crystals which melted at 163–164.5°. An analytical sample after recrystallization from water melted at 165–166°.

Anal. Calcd. for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.06. Found: C, 49.72; H, 5.53; N, 21.11.

Theobromine-1-acetamide.—Theobromine-1-acetic acid (6.0 g., 0.025 mole) was placed in a 100-ml. flask immersed in a Wood's metal bath; the bath temperature was maintained at 290–295° while ammonia was bubbled through the molten acid for one hour. The cooled melt was crystallized from water (100 ml.) giving 2.0 g. (34%) of crystals which melted at 301–302° (dec.).

Anal. Calcd. for $C_9H_{11}N_5O_3$: C, 45.56; H, 4.67; N, 29.53. Found: C, 45.43; H, 4.55; N, 29.55.

N,N-Diethyltheobromine-1-acetamide.—To a solution of sodium (1.4 g., 0.06 mole) in ethanol (100 ml.) there was added theobromine (10.8 g., 0.06 mole) followed by dropwise addition of N,N-diethylchloroacetamide (9.0 g., 0.06 mole) at below 10°. The mixture was allowed to come to room temperature and was then heated at reflux for two hours. The hot solution was filtered and the filtrate evap-

---

[4] H. Biltz and A. Beck, *J. prakt. Chem.*, [2] **118**, 198 (1928).

[5] J. A. King and F. H. McMillan, THIS JOURNAL, **73**, 4911 (1951).

[6] Melting points are uncorrected.

[7] Microanalyses were carried out under the direction of Dr. F. A. Bühler of this Institute.

orated to dryness under vacuum leaving a residue which after two crystallizations from ethanol weighed 2.0 g. (12%) and melted at 210-211°.

Anal. Calcd. for $C_{13}H_{19}N_5O_3$: C, 53.23; H, 6.53; N, 23.90. Found: C, 53.58; H, 6.35; N, 23.87.

WARNER-CHILCOTT RESEARCH LABORATORIES
113 WEST 18TH STREET
NEW YORK 11, NEW YORK

Syntheses in the Indene Series[1]

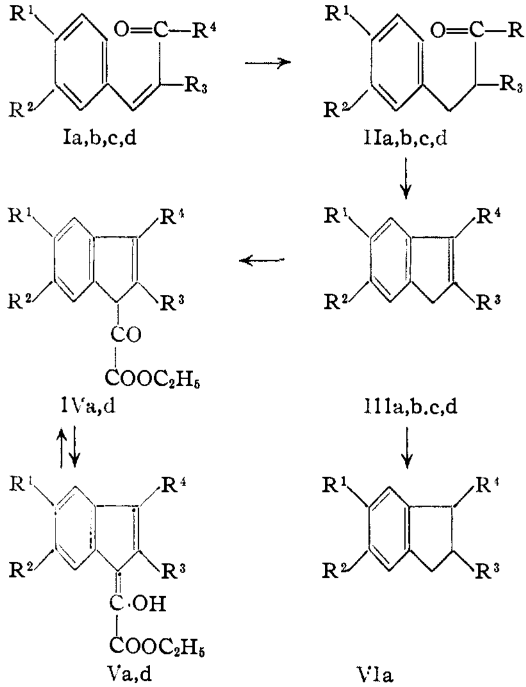
BY JOHN KOO[2]

RECEIVED DECEMBER 19, 1952

In connection with a projected synthesis of colchicine analogs, various substituted indenes were prepared as model compounds. Attempts were made to introduce substituents which, by cyclization, might yield tricyclic systems. The present note describes the synthesis of some of those indene derivatives.

Veratraldehyde and piperonal were condensed with ethyl acetoacetate by an extension of Knoevenagel's method,[3] and the resulting benzylideneacetoacetic esters (Ia,b) hydrogenated to the benzylacetoacetic esters (IIa,b).[4] Acid-catalyzed cyclodehydration of IIa and IIb produced the indene esters IIIa and IIIb, in addition to small amounts of the corresponding carboxylic acids, which resulted from hydrolysis accompanying the cyclization. Analogously, veratrylacetone (IIc)[5] and veratrylacetophenone (IId)[6] were cyclized to the indene derivatives IIIc and IIId. The indene ester IIIa and the phenylindene IIId condensed with ethyl oxalate to form IVa and IVd in 85 and 76% yields, respectively, while the methylindene IIIc failed to yield an oxalyl derivative. Apparently, activation by an aryl group in the 3- or by an ester group in the 2-position is required for formation or sufficient resonance stabilization of the carbanion which must be an intermediate in the condensation with ethyl oxalate. Since IVa and IVd form enol acetates, it is believed that they exist, at least partly, in the tautomeric enolic forms (Va,d). Attempts to reduce the carbonyl group in IVa to a methylene group by catalytic hydrogenation with palladium-carbon or by chemical reduction with aluminum amalgam failed or yielded inseparable mixtures. It was possible, however, to hydrogenate the indene ester IIIa to the indane ester VIa in 77% yield.

CHART 1



Series a: $R^1 = R^2 = OCH_3$; $R^3 = CO_2C_2H_5$; $R^4 = CH_3$
Series b: $R^1 = R^2 = -OCH_2O-$; $R^3 = CO_2C_2H_5$; $R^4 = CH_3$
Series c: $R^1 = R^2 = OCH_3$; $R^3 = H$; $R^4 = CH_3$
Series d: $R^1 = R^2 = OCH_3$; $R^3 = H$; $R^4 = C_6H_5$

Experimental[7]

Ethyl Veratrylideneacetoacetate (Ia).—A homogeneous mixture of 182.6 g. of veratraldehyde, 130 g. of ethyl acetoacetate and 70 ml. of benzene was refluxed with 3.4 g. of piperidine and 12.2 g. of glacial acetic acid. Water liberated in the reaction was collected in a moisture trap. The reaction was completed in two hours, at which time 25 ml. of water had been collected. The solution was then cooled, diluted with 300 ml. of ether, washed twice with 100 ml. each of very dilute acetic acid and once with water, and dried over maguesium sulfate. After removal of solvents, the product was distilled to yield 175 g. (63%) of a pale yellowish oil, b.p. 190-192° (1 mm.), which solidified after standing for two days and then melted at 75-81°.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.25. Found: C, 64.60; H, 6.60.

Ethyl Piperonylideneacetoacetate (Ib).—This compound was obtained from piperonal in 62% yield by the procedure used for the preparation of Ia. The pale yellow oil, b.p. 179° (1.6 mm.), solidified on standing and remelted at 74-77°.

Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.11; H, 5.37. Found: C, 63.78; H, 5.49.

Ethyl Veratrylacetoacetate (IIa).—A solution of 139 g. of IIa in 150 ml. of ethyl acetate was hydrogenated with 9 g. of 5% palladium-carbon catalyst at room temperature and 45 lb. pressure for two hours. Removal of catalyst and solvent, followed by vacuum distillation, provided 100 g. (70%) of colorless oil, b.p. 169° (1 mm.).

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.27; H, 7.01.

The **2,4-dinitrophenylhydrazone** formed yellowish crystals (from dilute ethanol), m.p. 116-117°.

Anal. Calcd. for $C_{21}H_{24}O_8H_4$: C, 54.78; H, 5.28. Found: C, 54.74; H, 5.36.

Ethyl Piperonylacetoacetate (IIb).—Hydrogenation of Ib by the above procedure gave a 52% yield of colorless oil, b.p. 151-153° (0.8 mm.) (reported[4] 160-161° (4 mm.)).

Veratrylacetone (IIc).—This compound was similarly obtained in 83% yield by reducing 69 g. of veratrylideneacetone (Ic),[5,8] m.p. 84-86° (reported 91-92°,[5] 84-85°[8]), with 5 g. of palladium-carbon catalyst in 150 ml. of glacial acetic acid for 35 minutes. The colorless material had b.p. 127-129° (0.5 mm.) and m.p. 53-56° (reported[5] b.p. 181° (14 mm.), m.p. 55°).

---

[1] Supported in part by a grant-in-aid from the American Cancer Society recommended by the Committee on Growth of the National Research Council.

[2] American Cancer Society Postdoctoral Fellow, 1948-1950; Special Research Fellow of the National Cancer Institute, National Institutes of Health.

[3] E. Knoevenagel, *Ber.*, **29**, 172 (1896); **31**, 730 (1898).

[4] R. H. Barry, A. M. Mattocks and W. H. Hartung, THIS JOURNAL, **70**, 693 (1948), prepared IIb from piperonal *via* piperonyl alcohol and piperonyl chloride.

[5] A. Kaufmann and R. Radosević, *Ber.*, **49**, 675 (1916).

[6] P. Pfeiffer, E. Kalckbrenner, W. Kunze and K. Levin, *J. prakt. Chem.*, [2] **119**, 109 (1928).

[7] Melting points are corrected and boiling points uncorrected. Analyses were carried out by Mrs. S. M. Woods of the University of Pennsylvania, and by Dr. W. C. Alford and his associates of the National Institutes of Health.

[8] C. F. Van Duin, *Rec. trav. chim.*, **45**, 345 (1926).

Veratrylacetophenone (IId).—Veratrylideneacetophenone (Id), m.p. 90–92° (reported 85°,[8] 88°[9]) was hydrogenated with palladium–carbon catalyst in ethyl acetate for four hours to give a 93% yield of solid, m.p. 68–70° (reported[6] 67.5–68.5°) which crystallized from dilute ethanol in colorless scales, with no change in m.p.

Ethyl 5,6-Dimethoxy-3-methylindene-2-carboxylate (IIIa).—A solution of 56 g. of IIa in 45 ml. of 85% phosphoric acid was added slowly with vigorous stirring to a mixture of 90 ml. of concd. sulfuric acid and 45 ml. of 85% phosphoric acid at 0–5°. The reaction mixture became rapidly red, then bluish, and solidified. It was stirred into ice-water almost immediately. The white precipitate was collected, washed with cold water, dissolved in ether, and the solution washed with 10% sodium bicarbonate. Evaporation of the solvent gave 24 g. (46%) of a colorless solid, which after recrystallization from 70% ethanol formed large colorless crystals, m.p. 136–136.5°.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.54; H, 6.92.

Acidification of the sodium bicarbonate washings with concd. hydrochloric acid yielded 5 g. (10%) of **5,6-dimethoxy-3-methylindene-2-carboxylic acid** as a heavy white solid, which after recrystallization from acetone melted at 228–230°.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.49; H, 5.85.

Ethyl 5,6-Methylenedioxy-3-methylindene-2-carboxylate (IIIb).—A solution of 1 g. of IIb in 3 ml. of sulfuric and 3 ml. of phosphoric acid was prepared and kept at 0° for 40 minutes, at which time the color had changed from yellow to greenish-blue. The pale green crude solid (0.79 g.), obtained as above after treatment with bicarbonate, was recrystallized from dilute ethanol, but the product was still quite impure. It was, therefore, dissolved in ether–ethyl acetate, and the solution shaken exhaustively with 2% aqueous sodium hydroxide, then with water. Drying and evaporating the solvent yielded 0.443 g. (48%) of a solid, m.p. 105–107°, which was recrystallized from 70% ethanol to give tiny colorless needles, m.p. 107–108°.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.72. Found: C, 68.08; H, 5.71.

From the sodium bicarbonate washings, there was obtained 0.032 g. (3.6%) of **5,6-methylenedioxy-3-methylindene-2-carboxylic acid**, which separated from ethyl acetate–70% ethanol in small colorless crystals, m.p. 280–281° (dec.).

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.04; H, 4.62. Found: C, 66.27; H, 4.61.

5,6-Dimethoxy-3-methylindene (IIIc).—This compound was obtained from 21 g. of IIc in 42 ml. of phosphoric acid and 42 ml. of sulfuric acid at 10–15° by the method used for preparing IIIa, except that the crude product (10 g., 52%) was obtained directly by pouring the reaction mixture into 400 ml. of ice-water after 0.5 hour, with omission of the bicarbonate treatment. The product formed small colorless scales (from dilute ethanol), m.p. 132–133°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.60; H, 7.63.

5,6-Dimethoxy-3-phenylindene (IIId).—A 91% yield of crude material was obtained similarly from IId, except that the reaction mixture was heated at 60–70° for 30 minutes. Recrystallization from dilute ethanol gave small colorless scales, m.p. 112–113.5°. The yield dropped to 10% when the reaction was carried out below 25°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.75; H, 6.25.

Ethyl 1-Ethoxalyl-5,6-dimethoxy-3-methylindene-2-carboxylate (IVa).—To a still warm solution of 1.15 g. of sodium in 50 ml. of absolute ethanol was added rapidly with vigorous swirling 7.5 g. of ethyl oxalate, then a suspension of 18 g. of IIIa in 100 ml. of hot absolute ethanol. The mixture was shaken for another two minutes, the yellowish paste stirred into cold water, and the mixture acidified with dilute hydrochloric acid. The solid was collected, washed with water and purified from 70% ethanol to yield 19 g. (77%) of yellowish crystals, m.p. 143–146°.

Anal. Calcd. for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12. Found: C, 62.92; H, 5.99.

The **2,4-dinitrophenylhydrazone** formed small yellow crystals (from ethyl acetate), m.p. 180–182°.

Anal. Calcd. for $C_{25}H_{26}O_{10}N_4$: C, 55.35; H, 4.83. Found: C, 55.20; H, 4.73.

The deep yellow crystalline **enol acetate**, m.p. 132–133°, was prepared by refluxing IVa with acetic anhydride and pyridine, followed by diluting with ice-water and recrystallization from dilute ethanol.

Anal. Calcd. for $C_{21}H_{24}O_8$: C, 62.37; H, 5.98. Found: C, 62.36; H, 6.03.

1-Ethoxalyl-5,6-dimethoxy-3-phenylindene (IVd).—This compound was obtained in 76% yield from 0.46 g. of sodium, 15 ml. of ethanol, 3 g. of ethyl oxalate and 4.2 g. of IIId, and formed deep red needles, m.p. 122–124°.

Anal. Calcd. for $C_{21}H_{20}O_5$: C, 71.50; H, 5.75. Found: C, 71.46; H, 5.57.

The **enol acetate** crystallized from ethanol in orange-colored cottony needles, m.p. 165–167°.

Anal. Calcd. for $C_{23}H_{22}O_6$: C, 70.03; H, 5.62. Found: C, 69.88; H, 5.86.

Ethyl 5,6-Dimethoxy-3-methylindane-2-carboxylate (VIa).—Hydrogenation of 1 g. of IIIa in 15 ml. of glacial acetic acid with 0.5 g. of 5% palladium–carbon catalyst at 60° and 40 lb. pressure for 2.5 hr. yielded 0.95 g. of oil, which was crystallized from ether–ethyl acetate–pentane to give 0.85 g. (85%) of small colorless crystals, m.p. 48–49°.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.15; H, 7.62. Found: C, 68.03; H, 7.57.

Saponification of VIa provided **5,6-dimethoxy-3-methylindane-2-carboxylic acid** as small colorless crystals (from dilute ethanol), m.p. 176–177°.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.82. Found: C, 65.85; H, 6.77.

Acknowledgment.—The author wishes to express his appreciation to Dr. E. C. Horning for many helpful suggestions during the course of this work at the University of Pennsylvania.

JOHN HARRISON LABORATORY
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA., AND
LABORATORY OF CHEMICAL PHARMACOLOGY
NATIONAL CANCER INSTITUTE
BETHESDA 14, MD.

Non-additivity of Polarographic Diffusion Currents with Mixtures of Certain Reducible Species

BY STANLEY L. MILLER[1] AND EDWIN F. ORLEMANN

RECEIVED DECEMBER 17, 1952

Under certain conditions we have found that the polarographic diffusion currents of two species are not additive. This effect has been studied for mixtures of Ce(IV) and O_2 and for mixtures of Fe(III) and Cr(VI) in 1 M H_2SO_4 and 1 M $HClO_4$. The results show that non-additivity of diffusion currents to give either a larger or smaller current than expected can occur as a result of very fast reactions in the diffusion layer when the species have significantly different diffusion coefficients. The effect is of some theoretical interest and its occurrence must be recognized in connection with a limited number of analytical applications.

Experimental

The polarograms were recorded on a Sargent model XII polarograph. The drop time was about three seconds, and the temperature was 25.00 ± 0.05°. Runs were made with both an internal anode and with an external calomel cell

---

(9) R. Dickinson, I. M. Heilbron and F. Irving, *J. Chem. Soc.*, 1888 (1927).

(1) Department of Chemistry, University of Chicago, Chicago, Ill., National Science Foundation Predoctoral Fellow, 1952–1953.

connected by a potassium chloride salt bridge. The vessel for the internal anode had a very small area of mercury exposed to the solution so that no appreciable portion of the species in the solution reacted with the mercury. The results were essentially the same with either anode. Oxygen was eliminated from the solution by tank nitrogen heated over copper at 350°. Freshly prepared gelatin was used as a maximum suppressor.

The ceric solution was prepared by diluting G. F. Smith 0.5 *M* "Perchlorato Ceric Acid" to 0.1 *M* and standardizing with a iodine–thiosulfate titration. The ferric solution was prepared by oxidizing G. F. Smith $Fe(ClO_4)_2 \cdot 6H_2O$ with hydrogen peroxide, adding $HClO_4$ to make 1.0 *M*, boiling off the excess hydrogen peroxide, and standardizing by the usual dichromate procedure. The potassium dichromate solution was prepared by direct weighing, and the oxygen was standardized by letting the solution remain in equilibrium with the air overnight. The concentration of oxygen was taken to be 2.5×10^{-4} *M* although due to the salting out the concentration was probably somewhat lower.

The mixtures were prepared for a run by diluting the appropriate quantity of the stock solution to 100.0 cc. with the 1 *M* acid, adding gelatin and bubbling with nitrogen.

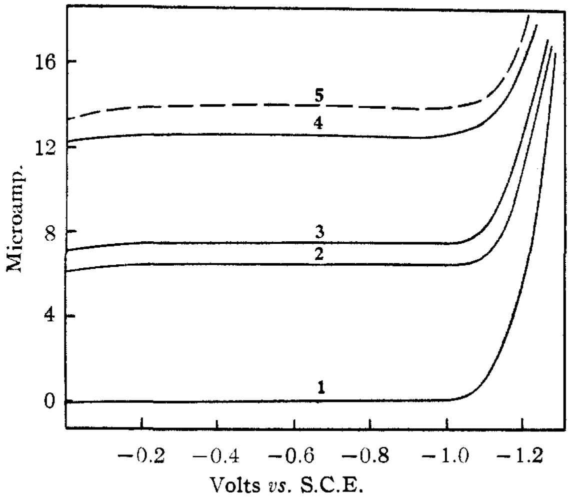


Fig. 1.—Mixtures of ferric and dichromate in 1.0 *M* H_2SO_4: 1, residual current; 2, 2.38×10^{-3} *M* Fe^{+3}; 3, 3.30×10^{-4} *M* $Cr_2O_7^{=}$; 4, 2.38×10^{-3} *M* Fe^{+3} + 3.30×10^{-4} *M* $Cr_2O_7^{=}$; 5, sum of 2 and 3.

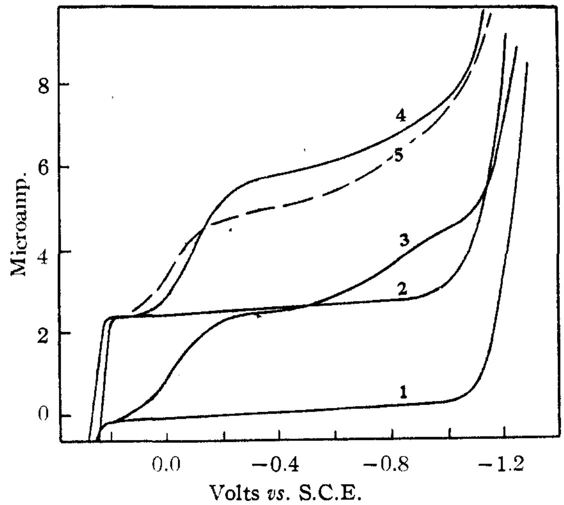


Fig. 2.—Mixtures of ceric and oxygen in 1.0 *M* H_2SO_4: 1. residual current; 2, 0.936×10^{-3} *M* Ce^{+4}; 3, 2.5×10^{-4} *M* O_2; 4, 0.936×10^{-3} *M* Ce^{+4} + 2.5×10^{-4} *M* O_2; 5. sum of 2 and 3.

Typical results for the dichromate–ferric system and the ceric–oxygen system are shown in Figs. 1 and 2, respectively. At concentrations of 2.38×10^{-3} *M* ferric and 3.30×10^{-4} *M* dichromate the current is 9% lower than would be expected if the currents were additive. The percentage reduction in current becomes less at lower concentrations of reducible species and is about 6% at concentrations of 3.80×10^{-4} *M* ferric and 0.678×10^{-4} *M* dichromate. In the ceric–oxygen case with respective concentrations of 0.936×10^{-3} *M* ceric and 2.5×10^{-4} *M* oxygen the observed current is 14% high at 0.3 v. and 7% high at 0.8 v. (S.C.E.). The percentage reduction or enhancement of current is the same in both 1 *M* H_2SO_4 and 1 *M* $HClO_4$.

This effect was also observed in the cases of chromic–oxygen and chromic–iodine in 1 *M* $HClO_4$. With concentrations of 1.23×10^{-3} *M* chromic and 2.5×10^{-4} *M* oxygen the observed current is 8% lower than expected in the diffusion current region of chromic (1.0 v.). In the chromic–iodine case the concentrations were 2.26×10^{-3} *M* chromic, 1.03 *M* I_3^- and 4×10^{-2} *M* NaI. The current was 9% lower than expected at 1.0 v.

Discussion

The decrease in total current in the ferric–dichromate solutions can be understood in the following terms. The ferrous ion formed from the reduction of the ferric diffuses into the body of the solution and encounters the dichromate ions that are diffusing to the electrode. In this diffusion layer the following reaction takes place very rapidly

$$6Fe^{+2} + Cr_2O_7^{--} + 14H^+ = 6Fe^{+3} + 2Cr^{+3} + 7H_2O$$

To the extent that this reaction occurs one equivalent of dichromate having a diffusion coefficient of about 13×10^{-6} cm.^{2} sec.$^{-1}$ is replaced by one equivalent of ferric having a diffusion coefficient of about 7×10^{-6} cm.^{2} sec.$^{-1}$. The same number of equivalents of reducible material is diffusing to the electrode, but is diffusing at a reduced rate. The current is therefore decreased. The decrease in percentage reduction of current at lower concentrations is consistent with this picture because at lower concentrations the fraction of dichromate replaced by the ferric is decreased.

The increase in current in the ceric–oxygen solution can be readily understood in an analogous manner. The hydrogen peroxide formed from the reduction of the oxygen diffuses into the body of the solution and encounters ceric ions that are diffusing to the electrode. The reaction that takes place very rapidly in the diffusion layer is

$$2Ce^{+4} + H_2O_2 = O_2 + 2Ce^{+3} + 2H^+ \qquad (1)$$

The ceric ion having a diffusion coefficient of about 6×10^{-6} is thus replaced by an equivalent of oxygen having a diffusion coefficient of about 26×10^{-6}. The same number of equivalents is being transported to the mercury drop, but at an increased rate. The current is therefore increased. Between the potentials of 0.5 and 1.0 v. where a significant portion of the oxygen is being reduced directly to water, less of the hydrogen peroxide can diffuse back into the body of the solution and react with the ceric. As is seen in Fig. 2, the difference between the expected and observed current is correspondingly reduced.

The above interpretation would not be correct if the number of equivalents of reducible material could be increased by a catalytic reduction of the hydrogen peroxide to water. It has been shown by Cahill and Taube[2] in tracer experiments that when

---

(2) A. E. Cahill and H. Taube, This Journal, 74, 2312 (1952).

hydrogen peroxide is oxidized by Ce^{+4} the O–O bond is not severed. Thus a possible reaction mechanism for eq. 1 would be

$$Ce^{+4} + H_2O_2 = Ce^{+3} + H^+ + HO_2 \qquad (2)$$

followed by

$$HO_2 + Ce^{+4} = Ce^{+3} + O_2 + H^+ \qquad (3)$$

or at the electrode

$$e^- + HO_2 + H^+ = H_2O_2 \qquad (4)$$

If HO_2 is produced at the electrode by the reduction of O_2 and diffuses into the solution, it will react with the Ce^{+4} as in eq. 3. In any of the cases, eq. 3 or 4 or the production of HO_2 at the electrode, the same number of equivalents of material is being reduced. Because the O–O bond is not severed, the reaction

$$HO_2 + H_2O_2 = H_2O + O_2 + HO\cdot \qquad (5)$$

cannot take place at an appreciable rate in the body of the solution. However, since the reduction of O_2 takes place at a metal surface, it may be that there is still some mechanism by which H_2O_2 can be reduced to H_2O. Additional experiments would be necessary to determine if the non-additivity in the case of ceric and oxygen is due to reduction of the H_2O_2 to H_2O or by the replacement of the ceric by a faster diffusing O_2.

The reduction in current for mixtures of chromic and oxygen and for chromic and iodine can be explained in the same manner as the ferric–dichromate mixture. The reactions in the diffusion layer are, respectively

$$4H^+ + 4Cr^{+2} + O_2 = 4Cr^{+3} + 2H_2O$$
$$2H^+ + 2Cr^{+2} + H_2O_2 = 2Cr^{+3} + 2H_2O$$
$$2Cr^{+2} + I_3^- = 2Cr^{+3} + 3I^-$$

In these last two cases, although the current reduction is significant, it is somewhat difficult to make a residual current correction because of the rapidly rising hydrogen wave.

The hydrogen ion concentration of 1 *M* is high enough so that there will be very little change in its concentration at the surface of the electrode. Therefore these results cannot be due to precipitation of hydroxides or other compounds such as have been reported previously.[3]

A quantitative treatment of the decrease or increase in current cannot be made on the basis of a simple replacement of the oxidized form of one species by the oxidized form of another species. Thus in the dichromate–ferric case the difference in the observed current from the sum is not the fraction of the replaced ions (which cannot be determined) times the fractional difference in diffusion coefficients. An exact treatment must take into account the combined factors of diffusion and reaction kinetics. The equations describing these combined factors can be formulated readily as a system of four non-linear partial differential equations with appropriate boundary conditions. The difficulty of solving these equations is too great to permit a quantitative treatment at this time.

DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA

---

[3] I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1952, pp. 105–121.

The Preparation and Properties of Brown Phosphorus

BY FRANCIS OWEN RICE, RITA POTOCKI AND KENNETH GOSSELIN

RECEIVED DECEMBER 6, 1952

Of the various allotropic forms of phosphorus, the common white form has been most thoroughly studied. Both vapor density[1] and cryoscopic measurements,[2] as well as X-ray[3] and electron diffraction studies,[4] all indicate that the molecule is P_4. Vapor density measurements[1] show that P_4 is an extremely stable molecule that dissociates appreciably to P_2 only near 1000° even at 1 mm. pressure. A spectroscopic study[5] of the P_2 molecule indicates that the strength of the bond in P_2 is 115.5 kcal. and that any thermal dissociation at 1000° even at very low pressures, would be negligible.

Although the other common form, red phosphorous, has been studied extensively, its structure has not as yet been settled conclusively. Pauling[6] has suggested that red phosphorus is formed from from white phosphorus by rupture of one bond and formation of long chains of P_4 units, each unit consisting of two equilateral triangles with a common base. This view is consistent with the results of X-ray studies,[3] which indicate that each atom in red phosphorus has three nearest neighbors and is also consistent with the results of kinetic studies[7] on the rate of reaction of white to red phosphorus. If, however, red phosphorus actually consists of long chains of P_4 units, the results of two studies of Melville and Gray[8] are rather unexpected. They concluded that the abnormally high vapor pressure of red phosphorus in a closed system could be understood on the basis that only P_2 molecules evaporate from red phosphorus *in vacuo* and these immediately dimerize to P_4 since the equilibrium, $2P_2 \rightleftarrows P_4$, even at red heat is almost entirely on the P_4 side. Our own work helps confirm this conclusion.

Our preliminary experiments were performed with white phosphorus in an apparatus described in previous work.[9] The phosphorus was kept at a temperature of about 45° where its vapor pressure is about 0.2 mm. According to vapor density measurements, the dissociation of phosphorus vapor at 1000° is

Pressure	P_4 at equilibrium, %
1.0	3.36
0.5	1.73
0.1	0.35
0.04	0.25

---

[1] (a) A. Stock, G. Gibson and E. Stamm, *Ber.*, **45**, 3527 (1912); (b) G. Preuner and J. Brockmuller, *Z. physik. Chem.*, **81**, 129 (1912).

[2] D. M. Yost and H. Russell, "Systematic Inorganic Chemistry," Prentice–Hall, Inc., New York, N. Y., 1946, p. 161.

[3] (a) C. D. Thomas and N. S. Gingrich, *J Chem. Phys.*, **6**, 659 (1938); (b) R. Haltgren, N. S. Gingrich and B. E. Warren, *ibid.*, **3**, 351 (1935).

[4] L. R. Maxwell, S. B. Hendricks and V. M. Mosley, *ibid.*, **3**, 699 (1935).

[5] (a) G. Herzberg, L. Herzberg and G. G. Milne, *Can. J. Research*, **18A**, 139 (1940); (b) D. P. Stevenson and Don M. Yost, *J. Chem. Phys.*, **9**, 403 (1941).

[6] L. Pauling and M. Simonetta, *ibid.*, **20**, 32 (1952).

[7] T. W. DeWitt and S. Skolnik, THIS JOURNAL, **68**, 2305 (1946).

[8] H. W. Melville and S. C. Gray, *Proc. Faraday Soc.*, **32**, 271, 1026 (1936).

[9] F. O. Rice and M. J. Freamo, THIS JOURNAL, **73**, 5529 (1951).

We found that when the vapors pass through a furnace and condense on a liquid nitrogen cooled finger, only white phosphorus condenses when the furnace is below 600°. Above this temperature the condensed material is colored and when the furnace temperature is about 1000°, or higher, a dark brown deposit is obtained. The material is insoluble in propane and ethylene at their boiling points and in carbon bisulfide at −103°. A qualitative test with a powerful magnet indicated that the material is not paramagnetic. Brown phosphorus is stable indefinitely at liquid nitrogen temperatures, but on heating, changes irreversibly to a mixture of red and white phosphorus. This change occurs at a measurable rate in the range −100 to −50° but almost instantly at room temperature or higher. We analyzed the mixture by subliming off the volatile white phosphorus onto another cold finger and weighing each separately. Analysis of samples obtained by heating brown phosphorus to −80°, room temperature and 100° all gave the same result (within ±5%), namely, 20% red phosphorus and 80% white phosphorus. The non-volatile red phosphorus remaining on the finger after evaporation of the white phosphorus varied somewhat in color according to the method of preparation, a heavy coating of brown phosphorus heated to room temperature or higher giving an almost black material. We determined that the density of this almost black material was 2.05 to 2.06 by a flotation method using aqueous barium iodide of varying densities. The density at room temperature of white phosphorus is 1.83, of red phosphorus 2.04 to 2.34 (depending on the method of preparation)[10] and of the high pressure black phosphorus, 2.69. Since our black material did not conduct electricity and had a density in the range of red phosphorus, we have assumed that the polymerization of P_2 may yield substances somewhat different in color depending on the molecular weight but are all essentially "red" phosphorus.

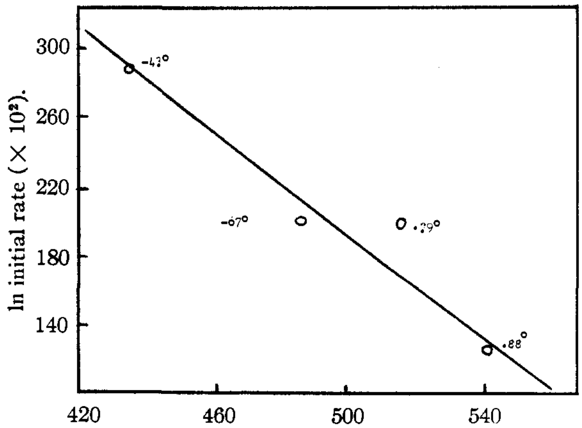


Fig. 1.

Brown phosphorus may also be prepared by heating ordinary red phosphorus in an evacuated jacket at 350–360° or higher and condensing the vapor on a liquid nitrogen cooled finger. The material prepared in this way seems to be identical in all respects with that prepared in the manner described for white phosphorus. We have also found that white phosphorus at −190° exposed to the light from a quartz mercury lamp, gradually changes to the brown form.

We tried a number of different methods for measuring the rate of change of brown phosphorus at various temperatures and finally adopted a method of distilling a thin layer of P_2 onto a liquid nitrogen cooled finger. The P_2 was produced by heating ordinary red phosphorus in a small side arm to 350° for a fixed length of time so that a layer of constant thickness would be obtained. The whole apparatus was then surrounded by a vacuum vessel containing a window and the liquid nitrogen cooled finger was rotated so that the deposit of brown phosphorus was opposite the window. Light from a tiny electric bulb in the cold finger passed through the brown phosphorus and onto a photocell attached to a galvanometer. We measured the rate of change in arbitrary units of galvanometer deflections at four temperatures obtained by filling the vacuum vessel and cold finger with ethane (b.p. −88°), hydrogen bromide (b.p. −67°), chlorotrifluoromethane (b.p. −79°) and propane (b.p. −43°). From the graphs we estimated the initial rate of change in terms of galvanometer deflection per minute and plotted the initial rate against $1/T$. The result is shown in Fig. 1 and gives an activation energy of about 3 kcal. for the change.

DEPARTMENT OF CHEMISTRY
THE CATHOLIC UNIVERSITY OF AMERICA
WASHINGTON 17, D. C.

A Preparation of Carrier-free Sb^{125} from Neutron Irradiated Stannous Chloride[1]

BY JOSEPH D. ROBINSON AND MILTON KAHN

RECEIVED NOVEMBER 29, 1952

Only one method for the preparation of carrier-free[2] antimony has been reported.[3] This method involves the deuteron bombardment of tin followed by one precipitation and two distillations to effect the separation of the antimony. Since facilities for deuteron bombardment are often not available and the separation procedure reported requires considerable time, a search for a simpler method which would require only thermal neutron irradiation of the target was undertaken.

This communication reports a procedure for the separation of 2.7-year Sb^{125} from solutions of irradiated stannous chloride employing deposition of the antimony from halide acid solution on metallic copper without the use of external electro-

---

[10] See E. Cohen and J. Olie, *Z. physik. Chem.*, **71**, 1 (1910); P. Jolibois, *Compt. rend.*, **151**, 383 (1910).

[1] This communication is based on work done under the auspices of the Los Alamos Scientific Laboratory and the Atomic Energy Commission and submitted in partial fulfilment of the requirements for the degree of Master of Science in the Graduate School of the University of New Mexico, August, 1952, by Joseph D. Robinson.

[2] The term carrier-free as used by the authors denotes that no isotopic carrier has been knowingly mixed with the nuclide under discussion.

[3] R. Maxwell, H. Haymond, W. Garrison and J. Hamilton, *J. Chem. Phys.*, **17**, 1340 (1949).

motive force, the Reinsch reaction, which has been subsequently studied by Evans.[4]

Experimental

Chemicals and Glassware.—The anhydrous stannous chloride used as a target was obtained from the Metal and Thermit Corporation and was found to be spectrographically free from antimony.[5] The stannic chloride pentahydrate also used as a target was Mallinckrodt analytical reagent grade and was found to be spectrographically free from antimony.[6] Standard antimony trichloride was prepared by dissolving the Baker and Adamson reagent grade salt in 6 *f* hydrochloric acid, and titrating with 0.01 *N* potassium bromate, using sodium indigo sulfonate as an indicator. A correction was made for the indicator blank. Compressed gases were employed from tanks as supplied. All of the other chemicals employed were of analytical reagent grade. None of the glassware used in experiments with solutions containing carrier-free antimony had a history of previous use with solutions containing macro amounts of antimony. Glassware was cleaned with an Alconox[7] solution followed by chromic acid cleaning solution. A separate stock of cleaning solution (free from carrier antimony) was used for glassware coming in contact with carrier-free antimony solutions.

Radioactivity and Counting.—Samples of target material were weighed into quartz vessels and irradiated in a thermal column of a Los Alamos reactor. The irradiated samples were dissolved in the desired solvent and stored in glass-stoppered flasks.

To determine the total Sb^{125} activity in a solution of an irradiated tin chloride, a measured volume of standard antimony trichloride carrier was added to an aliquot of the active solution and the antimony precipitated as the trisulfide from a solution 2 *f* in hydrochloric acid and 1 *f* in hydrofluoric acid containing the tin in the tetravalent state. The precipitation was repeated three times, the antimony counted and the over-all yield determined by titration with potassium bromate. As a verification of the sulfide procedure, a separation of antimony by the distillation method of Scherrer[8] was performed on a duplicate sample and the results were in agreement.

Liquid samples of Sb^{125} were prepared for counting by dilution to a standard height in calibrated 18 × 150 mm. Pyrex tubes. The γ-ray associated with the decay of Sb^{125} was detected with a sodium iodide scintillation counter. The Te^{125m} which grows from Sb^{125} [9] was not detected in the above counting arrangement. Thus, when tellurium carrier was added to a solution of irradiated stannous chloride in 6 *f* hydrochloric acid which was six months old and the tellurium separated by the procedure of Novey,[10] no activity was found associated with the tellurium, and an antimony fraction separated by the sulfide procedure exhibited no growth in a period of two months following irradiation of the stannous chloride.

Procedure.—The metallic copper employed in the deposition of Sb^{125} consisted of spirals of #18 B&S gage wire formed on a quarter inch mandrel. The wires were so prepared that the first bend of the spiral portion occurred at the point such that the spiral had an apparent surface area of 5 sq. cm. When immersed in a solution up to the first bend, the stated area of copper was in contact with the solution. The straight ends of the wires were sealed into 6 × 1.25 mm. capillary tubing, about 15 cm. long, using jewelers' wax. In operation the spirals served both as reactants and stirrers. The copper was prepared for an experiment by washing the formed spiral for three 10-minute periods with carbon tetrachloride, drying and inserting in a glass capillary using forceps to manipulate the wire, and, just prior to use, immersing for three 10-minute periods in concentrated hydrochloric acid. Before inserting in a test solution the copper was dried with absorbent tissue. The copper was rotated in the test solution at about 100 r.p.m. The rate of rotation did not affect the rate of deposition of Sb^{125} over the range 1–150 r.p.m.

The test solutions were 0.21 *f* in tin, either 3 *f* or 6 *f* in hydrochloric acid, and contained 1000 to 1500 counts/minute of Sb^{125} in a total volume of 4 ml. The reaction tubes containing the test solutions were thermostated throughout the period of deposition and for at least 30 minutes prior to insertion of the copper. A separate spiral was immersed in a separate test solution for each experiment.

Upon removal from a test solution the copper was rinsed by three brief immersions in 3 *f* hydrochloric acid and placed in a counting tube. Three ml. of 6 *f* nitric acid was added and the dissolution of copper and antimony allowed to proceed for two minutes. The copper was rinsed with water, the washings added to the counting tube and the activity determined. Antimony, tin and indium carriers were added to the Sb^{125} activity and the antimony separated from the other carriers *via* sulfide precipitation. The constancy of the specific activity of the separated antimony served as a check on the radiochemical purity of the Sb^{125} activity.

The separation of Sb^{125} from copper was effected by adding 1 *f* sodium hydroxide to the nitric acid solution of the metals, with constant stirring, until the desired *p*H or sodium hydroxide formality was attained in the supernatant liquid. The antimony was retained in the supernatant liquid.

Results

The fraction of the total Sb^{125} deposited as a function of time from solutions of irradiated stannous chloride was determined at three temperatures. A typical deposition curve is shown in Fig. 1.

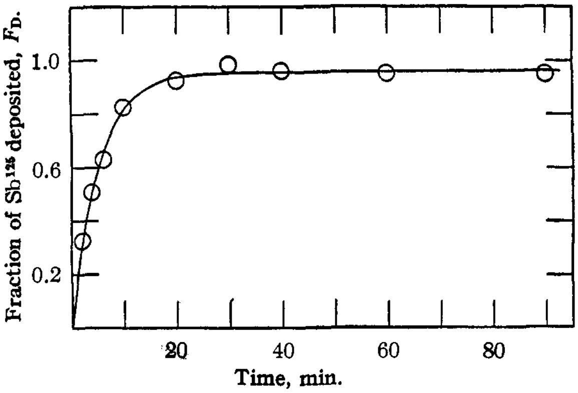


Fig. 1.—Rate of deposition of Sb^{125} at 31° from 6 *f* hydrochloric acid solutions of irradiated stannous chloride. The circles represent experimentally determined values of F_D. The curve was calculated from equation (1) using values of $k_1 = 0.185$ and $k_2 = 0.0074$.

The deposition was found to be consistent with the equation

$$F_D = \left[\frac{k_1}{k_1 + k_2}\right][1 - e^{-(k_1+k_2)t}] \qquad (1)$$

where k_1 and k_2 are constants whose values were determined empirically from curves fitted to the experimental data and F_D is the fraction of Sb^{125} deposited on the copper in time, *t*. Equation (1) was obtained by assuming that the rate of deposition on copper is proportional (k_1) to the amount of antimony in solution and the rate of dissolution is proportional (k_2) to the amount of antimony on the copper. The deposition of polonium on a gold cathode was found to obey an analogous equation.[11] In Table I are recorded values of k_1

---

[4] B. S. Evans, *Analyst*, **47**, 1 (1922).

[5] (a) W. B. Coleman and Co., Philadelphia, Pennsylvania, performed the spectrographic analyses. (b) The limit of detection was 0.004%.

[6] See ref. 5.

[7] Manufactured by Alconox Inc., Jersey City, N. J.

[8] J. A. Scherrer, *J. Research Natl. Bur. Standards*, **21**, 95 (1938).

[9] G. Friedlander, M. Goldhaber and G. Scharff-Goldhaber, *Phys. Rev.*, **74**, 981 (1948).

[10] C. D. Coryell and N. Sugarman, "Radiochemical Studies: The Fission Products," McGraw-Hill Book Co., Inc., New York, N. Y., 1951, pp. 1611–1612.

[11] F. Joliot, *J. chim. phys.*, **27**, 119 (1930).

and k_2 for various experimental conditions. The logarithms of the rate constants bear a linear relation to the reciprocal of the absolute temperature. The fraction deposited, F_D, was found to have the same value in a solution 3 *f* in both sodium chloride and hydrochloric acid as it had in a solution 6 *f* in hydrochloric acid under otherwise identical experimental conditions.

When solutions of irradiated stannous chloride in 3 *f* hydrochloric acid were oxidized with chlorine, F_D was 0.01 at 30 minutes at 25°. When the oxidized solution was reduced with sulfur dioxide at room temperature, F_D was 0.18 at 30 minutes, and when the reduction was continued at 95°, F_D was 0.08 at 30 minutes.

TABLE I

EMPIRICALLY DERIVED VALUES OF THE RATE CONSTANTS

Temp., °C.	Hydrochloric acid, *f*	k_1, min.$^{-1}$	k_2, min.$^{-1}$
20.25 ± 0.05	3	0.102	0.0145
	6	.102	.0040
25.15 ± 0.05	3	.135	.0169
	6	.135	.0056
30.95 ± 0.05	3	.185	.0204
	6	.185	.0074

Solutions of irradiated stannic chloride in 6 *f* hydrochloric acid were found to change in such a manner that the amount of antimony removable by copper in two-minute immersions was reduced by a factor of two for each three days of age of the solution. Because of the aging of the irradiated stannic chloride solutions reproducible deposition curves were not obtained. Aging of solutions of irradiated stannous chloride in 6 *f* hydrochloric acid did not occur until after three months.

In the separation of antimony from copper in nitric acid solution by the addition of sodium hydroxide, the amount of antimony retained in solution was found to increase with increasing *p*H from 33% at a *p*H of 10, to 74% when the supernatant liquid was 0.1 *f* in sodium hydroxide. Thus, the maximum over-all yield of Sb^{125} attainable from neutron irradiated stannous chloride under the experimental conditions investigated is 71%.

Acknowledgment.—The coöperation of Dr. Roderick W. Spence, Mr. James Sattizahn and Mr. Gordon Knobeloch of the Los Alamos Scientific Laboratory in the performance of the neutron irradiations is gratefully acknowledged.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NEW MEXICO
ALBUQUERQUE, NEW MEXICO

Thermodynamic Functions of 2,2,3-Trimethylbutane

BY DONALD W. SCOTT AND GUY WADDINGTON

RECEIVED DECEMBER 29, 1952

The thermodynamic functions of four methyl-substituted butanes, 2-methylbutane,[1] 2,2-dimethylbutane,[2] 2,3-dimethylbutane[1] and 2,2,3,3-tetramethylbutane,[3] have previously been calculated from spectroscopic and molecular-structure data by the methods of statistical mechanics. This note reports a similar calculation of the thermodynamic functions of 2,2,3-trimethylbutane, the remaining member of the group of compounds.

Calorimetric values of the vapor heat capacity and entropy of 2,2,3-trimethylbutane were available for the evaluation of certain necessary parameters. The values of the vapor heat capacity had been reported in a previous publication from this Laboratory.[4] The values of the entropy were computed as shown in Table I from data from several different sources.

TABLE I

MOLAL ENTROPY OF 2,2,3-TRIMETHYLBUTANE, CAL. DEG.$^{-1}$

T, °K.	298.16	313.84	353.96
Entropy of liquid[a]	69.88	72.54	79.12
Vaporization, $\Delta H_{vap.}/T$[b]	25.68	23.77	19.54
Gas imperfection[c]	0.06	0.08	0.16
Compression, $R \ln (p/760)$[d]	−3.98	−2.70	0.00
Entropy (±0.30) of ideal gas at 1 atm.	91.64	93.69	98.82

[a] Unpublished results from this Laboratory. [b] Heat of vaporization at 298.16°K., N. S. Osborne and D. C. Ginnings, *J. Research Natl. Bur. Standards*, **39**, 453 (1947); at the other two temperatures, ref. 4. [c] Calculated from the equation for the second virial coefficient, $B = (PV - RT)/P = -643 - 22.98 \exp (1200/T)$ cc. mole^{-1}, based on data of ref. 4. [d] Vapor pressure equation from American Petroleum Institute Research Project 44 at Carnegie Institute of Technology, Selected Values of Properties of Hydrocarbons, Table No. 2k, dated Dec. 31, 1948.

The thermodynamic functions were calculated by means of the usual rigid rotator, harmonic oscillator, independent internal rotator approximation. The moments and reduced moments of inertia were computed by the methods of Kilpatrick and Pitzer.[5] All bond angles were assumed to be tetrahedral and the bond distances were taken to have their normal values (C–C, 1.54 Å., C–H, 1.09 Å.) with one exception. The exception is the central C–C bond distance, which is expected to be longer than normal on account of steric repulsion between the isopropyl and tertiary butyl groups. The estimated value that was used for this distance, 1.56 Å., is midway between the normal value and that in 2,2,3,3-tetramethylbutane, 1.58 Å.[6] The product of the three principal moments of inertia was calculated to be 4.638×10^{-113} g.^{3} cm.^{6} The diagonal elements of the reduced internal rotational kinetic energy matrix were 68.50×10^{-40} for the skeletal rotation, 5.239×10^{-40} for one methyl rotation, and 5.221×10^{-40} g. cm.^{2} for the other four methyl rotations. The off-diagonal elements were small enough that these diagonal elements could be used as the reduced moments of inertia. An average value of 5.225×10^{-40} g. cm.^{2} was used for all five methyl rotations.

---

[1] D. W. Scott, J. P. McCullough, K. D. Williamson and Guy Waddington, THIS JOURNAL, **73**, 1707 (1951).

[2] J. E. Kilpatrick and K. S. Pitzer, *ibid.*, **68**, 1066 (1946).

[3] D. W. Scott, D. R. Douslin, M. E. Gross, G. D. Oliver and H. M. Huffman, *ibid.*, **74**, 883 (1952).

[4] G. Waddington, S. S. Todd and H. M. Huffman, *ibid.*, **69**, 22 (1947).

[5] J. E. Kilpatrick and K. S. Pitzer, *J. Chem. Phys.*, **17**, 1064 (1949).

[6] S. H. Bauer and J. Y. Beach, THIS JOURNAL, **64**, 1142 (1942).

Examination of the Raman and infrared data[7-11] for 2,2,3-trimethylbutane showed that in the region below 1350 cm.$^{-1}$ there were 22 observed frequencies that could reasonably be assigned as fundamentals. The 8 skeletal bending, 6 C–C stretching, 10 CH_3 rocking and 2 C–H wagging modes, 26 in all, are expected to have frequencies in this region. Four frequencies are therefore unobserved. Regularities in the frequencies of related molecules suggest that one of these four is a skeletal bending frequency, probably the very lowest, and that the other three are in the upper half of the range, *i.e.*, between 675 and 1350 cm.$^{-1}$. The parameters that had to be evaluated from the calorimetric data included these four unobserved frequencies in addition to the heights of the potential barriers hindering internal rotation. It was practical to evaluate at most three empirical parameters from the available calorimetric data. These parameters were selected to be: (a) the average value of the heights of the barriers hindering internal rotation, (b) the value of the unobserved skeletal bending frequency and (c) the average value of the three unobserved higher frequencies. The validity of assuming the same barrier heights for all internal rotations, as has previously been done in the cases of 2,2-dimethylbutane and 2,2,3,3-tetramethylbutane, is discussed in refs. 2 and 3. A satisfactory fit to the calorimetric data was obtained with the following values of the parameters: (a) 4200 cal. mole^{-1} for the average barrier height, (b) 232 cm.$^{-1}$ for the skeletal bending frequency and (c) 1330 cm.$^{-1}$ for the average value of the three higher frequencies. Average or conventional values were used for the CH_3 bending and C–H stretching frequencies, which are not all resolved in the observed spectra. The complete set of vibrational frequencies that was used for the thermodynamic calculations is as follows (the empirical values are italicized): *232*, 261, 298, 362, 392, 442, 462, 524, 686, 832, 923,[12] 957, 1000, 1011, 1027, 1084, 1107, 1160, 1209, 1224, 1252, 1320, *1330* (*3*), 1334, 1375 (5), 1460 (10) and 2950 (16) cm.$^{-1}$.

The satisfactory fit obtained with the calorimetric data may be judged by the following comparison of observed and calculated values. The units of $S°$ and C_p° are cal. deg.$^{-1}$ mole^{-1}.

T, °K.	298.16	313.84	353.96
$S°$, obsd.	91.64	93.69	98.82
$S°$, calcd.	91.60	93.68	98.91

T, °K.	328.80	348.85	369.20	400.40	434.30	461.80
$C°_p$, obsd.	42.74	45.09	47.39	50.92	54.54	57.36
$C°_p$, calcd.	42.81	45.09	47.40	50.87	54.53	57.36

TABLE II

MOLAL THERMODYNAMIC FUNCTIONS OF 2,2,3-TRIMETHYLBUTANE

T, °K.	$-(F° - H°_0)/T$, cal. deg.$^{-1}$	$(H° - H°_0)/T$, cal. deg.$^{-1}$	$H° - H°_0$, kcal.	$S°$, cal. deg.$^{-1}$	$C°_p$, cal. deg.$^{-1}$
273.16	67.21	21.05	5.751	88.26	36.52
298.16	69.12	22.48	6.703	91.60	39.33
300	69.26	22.58	6.776	91.85	39.54
400	76.56	28.25	11.30	104.8	50.83
500	83.45	33.81	16.91	117.3	61.04
600	90.07	39.10	23.46	129.2	69.61
700	96.47	43.97	30.78	140.4	76.74
800	102.7	48.44	38.76	151.1	82.73
900	108.6	52.54	47.28	161.1	87.88
1000	114.3	56.30	56.30	170.6	92.32
1100	119.9	59.75	65.72	179.6	96.16
1200	125.2	62.92	75.50	188.1	99.48
1300	130.4	65.83	85.58	196.2	102.4
1400	135.4	68.52	95.94	203.9	104.8
1500	140.2	71.03	106.5	211.2	107.0

The calculated values of the functions $(F° - H_0^\circ)/T$, $(H° - H_0^\circ)/T$, $H° - H_0^\circ$, $S°$ and C_p° for selected temperatures up to 1500°K. are listed in Table II. For reasons of internal consistency, all values are given to four digits, although in some places in the table the retention of the last digit is not justified by the accuracy of the molecular-structure parameters used in the calculations or by the reliability of the approximations employed.

CONTRIBUTION NO. 32, THERMODYNAMICS LABORATORY
PETROLEUM EXPERIMENT STATION, BUREAU OF MINES
BARTLESVILLE, OKLAHOMA

---

(7) G. B. Bonino and R. Manzoni-Ansidei, *Proc. Indian Acad. Sci.*, **8A**, 405 (1938).

(8) E. J. Rosenbaum, A. V. Grosse and H. F. Jacobson, THIS JOURNAL, **61**, 689 (1939).

(9) M. R. Fenske, W. G. Braun, R. V. Wiegnad, D. Quiggle, R. H. McCormick and D. H. Rank, *Anal. Chem.*, **19**, 700 (1947).

(10) P. A. Bazulin, M. F. Bokshteĭn, A. L. Liberman, M. Yu. Lukina, E. I. Margolis, O. P. Solovava and B. A. Kazanskiĭ, *Bull. acad. sci. U. R. S. S., Classe sci. chim.*, 198 (1943).

(11) American Petroleum Institute Research Project 44 at Carnegie Institute of Technology, Catalog of Infrared Spectral Data, Serial No. 249, 443, 573, 587, 653 and 654.

(12) Fermi resonance of this frequency with the overtone, 2 × 462 = 924, accounts for the doublet, 919–927 cm.$^{-1}$, in the observed spectra.

The Free Energies and Entropies of Hydrogen, Chlorine and Hydrogen Chloride from Spectroscopic Data[1]

BY R. H. SHERMAN AND W. F. GIAUQUE

RECEIVED NOVEMBER 14, 1952

Recent work in this Laboratory has required the use of the free energy function for hydrogen chloride and it became apparent that no correct table of this function, in terms of recent values of the "natural" constants concerned, was available in the literature.

We have used the natural constants given by Du Mond and Cohen[2] and recently recommended by Rossini, Gucker, Johnston, Pauling and Vinal[3] to correct the $(F° - H_0^\circ)/T$ functions for hydrogen, chlorine and hydrogen chloride.

Hydrogen Chloride.—The free energy function for hydrogen cyloride was tabulated by Giauque and Overstreet.[4] It has recently been retabulated in Tables of the National Bureau of Standards[5] in terms of natural constants not much different than those of the Du Mond and Cohen (1951). We had expected to be able to use these values but it be-

---

[1] This work was supported in part by the Office of Naval Research, United States Navy.

[2] J. W. M. Du Mond and E. R. Cohen, *Phys. Rev.*, **82**, 555 (1951).

[3] F. D. Rossini, F. T. Gucker, Jr., H. L. Johnston, L. Pauling, and G. W. Vinal, THIS JOURNAL, **74**, 2699 (1952).

[4] W. F. Giauque and R. Overstreet, *ibid.*, **54**, 1731 (1932).

[5] Selected Values of Chemical Thermodynamic Properties, Nat. Bur. of Stds. (1948).

came evident that they were not correct. We do not know if the table of Giauque and Overstreet[4] was used as a basis for the recalculation but in any case it appears that the values are approximately those which would result if the presence of hydrogen chloride resulting from chlorine mass 37 had been overlooked. The corrections which should be applied to the table of Giauque and Overstreet are given in Table I. The correction can be applied to any of the isotopic species or their mixture. The effect of deuterium is not appreciable.

Chlorine.—Correction of the tables of Giauque and Overstreet for chlorine to the new natural constants gave results which differed from the retabulation in the Bureau of Standards Tables[5] by appreciable amounts which increased with temperature. No reason for this is evident since no revision of the molecular data has appeared. The corrections found are given in Table I.

TABLE I

CORRECTIONS TO BE ADDED TO TABLES OF $(F^0 - H_0^0)/T$ REFERRED TO ABOVE

Note: Values in tables are for $-(F^0 - H_0^0)/T$; thus the additive correction reduces the numerical values

Correction cal. deg.$^{-1}$ mole^{-1}	H_2	Cl_2	HCl
0.018	298–450°K.	250–400°K.	250–700°K.
.019	500–1300	450–750	750–1600
.020	1400–2200	800–1400	1700–2700
.021	2300–2700	1500–2400	2800–3000
.022	2800–3700	2500–2900	
.023	3800–4300	3000	
.024	4400–5000		

Hydrogen.—The $(F^0 - H_0^0)/T$ function was tabulated to 5000°K. by Giauque.[6] Davis and Johnston[7] called attention to errors at 3000 and 4000°K. in the calculations of Giauque and showed that values used for interpolation above 2000°K. were affected. They published a corrected table above 2000°K. The above calculations on hydrogen were made in terms of natural constants given in the "I.C.T."[8] Davis and Johnston had sent details from their calculation sheets to Giauque and comparison with his calculation sheets disclosed the two basic arithmetical errors involved in Giauque's table. Thus the two pieces of work are now in agreement with respect to the details which determine the free energy function.

Wagman, Kilpatrick, Taylor, Pitzer and Rossini[9] have corrected the data of Giauque and of Davis and Johnston to constants available in 1945. They do not differ much from the present constants but as there is a small effect we have included corrections in Table I which should be applied to the table of Giauque up to 2000°K. and to the table of Davis and Johnston in the range 2000–5000°K. In addition the amount $R \ln 4 = 2.754$ cal. deg.$^{-1}$ mole^{-1} should be added to the absolute values of $(F^0 - H_0^0)/T$ given by Giauque and by Davis and Johnston to eliminate the contribution of nuclear spin as is customary. The value 2.754 is in terms of "I.C.T." constants to correspond to the original table. Wagman, *et al.*,[9] have also corrected the values of $(H^0 - H_0^0)/T$ given by Davis and Johnston. The correction to the new natural constants is trivial amounting to a maximum of -0.0002 at 5000°K. Thus corrected values of the entropy of hydrogen can be obtained by combining the values of $(F^0 - H_0^0)/T$ resulting from Table I with the $(H^0 - H_0^0)/T$ values of Wagman, *et al.* The corrected values of C_p for hydrogen given by Wagman, *et al.*, are also not changed by the newer constants.

The values of the entropies at a fugacity of one atmosphere and 298.16°K. for H_2, Cl_2 and HCl are 31.208, 53.290 and 44.645 cal. deg.$^{-1}$ mole^{-1}, respectively.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA

---

[6] W. F. Giauque, THIS JOURNAL, **52**, 4816 (1930).

[7] C. O. Davis and H. L. Johnston, *ibid.*, **56**, 1045 (1934).

[8] "International Critical Tables," McGraw-Hill Book Co., Inc., New York, N. Y., 1926.

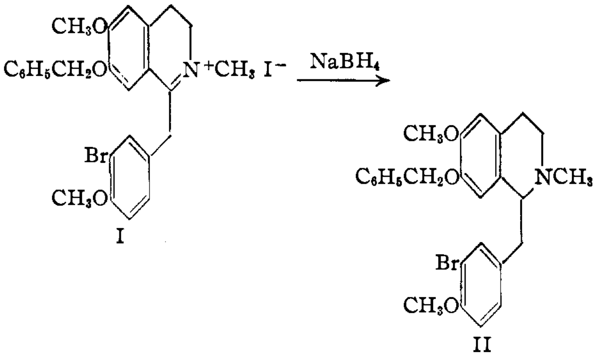
[9] D. D. Wagman, J. E. Kilpatrick, W. J. Taylor, K. S. Pitzer, and F. D. Rossini, *J. Res. Nat. Bur. Std.*, **34**, 143 (1945).

Sodium Borohydride Reduction of N-Alkyl-3,4-dihydroisoquinolinium Iodides[1]

BY WILSON M. WHALEY AND CHARLES N. ROBINSON

RECEIVED DECEMBER 22, 1952

The reduction of isoquinolinium salts with lithium aluminum hydride to the corresponding N-alkyl-1,2-dihydro- compounds[2] and of pyridinium salts with potassium borohydride to the N-alkyl-1,2-dihydro- and 1,2,3,4-tetrahydro- compounds[3,4] has been reported in the literature. Since the reduction of N-alkyl-3,4-dihydroisoquinolinium iodides containing other functional groups which are also reduced by lithium aluminum hydride is often of considerable importance in the synthesis of isoquinoline alkaloids, it seemed desirable to find a more specific reagent. Sodium borohydride is such a reagent. The present paper shows that N-alkyl-3,4-dihydroisoquinolinium iodides can also be reduced in very good yields to the corresponding N-alkyl-1,2,3,4-tetrahydroisoquinolines. Chaikin and Brown[5] have reported that, although this reagent reduces aldehydes, ketones and acid chlorides



---

[1] The authors wish to express their appreciation to the Tennessee Eastman Corporation for a Grant-in aid to the University of Tennessee which made this work possible.

[2] H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 960 (1949).

[3] J. J. Panouse, *Compt. rend.*, **233**, 260 (1951); *C. A.*, **46**, 2542 (1952).

[4] J. J. Panouse, *Compt. rend.*, **233**, 1200 (1951); *C. A.*, **46**, 6643 (1952).

[5] S. W. Chaikin and W. G. Brown, THIS JOURNAL, **71**, 122 (1949).

in good yields, its effect on acids, esters,[6] anhydrides and nitriles is negligible; they have also reduced the carbonyl function in the presence of side-chain halogens and aromatic nitro groups.

Experimental[7]

Reduction of 2-Methyl-6,7-dimethoxy-3,4-dihydroisoquinolinium Iodide to 2-Methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline.—To a solution of 10 g. (0.03 mole) of the methiodide in 200 ml. of absolute methanol was added 4 g. (0.105 mole) of solid sodium borohydride in small portions. The reaction was exothermic, hydrogen was evolved, and a clear, colorless solution was obtained at the end of the addition. It was evaporated to 25 ml., poured into 300 ml. of 2% sodium hydroxide, extracted with ether, and the combined ethereal extracts dried over anhydrous maguesium sulfate. The solution was then filtered and the ether removed by distillation to leave 5.5 g. (89% of the theoretical amount) of a light-yellow oil which quickly hardened to a white solid. This crude product melted at 55–57° and, on dissolving in a hot solution of picric acid in absolute ethanol and allowing to cool, formed a picrate (needles) of m.p. 157–158°.[8] Further recrystallization did not raise this melting point.

Reduction of 1-(3-Bromo-4-methoxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-3,4-dihydroisoquinolinium Iodide (I) to 1-(3-Bromo-4-methoxybenzyl)-2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (II).—To a slurry of 0.5 g. (0.0133 mole) of sodium borohydride in 85 ml. of absolute methanol was added, as quickly as foaming would allow, 0.5 g. (0.00082 mole) of the methiodide. The clear, colorless solution was then concentrated to 15 ml. and poured into 300 ml. of 1% sodium hydroxide. It was extracted three times with ether, the ether was dried over anhydrous magnesium sulfate and filtered, and hydrogen chloride gas was passed into the filtrate. A light-yellow oil separated. The ether was removed on the steam-cone and 30 ml. of benzene was added to the residual oil. On evaporation white crystals separated slowly. The last of the benzene was removed in a stream of dry air to give 0.35 g. (82% of the theoretical amount) of the hydrochloride. An analytical sample prepared by recrystallization from 2-propanol consisted of white needles which melted first at 104–105°, resolidified at 127–130°, and remelted at 202–204°. The sample was dried *in vacuo* at 64°.

Anal. Calcd. for $C_{26}H_{29}O_3NBrCl$: C, 60.17; H, 5.63; N, 2.70. Found: C, 60.01; H, 5.74; N, 2.83.

The first procedure outlined above, which involves the solution of the methiodide in the solvent and subsequent addition of borohydride, is preferable, since it allows the use of a much smaller molar ratio of the reducing agent. In the second procedure a large excess of sodium borohydride must be used in order to get all of the methiodide in before the heat of reaction causes complete destruction of the hydride by the solvent.

---

[6] M. L. Wolfrom and K. Anno, THIS JOURNAL, **74**, 5583 (1952), have reported that the esters and sodium salts of acids of sugars are reduced to alcohols.

[7] All melting points were obtained on a calibrated apparatus. Analysis by Galbraith Laboratories, Knoxville, Tenn.

[8] F. L. Pyman, *J. Chem. Soc.*, **95**, 1274 (1909), reports a melting point of 159–160° (cor.).

DEPARTMENT OF CHEMISTRY
THE UNIVERSITY OF TENNESSEE
KNOXVILLE, TENNESSEE

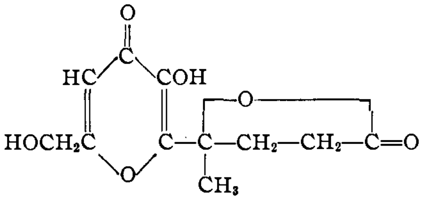
The Reaction of Kojic Acid with Ethyl Levulinate

BY L. L. WOODS[1]

RECEIVED DECEMBER 6, 1952

During the course of investigating the reactivity of kojic acid, many attempts have been made by the author to condense the pyrone with ketones, all unsuccessful except the one described in this report.

The compound produced as a result of the condensation of kojic acid with ethyl levulinate in mildly alkaline media is shown to be 3-(2-hydroxymethyl-5-hydroxy-4-pyrone-6)-3-valerolactone (I).



I

The derivatives of this compound were nearly all as expected; however, the reaction with 2,4-dinitrophenylhydrazine was unusual. Repeated experiments reveal that the compound reacts with two molecules of the hydrazine to form an addition compound of the pyridazinone.

Experimental[2]

Four grams of sodium bicarbonate, 28.4 g. of kojic acid, 28.8 g. of ethyl levulinate and 100 ml. of absolute ethanol were mixed together and refluxed vigorously for about 20 hours. The mixture was then acidified with hydrochloric acid, treated with a small amount of charcoal, and filtered while hot. The solution slowly deposited soft brown crystals as the alcohol was removed by surface evaporation, yield 39 g. Two recrystallizations from hot benzene, in which the compound is only fairly soluble, gave light tan crystals, m.p. 153.5°.

Anal. Calcd. for $C_{11}H_{12}O_6$: C, 55.00; H, 4.58. Found: C, 54.78; H, 4.16.

The acetylated derivative was made in the usual manner using acetic anhydride; the excess anhydride was decomposed with water and the ester extracted with benzene. The ester was recrystallized twice from benzene and once from a 1–4 mixture of benzene and ligroin. The compound produced rosettes of white prisms, m.p. 98–100°.

Anal. Calcd. for $C_{17}H_{20}O_{10}$: C, 53.12; H, 5.20. Found: C, 53.35; H, 5.18.

Treating compound (I) with an excess of thionyl chloride followed by recrystallization from hot water and then from absolute ethanol gave the expected 2-chloromethyl derivative of (I) which easily sublimed to give white needles, m.p. 167–169°. The compound gave a red color with dilute ferric chloride solutions.

Anal. Calcd. for $C_{11}H_{11}ClO_5$: C, 51.06; H, 4.25. Found: C, 51.30; H, 4.09.

The *p*-bromophenacyl derivative was prepared from (I) and *p*-bromophenacyl bromide in essentially the manner as before,[3] but in this instance 1.5 g. of the phenacyl halide was used for each gram of (I).

However, the bisphenacyl derivative was formed. The compound was of a very light texture resembling white wool after having been recrystallized three times from ethanol, m.p. 180°. It had no acidic character and gave negative results with dilute solutions of ferric chloride.

Anal. Calcd. for $C_{27}H_{24}Br_2O_9$: C, 49.69; H, 3.68. Found: C, 49.87, 49.83; H, 3.32, 3.26.

When equal weights of (I) and 2,4-dinitrophenylhydrazine were refluxed for 15 minutes in ethanol, an orange compound was obtained upon cooling and filtering. The substance was purified by washing with water followed by two recrystallizations from ethanol, an orange-yellow powder was obtained, m.p. 100–102°.

Anal. Calcd. for $C_{17}H_{16}N_4O_9 \cdot C_6H_6N_4O_4$: N, 18.12. Found: N, 18.05.

TEXAS SOUTHERN UNIVERSITY
HOUSTON, TEXAS

---

[1] The author wishes to acknowledge, with thanks, the financial support of the Research Corporation in this project. The kojic acid used in these experiments was furnished by the Corn Products Company.

[2] Analyses were performed by Dr. Carl Tiedcke, Teaneck, N. J., and Clark Microchemical Laboratory, Urbana, Ill. All melting points were determined on a Fisher–Johns melting point assembly.

[3] L. L. Woods, THIS JOURNAL, **74**, 3959 (1952).

Complex Metal–Nicotine Compounds

By Claude R. Smith

Received July 30, 1952

This work is a continuation of the efforts of this Laboratory to prepare a large number of derivatives and compounds of nicotine.[1,2] In one previous publication[3] 25 complex salts of nicotine, some involving acid dyes, were listed but not described. In another[4] the author described the preparation of 11 double sulfates. The present paper covers the preparation of 76 complex metal–nicotine compounds of two types—double salts and nicotinammino compounds.

Table I

Thiocyanates

No.	Compound[a]	Nicotine, % Calcd.	Nicotine, % Found	-CNS, % Calcd.	-CNS, % Found	Crystals
1	$ZnA_2 \cdot RN_2 \cdot HA$	40.2	40.2	43.2	42.9	Dimorphic, irregular or prisms
2	$CdA_2 \cdot 2(RN_2 \cdot HA)$	48.3	48.3	34.6	34.6	Irregular leaves
3	$CdA_2 \cdot 2RN_2$	58.6	59.7	21.0	21.3	Prisms (tricl.), often in rosettes
4	$CoA_2 \cdot 2(RN_2 \cdot HA)$	52.5	52.5	37.6	37.7	Red prisms (tricl.)
5	$NiA_2 \cdot 2(RN_2 \cdot HA)$	52.5	52.4	37.6	37.1	Blue-green prisms (tricl.)
6	$NiA_2 \cdot 3RN_2$	73.5	72.3	17.6	17.2	Brown, irregular
7	$MnA_2 \cdot 2(RN_2 \cdot HA)$	52.8	52.1	37.9	36.9	Prisms
8	$FeA_2 \cdot 2(RN_2 \cdot HA)$	52.8	52.4	37.8	37.7	Yellow prisms (tricl.)
9	$3AgA \cdot RN_2 \cdot HA$	22.5	22.6	(8.0)[b]	(8.0)[b]	Pink prismatic needles, m.p. 130–131°
10[c]	$CuA_2 \cdot 2(RN_2 \cdot HA)$	52.1	50.0	..	..	Irregular green
11[c]	$CuA \cdot RN_2 \cdot HA$	47.3	47.2	..	..	Irregular yellow
12[c]	$CuA \cdot RN_2$	57.1	55.6	..	..	Rod-like prisms
13[d]	$CrA_3 \cdot 1.3(RN_2) \cdot 4H_2O$	41.4	40.8	34.2	34.0	Purple, irregular
				Piperidine, %		
14	$CoA_2 \cdot 2(C_5H_{11}N \cdot HA)$	36.7	37.2	50.1	50.0	Deep-blue prisms

[a] A = -CNS; $RN_2 = C_{10}H_{14}N_2$. [b] Refers to -CNS combined with nicotine, determined by warming the compound in water acidified with nitric acid, cooling, and titrating. [c] No. 10, 11 and 12: calcd., Cu 10.2, 18.5 and 22.9, respectively; found, Cu, 10.9, 18.4 and 22.5, respectively. [d] Calcd., Cr, 10.2; found, Cr, 9.9.

Table II

Salicylates

No.	Compound[a]	Nicotine, % Calcd.	Nicotine, % Found	Salicylic acid, % Calcd.	Salicylic acid, % Found	Crystals
1	$CuA_2 \cdot 2(RN_2 \cdot HA)$	34.6	34.6	..	..	Purple prisms
2	$CuA_2 \cdot 2(RN_2 \cdot HA) \cdot H_2O$	34.3	34.3	56.7	57.1	Blue prisms
3	$CoA_2 \cdot 2(RN_2 \cdot HA) \cdot 2H_2O$	33.5	33.6	56.8	56.2	Pink plates, irregular
4	$MnA_2 \cdot 2(RN_2 \cdot HA) \cdot 2H_2O$	33.6	33.6	57.2	56.8	Irregular
5	$CdA_2 \cdot 2(RN_2 \cdot HA) \cdot 2H_2O$	31.7	31.5	54.4	54.4	Irregular
6	$ZnA_2 \cdot 2(RN_2 \cdot HA) \cdot 2H_2O$	33.3	33.4	56.7	56.4	Irregular
7	$NiA_2 \cdot 2(RN_2 \cdot HA) \cdot 2H_2O$	33.4	33.1	56.8	56.4	Irregular

[a] $A = -OOC(C_6H_4)OH$-*o*; $RN_2 = C_{10}H_{14}N_2$.

Table III

Picrates

No.	Compound[a]	Nicotine, % Calcd.	Nicotine, % Found	Picric acid, % Calcd.	Picric acid, % Found	H_2O, % Calcd.	Loss at 110°, % 15 min.	Loss at 110°, % 30 min.
1	$CoA_2 \cdot 2RN_2 \cdot 5H_2O$	34.9	34.9	48.9	48.3	9.7	9.8	9.8
2	$NiA_2 \cdot 2RN_2 \cdot 6H_2O$	34.3	34.1	48.4	48.9	11.4	11.4	11.4
3	$CdA_2 \cdot 2RN_2 \cdot 6H_2O$	32.4	32.4	45.8	46.1	10.8	7.6	7.9
4	$MgA_2 \cdot 2RN_2 \cdot 6H_2O$	35.5	35.4	50.2	51.1	11.8	11.5	12.7
5	$MnA_2 \cdot 2RN_2 \cdot 4H_2O$	35.7	35.7	50.5	51.1	7.3	7.3	7.9
6	$ZnA_2 \cdot 2RN_2$	38.3	38.3	54.2	54.7	..	..	..
7	$AlA_3 \cdot 3RN_2$	40.6	40.5	57.4	57.8	..	..	..
8	$FeA_3 \cdot 3RN_2$	39.7	39.7	56.0	56.2	..	..	..
9	$AgA \cdot RN_2$	32.6	33.3	46.0	45.8	..	..	..
10[b]	$CuA_2 \cdot 2(RN_2 \cdot HA)$	24.9	25.2	..	..	..	..	..
11	$ZnA_2 \cdot 2(RN_2 \cdot HA)$	24.8	24.3			..	..	..
12[c]	$AgA \cdot 2(RN_2 \cdot HA)$	29.0	29.1			..	..	..

[a] $A = -OC_6H_2(NO_2)_3$; $RN_2 = C_{10}H_{14}N_2$. [b] Calcd., Cu, 4.9; found, Cu, 5.1. [c] Calcd., Ag, 9.6; found, Ag, 9.0.

Double salts result from the combination of the metal and the nicotine salts of the same selected acid. Ammino compounds result when nicotine

---

[1] C. F. Woodward, A. Eisner and P. G. Haines, This Journal, **66**, 911 (1944); P. G. Haines, A. Eisner and C. F. Woodward, *ibid.*, **67**, 1258 (1945); P. G. Haines and A. Eisner, *ibid.*, **72**, 4618, 1719 (1950).

[2] C. F. Woodward, C. O. Budgett and J. J. Willaman, *Ind. Eng. Chem.*, **36**, 540, 544 (1944); U. S. Dept. Agric. E-725 (processed) (1947); *Arch. Biochem.*, **29**, 241 (1950).

[3] C. R. Smith, U. S. Dept. Agric. E-646 (processed) (1945).

[4] C. R. Smith, This Journal, **71**, 2844 (1949).

TABLE IV

o-BENZOYLBENZOATES

No.	Compound[a]	Nicotine, % Calcd.	Nicotine, % Found	HA, % Calcd.	HA, % Found	H_2O, % Calcd.	Loss at 110°, % 15 min.	Loss at 110°, % 30 min.
1	$CoA_2 \cdot 2RN_2 \cdot 6H_2O$	34.5	34.4	48.0	48.5	11.4	9.9	10.6
2	$NiA_2 \cdot 2RN_2 \cdot 6H_2O$	34.5	34.3	48.1	47.8	11.4	10.1	10.1
3	$MnA_2 \cdot 2RN_2 \cdot 6H_2O$	34.6	34.5	48.2	48.6	11.5	9.7	11.0
4	$CdA_2 \cdot 2RN_2 \cdot 6H_2O$	32.5	32.6	45.4	45.2	10.8	10.0	10.6
5	$ZnA_2 \cdot 2RN_2 \cdot 6H_2O$	34.2	34.0	47.7	48.3	11.4	8.8	9.9
6	$MgA_2 \cdot 2RN_2 \cdot 6H_2O$	35.8	35.9	49.9	49.8	11.9	11.8	13.6
7	$FeA_2 \cdot 2RN_2 \cdot 6H_2O$	34.6	34.4	48.2	48.4	11.5	9.4	9.9
8[b]	$CuA_2 \cdot 2RN_2 \cdot 5H_2O$	35.0	35.0	..	..	9.7	9.3	9.4
9[b]	$CuA_2 \cdot 2RN_2 \cdot 2C_2H_5OH$	34.8	34.8	..	..	(9.9)[c]	9.6	10.5
10[d]	$(AgA)_2 \cdot RN_2$	19.6	20.6	..	..	..	..	..
11[b]	$CuA_2 \cdot 2(RN_2 \cdot HA)$	25.0	24.2	..	..	..	..	..

[a] A = $OOC \cdot C_6H_4(OC \cdot C_6H_5)$-*o*; $RN_2 = C_{10}H_{14}N_2$. [b] No. 8, 9 and 12: calcd., Cu, 6.8, 6.8 and 4.8, respectively; found, Cu. 6.8, 6.8 and 4.6. respectively. [c] Ethanol. [d] Calcd., Ag, 26.1; found, Ag, 26.0.

TABLE V

p-NITROBENZOATES

No.	Compound[a]	Nicotine, % Calcd.	Nicotine, % Found	HA, % Calcd.	HA, % Found	H_2O, % Calcd.	Loss at 110°, % 15 min.	Loss at 110°, % 30 min.
1	$CoA_2 \cdot 2RN_2 \cdot 4H_2O$	41.1	40.7	42.4	42.6	9.1	8.2	8.2
2	$CdA_2 \cdot 2RN_2 \cdot 4H_2O$	38.5	38.3	39.7	39.7	8.6	9.1	9.3
3	$MnA_2 \cdot 2RN_2 \cdot 4H_2O$	41.4	40.9	42.6	42.9	9.2	9.1	10.9
4	$CuA_2 \cdot 2RN_2 \cdot 2H_2O$	42.8	42.9	44.2	44.5	4.8	4.8	4.8
5	$NiA_2 \cdot 2RN_2 \cdot 2H_2O$	43.1	42.0	44.5	44.8	4.7	4.1	4.1
6[b]	$CuA_2 \cdot 2RN_2 \cdot 4HA$	23.4	23.3	..	..	...	...	

[a] A = $-OCC \cdot C_6H_4 \cdot NO$-*p*; $RN_2 = C_{10}H_{14}N_2$. [b] No. 7: calcd., Cu, 4.6; found, Cu, 4.6.

TABLE VI

DIBASIC ACIDS

No.	Compound[a]	Base, % Calcd.	Base, % Found	Copper, % Calcd.	Copper, % Found	Crystals
1[b]	$CuC_2O_4 \cdot Na_2C_2O_4 \cdot 2H_2O$	..	..	19.8	19.6	Blue prismatic needles
2	$CuC_2O_4 \cdot RN_2 \cdot H_2C_2O_4$	40.1	39.3	15.7	15.7	Blue prisms (moncl.)
3	$CuC_2O_4 \cdot RN_2 \cdot H_2C_2O_4 \cdot H_2O$	38.4	38.7	14.9	14.8	Prisms, round ends
4[c]	$2CoC_2O_4 \cdot RN_2 \cdot H_2C_2O_4 \cdot 5H_2O$	25.5	24.7	..	..	......
5[d]	$2ZnC_2O_4 \cdot RN_2 \cdot H_2C_2O_4 \cdot 5H_2O$	25.5	25.0	..	..	......
6	$CuPhth \cdot RN_2 \cdot H_2Phth \cdot H_2O$	28.3	28.2	11.1	11.1	Green, irreg.
7	$CuPhth \cdot 2HN_3$	13.0	12.9	24.3	24.2	Blue prisms (tetrag.)
8	$CuCr_2O_7 \cdot 2RN_2 \cdot H_2Cr_2O_7$	39.5	39.3	7.7	7.6	Brown to orange, irreg.
9	$CdCr_2O_7 \cdot 2RN_2 \cdot H_2Cr_2O_7$	37.2	36.0	..	..	Salmon to brown
10	$Cu(OOC \cdot CH_2)_2 \cdot RN_2$	47.4	42.9	19.6	18.0	Green cubes
11	$Cu(OOC \cdot CH_2)_2 \cdot 2NH_3 \cdot 2H_2O$	13.6	13.9	25.4	25.3	Purple prisms (tricl.)
12	$Cu(OOC \cdot CH_2)_2 \cdot 2NH_3$	15.9	15.5	29.7	29.3	Blue prisms (tetrag.)
13	$Cu(OOC{=}CH)_2 \cdot 2RN_2 \cdot 10H_2O$	47.5	47.3	9.3	9.3	Blue prisms (tricl.)
14[e]	$ZnC_2O_4 \cdot NH_3 \cdot 3H_2O$	7.6	7.2	..	..	White prisms

[a] $RN_2 = C_{10}H_{14}N_2$; Phth = $-(OOC)_2C_6H_4$-*o*. [b] Calcd.: $H_2C_2O_4$, 78.4; H_2O, 24.0. Found: $H_2C_2O_4$, 79.0; H_2O loss at 110°, 22.6. [c] Calcd.: $H_2C_2O_4$, 42.5; H_2O, 14.1. Found: $H_2C_2O_4$, 42.8; H_2O loss at 110°, 13.7. [d] Calcd.: $H_2C_2O_4$, 42.5; H_2O, 14.1. Found: $H_2C_2O_4$, 42.5; H_2O loss at 110°, 14.0. [e] Calcd.: $H_2C_2O_4$, 39.2; H_2O, 24.0. Found: $H_2C_2O_4$, 39.0; H_2O loss at 110°, 22.6.

alkaloid reacts with a metal salt of the selected acid. The metals which made double salts were Ag, Cd, Co, Cu (-ous and -ic), Fe (-ous and -ic), Mn (-ous) and Ni (-ous). All of these, plus Al, Cr and Mg, formed ammino compounds. The acids successfully incorporated into double salts were benzoic, *o*-benzoylbenzoic, *p*-nitrobenzoic, chromic, hydrocyanic, oxalic, phthalic, picric, salicylic and thiocyanic. Those in ammino compounds were benzoic, *o*-benzoylbenzoic, *p*-nitrobenzoic, ferrocyanic, fumaric (but not maleic), hydrobromic, hydriodic, α-naphthoic, phthalic, picric, succinic and thiocyanic.

Univalent cations combined with univalent anions added only 1 mole of base, forming a mononicotinammino product. Bivalent cations combined with univalent anions formed dinicotinammines, and trivalent cations combined with univalent

TABLE VII

BENZOATES AND NAPHTHOATE

No.	Compound[a]	Nicotine, % Calcd.	Nicotine, % Found	Metal, % Calcd.	Metal, % Found	Crystals
1	$CuA_2 \cdot 2(RN_2 \cdot HA)$	37.1	35.9	7.3	7.5	Blue prisms
2	$CuA_2 \cdot 2RN_2 \cdot 2H_2O$	48.7	48.6	9.6	9.8	Blue prisms
3	$CuA_2 \cdot RN_2$	34.4	34.0	13.6	13.4	Green hex. plates
4	$CoA_2 \cdot 2(RN_2 \cdot HA)$[b]	37.3	35.6	..	..	
5	$NiA_22(RN_2 \cdot HA)$[c]	37.3	33.4	..	..	
6	$ZnA_2 \cdot RN_2 \cdot HA$	27.3	27.4	..	..	
7	$CdA_2 \cdot 2RN_2$	47.7	46.2	..	..	Plates
8	$CuN_2 \cdot 2RN_2$[d]	44.4	44.4	8.7	8.8	

[a] A = $-OOC \cdot C_6H_5$; $RN_2 = C_{10}H_{14}N_2$. [b] Calcd., $C_6H_5CO_2H$, 56.1; found, $C_6H_5CO_2H$, 53.4. [c] Calcd., $C_6H_5CO_2H$, 56.2; found, $C_6H_5CO_2H$, 54.3. [d] N = $-OOCC_{10}H_7$-α.

TABLE VIII

HALIDES, CYANIDES AND FERROCYANIDES

No.	Compound[a]	Nicotine, % Calcd.	Nicotine, % Found	Copper, % Calcd.	Copper, % Found	Crystals
1	$2CuCN \cdot RN_2 \cdot HCN$	44.0	43.0	34.5	34.2	Prisms (tricl.)
2	$CuI \cdot RN_2$	46.0	43.2	..	..	Hydrous, irregular
3[b]	$Ag_2 \cdot RN_2 \cdot H_2FeCy_62H_2O$	25.9	25.9			

[a] $RN_2 = C_{10}H_{14}N_2$. [b] Calcd., Ag, 34.2; found, Ag, 34.8.

anions formed trinicotinammines; nickelous trinicotinammino thiocyanate was an exception. Bivalent cations (principally limited to copper) combined with bivalent anions usually added 2 moles of ammonia or 1 mole of nicotine; the nicotine double salts usually contained only 1 mole of nicotine, but cupric dinicotine dichromate was an exception. The author prepared only two trinicotinammines of trivalent cations—the trinicotinammino picrates of aluminum and iron. Bivalent cations were often associated with 2 moles of nicotine and up to 6 moles of water.

In general, both types of salts were well crystallized, highly water-insoluble compounds of definite and repeatable composition. Many of them contained definite amounts of water of crystallization; in others this was indefinite or fluctuating. Usually they could be prepared by mixing normal solutions of the required salts in water or in water–ethanol, using the acetates of the desired metals and the sodium or ammonium salts of the desired anions. Manipulations had to be juggled in some cases to avoid the formation of metal hydroxides, or to produce the latter in finely dispersed and reactive form. Sometimes one listed compound was prepared from another, as in Table VI, no. 3 from no. 2; and in Table VII, 3 from 2. Usually the crystals formed immediately, sometimes after a few days at room temperature.

Many of the compounds fluoresced. Some of these were cuprous nicotine thiocyanate (Table I), the cadmium salts of nicotine salicylate (Table II) and thiocyanate, and the zinc salts of nicotine thiocyanate, salicylate and benzoate (Table VII).

In the tables, RN_2 is used as an abbreviation for nicotine, $C_{10}H_{14}N_2$, where R represents $C_{10}H_{14}$, obviously not a definite radical, and N_2 indicates possible chelation of two nitrogens.

EASTERN REGIONAL RESEARCH LABORATORY[5]
PHILADELPHIA 18, PENNA.

---

[5] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

Theory of the Variation of Bond Length with Bond Environment

BY RICHARD P. SMITH[1]

RECEIVED NOVEMBER 5, 1952

Recently a theory of the distribution of electronic charge in aliphatic organic molecules has been published.[2] This theory is particularly useful for calculating the variation of the moment of a C–X (X = halogen or hydrogen) bond with the environment of the bond. Concurrently with the development of this theory and its successful application to several problems, a number of C–X internuclear distances ("bond lengths") in substituted methanes have been accurately determined with the use of microwave spectroscopy. In this paper we propose to show that most of the bond length variations with environment which are observed may be related quantitatively to the bond moment variations calculated with inductive effect theory.

Our theory of bond length variation in saturated molecules is based on the model used in discussing charge distributions.[2] This model has a molecule consisting of touching spheres, each sphere representing an atom and having a radius equal to the covalent bond radius. Spread out over the surface of the sphere representing atom a is an amount of electronic charge equal to the "net charge," ϵ_a, which atom a carries. This net charge "sees" charge Z_a, the effective nuclear charge of atom a, given by

$$Z_a = Z_a^\circ + s_a(\epsilon_a/e) \qquad (1)$$

where e is the negative of the charge of an electron, Z_a° is the effective nuclear charge of atom a when it carries zero net charge, and s_a is 0.30 or 0.35 accordingly as a is or is not hydrogen. Equation (1) is an interpolation of one of Slater's screening rules.[2,3]

Let us now consider an equation holding for Slater approximate atomic orbitals,[3] namely

$$R_a = ((n_a^*)^2/Z_a)a_0 \qquad (2)$$

where a_0 = Bohr radius = 0.53 Å., n_a^* is the "effective quantum number" for atom a, and R_a is the distance from the nucleus for which the electronic density for the shell under consideration is a maximum, and may be considered to be the radius of the atom. From equation (2) we see that, for a given effective quantum number (electron shell), an increase in effective nuclear charge goes along with a decrease in effective radius, and *vice versa*. This may be pictured as a "pulling in" of the electron shell by the increased positive effective nuclear charge.

If we consider molecules from the atomic orbital point of view, which is essentially what we are doing when we use the charged sphere model under discussion, we may expect that equation (2) may have a degree of applicability to molecules; just what this degree is cannot be given a clear-cut theoretical answer, but it must be determined empirically. Let us make the following supposition, to be tested empirically. We suppose that equation (2), when coupled with equation (1), may satisfactorily be used for discussing the *variation* of the *effective radius* of an atom *in a*

---

[1] Junior Fellow, Harvard Society of Fellows, 1951–.

[2] R. P. Smith, T. Ree, J. L. Magee and H. Eyring, THIS JOURNAL, **73**, 2263 (1951).

[3] H. Eyring, J. Walter and G. E. Kimball, "Quantum Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 162–163.

molecule, disregarding the theoretical difficulties which strict interpretations of this idea may encounter. Then the variation of the length of a given type of bond, *e.g.*, C–Cl, will be the sum of the atomic radius variations, and may be discussed in terms of the net charges, which may be calculated from our inductive effect theory, the latter theory being based essentially on the same model. It is the purpose of this paper to show the results of a test of this idea, using accurately measured bond lengths from the recent literature, and charge distributions calculated with the same theory and parameters as used in our first paper on inductive effect theory.[2] We wish to emphasize that we do not consider that equation (2) will hold well for the actual covalent radii of atoms, but that we are merely using it to discuss *small variations*.

Combining equations (1) and (2), and using, from (2)

$$R_a^\circ = ((n_a^*)^2/Z_a^\circ)a_0 \qquad (3)$$

we find

$$R_a = R_a^\circ\left(1 - \frac{s_a R_a^\circ}{(n_a^*)^2 a_0}\frac{\epsilon_a}{e}\right) \qquad (4)$$

correct to first order in (ϵ_a/e), which is sufficient, as the second term in parentheses in (4) is small as compared with unity. Then

$$R_{ab} = R_a + R_b = R_a^\circ + R_b^\circ - \frac{s_a(R_a^\circ)^2}{(n_a^*)^2 a_0}\frac{\epsilon_a}{e} - \frac{s_b(R_b^\circ)^2}{(n_b^*)^2 a_0}\frac{\epsilon_b}{e} \qquad (5)$$

Particularizing equation (5) to C–X bonds, where[2]

$$\epsilon_X = \gamma_{XC} + \beta_{XC}\epsilon_C \qquad (6)$$

where γ_{XC} and β_{XC} are constants for a given C–X bond,[2] we find

$$R_{CX} = A_{CX} - B_{CX}\epsilon_X \qquad (7)$$

where A_{CX} and B_{CX} are constants for a given C–X bond (independent of the environment of the bond). The constant of importance in (7) is B_{CX}, given by

$$B_{CX} = \frac{s_C(R_C^\circ)^2}{(n_C^*)^2\beta_{XC}ea_0} + \frac{s_X(R_X^\circ)^2}{(n_X^*)^2 ea_0} \qquad (8)$$

for it determines the extent of the variation of R_{CX} with ϵ_X. The value of this constant may be estimated using the appropriate screening constants ($s_C = s_X = 0.35$ except $s_H = 0.30$), the appropriate effective quantum numbers,[3] the values of β_{XC} from reference (2), and the R_C° and R_X° may be taken to be the Pauling covalent radii,[4] since we need only approximate values of these radii in calculating the B_{CX} constants. The values of the B_{CX} thus obtained, with values of the component parts, are tabulated in Table I for the carbon–hydrogen and carbon–halogen bonds.

TABLE I

THEORETICAL VALUES OF THE B_{CX} OF EQUATION (8)

Bond C–X	β_{XC}[2]	R_X°(4)	n_X^*	B_{CX} (Å./10^{-10} e.s.u.)
C–H	0.13	0.30	1	0.167
C–F	.25	.64	2	.096
C–Cl	.71	.99	3	.0437
C·Br	.91	1.14	3.7	.0354
C–I	1.29	1.33	4.0	.0310

$n_C^* = 2$; $R_C^\circ = 0.77$ Å.

According to our theory, then, if we plot, for a given type of bond (*e.g.*, C–Cl), the value of $(-\epsilon_X)$ against R_{CX}, the result should be a straight line with slope B_{CX}. The theory says nothing about A_{CX}—we are concerned only with bond length *variations*.

Figure 1 shows R_{CX} as a function of $(-\epsilon_X)$ for X = F, Cl and Br, for the substituted methanes. The circles represent experimental values of the bond lengths; the charges are calculated by the procedure outlined in reference 2, with the same parameters as used therein.

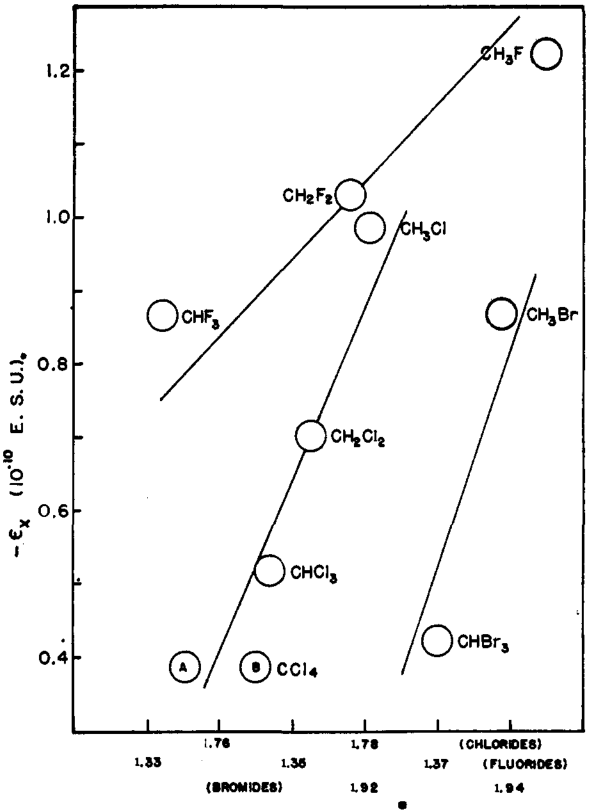


Fig. 1.—Calculated slopes, observed C–X distances plotted against halogen net charges; references for C–X distances: CH_3F[5]; CH_2F_2[6]; CHF_3, $CHCl_3$[7]; CH_3Cl, CH_3Br[8]; CH_2Cl_2[9]; CCl_4[10]; $CHBr_3$.[11]

Except for CCl_4, the experimental values are the best values obtained from microwave spectroscopy. The magnitude of the experimental error involved is uncertain[8]; we have drawn the circles with a

---

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

(5) O. R. Gilliam, H. D. Edwards and W. Gordy, *Phys. Rev.*, **75**, 1014 (1949).

(6) D. R. Lide, Jr., THIS JOURNAL, **74**, 3548 (1952).

(7) S. N. Ghosh, R. Trambarulo and W. Gordy, *J. Chem. Phys.*, **20**, 605 (1952).

(8) S. L. Miller, L. C. Aamodt, G. Dousmanis, C. H. Townes and J. Kraitchman, *ibid.*, **20**, 1112 (1952).

(9) R. J. Myers and W. D. Gwinn, *ibid.*, **20**, 1420 (1952).

(10) "A" and "B" represent the probable upper and lower limits of the CCl_4 bond length, this not being known accurately, as only electron diffraction results are available. L. O. Brockway, *ibid.*, **41**, 747 (1937), gives 1.755 ± 0.005; C. Finbak and O. Hassel, *Arch. Math. Naturvidenskab*, **45**, No. 3 (1941) give 1.770. Other observers give intermediate values.

(11) Q. Williams, J. J. Cox and W. Gordy, *J. Chem. Phys.*, **20**, 1524 (1952).

diameter of 0.002 Å., which is probably reasonable for the experimental error in most cases.

The straight lines in the accompanying figure have the theoretical slopes, that is, the B_{CX} value of Table I. The intercepts, as mentioned above, are arbitrary. The scales of the three graphs are the same, so that the relative slopes may readily be observed also. The calculated and observed slopes are all approximately the same for each series of halogens, and the relative slopes for the different series are predicted correctly.

The particular molecules included in this study are chosen simply because they are the ones for which accurate bond-length data are available. One other series might be considered: C–H bonds. Here, however, it is found that there is so much variation in the experimental values, due to difficulties encountered in averaging the results for the deuterium isotopes studied, and the results are so sensitive to the methods employed,[8] that it proves impossible to distinguish bond length variations from experimental error and ambiguity for C–H bonds.

We emphasize that, in calculating our theoretical slopes, no "adjustable parameters" have been employed; the constants involved are all carried over directly from the theory of reference (2), which in turn uses only accepted polarizabilities, screening constants, and covalent radii. Hence the results are believed to lend some support both to the theory outlined here and to the theory of reference (2).

CAMBRIDGE, MASS.

Polyphosphoric Acid as a Reagent in Organic Chemistry. IV. Conversion of Aromatic Acids and their Derivatives to Amines[1]

BY H. R. SNYDER, CLAYTON T. ELSTON AND DAVID B. KELLOM

RECEIVED DECEMBER 8, 1952

In a continuation of investigations of the use of polyphosphoric acid as a reagent in organic reactions[2,3] it has been found that aromatic acids can be converted to aryl amines by treatment with hydroxylamine and commercial polyphosphoric acid.[4] The reaction is carried out by heating a mixture of the reactants, with stirring, until rapid evolution of carbon dioxide begins, usually in the range of 150–170°. At such temperatures the reaction normally is complete in five to ten minutes, and the mixture is poured over crushed ice to give an aqueous solution of the amine phosphate.

The yields of crude products obtained from various acids are reported in Table I. In general, acids containing electron-donating substituents were found to give higher yields than those containing electron-withdrawing groups. This is in agreement with the results obtained by Hauser[5] in his studies on the effect of substituents on the Lossen rearrangement. Acids which gave poor yields of amines produced large amounts of dark colored, acid-insoluble material of very indefinite melting point. The two aliphatic acids studied, valeric acid and caprylic acid, failed to yield more than mere traces of the expected amines. Caprylohydroxamic acid likewise failed to yield *n*-heptylamine when subjected to similar conditions.

Many acid derivatives also underwent the reaction (see Table I). However, with the exception of esters, the yields were generally lower than with the corresponding acids themselves. *p*-Chlorobenzamide, N-methyl-*p*-chlorobenzamide and N-methylbenzamide yielded no *p*-chloroaniline or other identifiable product. The reason for this unexpected discrepancy is not known. It is interesting to note that some ketones may be transformed into the corresponding amines by treatment with two moles of hydroxylamine. The first step involves a Beckmann rearrangement[3] to the substituted amide while the second step involves cleavage of this acid derivative to give two moles of amine.

The exact course of the reaction has not been elucidated but it seems likely that a hydroxamic acid is an intermediate. Indeed, hydroxamic acids themselves are smoothly converted to amines in hot polyphosphoric acid. Potassium benzohydroxamate and potassium α-naphthohydroxamate yielded aniline (67%) and α-naphthylamine (73%), respectively. The transformation of *o*-phenylbenzoic acid into phenanthridone and that of salicylic acid into benzoxazolone can be explained by assuming an isocyanate to be an intermediate. Thus it seems likely that the process is a variant of the Lossen reaction.

For most of the reactions the sulfate and hydrochloride of hydroxylamine could be used interchangeably with but little influence on the course of the reaction. However, there were three notable exceptions; hydroxylamine hydrochloride gave markedly better yields with salicylic acid and with benzophenone, but hydroxylamine sulfate was required with *p*,*p*′-dichlorobenzophenone.

Although the method appears to be less generally applicable than the Curtius and Hofmann conversions of acids to amines, it is very attractive within its field of application. Only the simplest apparatus is required and the total reaction time is ten minutes or less. It is more conveniently carried out than the Schmidt reaction, which must be conducted with due regard to the properties of hydrazoic acid.

Experimental

General Method.—To 25–50 g. of polyphosphoric acid was added 5 g. of the carboxylic acid and slightly more than the theoretical amount of hydroxylamine sulfate or hydrochloride. The mixture was stirred mechanically and heated slowly on an oil-bath. When the chloride salt was used hydrogen chloride was evolved from the reaction mixture as the temperature approached 100°. Upon further increase in temperature the reactants gradually entered solution. In the range 150–170° there was a rapid evolution of carbon dioxide and the mixture darkened considerably. When the frothing had ceased the mixture was poured onto crushed ice. The insoluble material was removed and the filtrate was neutralized with potassium hydroxide. The liberated amine, if liquid, was extracted with several portions of benzene. The combined extracts were dried over sodium hydroxide pellets and then treated with dry hydrogen chloride gas. The precipitated hydrochloride was collected and dried in a desiccator. If the amine was solid

---

[1] Presented in part at the 122nd Meeting of the American Chemical Society, Atlantic City, N. J., September 17, 1952.

[2] H. R. Snyder and R. W. Roeske, THIS JOURNAL, **74**, 5820 (1952).

[3] E. C. Horning, V. L. Stromberg and H. A. Lloyd, *ibid.*, **74**, 5153 (1952).

[4] The authors are indebted to Dr. Howard Adler, Victor Chemical Works, Chicago, Ill., for generous supplies of polyphosphoric acid.

[5] C. R. Hauser and collaborators, THIS JOURNAL, **59**, 121, 2308 (1937); **61**, 618 (1939).

TABLE I

Reactant	Isolated or expected product	Yield, %	M.p., °C.	Reported m.p., °C.
β-Naphthoic acid	β-Naphthylamine	82	107–109	111–112
α-Naphthoic acid	α-Naphthylamine	80	43–45	50
Benzoic acid	Aniline hydrochloride	66	190–192	198
m-Toluic acid	*m*-Toluidine hydrochloride	76	223–225	228
p-Toluic acid	*p*-Toluidine hydrochloride	72	238–239	243
o-Bromobenzoic acid	*o*-Bromoaniline hydrochloride	53[a]		
m-Bromobenzoic acid	*m*-Bromoaniline hydrochloride	46[a]		
p-Bromobenzoic acid	*p*-Bromoaniline hydrochloride	43[a]		
p-Chlorobenzoic acid	*p*-Chloroaniline	32	69–70	70–71
Salicylic acid	Benzoxazolone	33[b]	137–138	138
o-Phenylbenzoic acid	Phenanthridone	40	292	293
m-Nitrobenzoic acid	*m*-Nitroaniline	53	109–110	112
o-Nitrobenzoic acid	*o*-Nitroaniline	0		
p-Nitrobenzoic acid	*p*-Nitroaniline	0		
Valeric acid	*n*-Butylamine	0		
Caprylic acid	*n*-Heptylamine	0		
Ethyl benzoate	Aniline hydrochloride	68	190–193	198
Benzamide	Aniline hydrochloride	43	190–193	198
Benzoyl chloride	Aniline hydrochloride	51	189–192	198
Benzonitrile	Aniline hydrochloride	20	190–192	198
p-Chlorobenzamide	*p*-Chloroaniline	0		
Benzanilide	Aniline hydrochloride	76	188–191	198
p,p'-Dichlorobenzanilide	*p*-Chloroaniline	48	66–70	70–71
p,p'-Dichlorobenzophenone oxime	*p*-Chloroaniline	40	65–68	70–71
p,p'-Dichlorobenzophenone	*p*-Chloroaniline	15	69–70	70–71
Benzophenone	Aniline hydrochloride	66	188–191	198
N-Methyl-*p*-chlorobenzamide	*p*-Chloroaniline, methylamine	0		
N-Methylbenzamide	Aniline, methylamine	0		

[a] Identity confirmed by conversion to acetyl derivative. [b] Recrystallized once from water.

it was filtered from the basic solution directly and then dried. The yields of crude amines or amine hydrochlorides obtained in this way are reported in Table I.

β-Naphthylamine.—To a mixture of 1.7 g. (0.24 mole) of hydroxylamine hydrochloride and 4.0 g. (0.23 mole) of β-naphthoic acid was added 50 g. of polyphosphoric acid. The mixture was stirred mechanically and the temperature was gradually raised. At 160° the evolution of carbon dioxide had ceased and the brown mixture was poured over 250 g. of crushed ice. Filtration of the resulting mixture yielded 0.7 g. of an orange colored solid, which displayed no definite melting point. The filtrate was neutralized with potassium hydroxide and the precipitated amine was collected and dried. The yield was 2.7 g. (82%) of light tan α-naphthylamine, m.p. 107–109° (lit. 111–112°).

Aniline from Benzophenone.—To a mixture of 2.1 g. (0.030 mole) of hydroxylamine hydrochloride dissolved in 20 g. of polyphosphoric acid was added 1.82 g. (0.010 mole) of benzophenone. The mixture was heated with constant stirring to 160–165° for ten minutes. The purple mixture was poured over 100 g. of crushed ice and the small amount of insoluble material was removed by filtration. The filtrate was made strongly basic with potassium hydroxide and then extracted thoroughly with benzene. The extracts were dried over sodium hydroxide and then saturated with dry hydrogen chloride. The precipitated aniline hydrochloride was collected and dried in a desiccator. The dry hydrochloride had a light purple tinge and melted at 188–191°. The yield was 1.72 g. (66%).

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS

Predicted Isotopic Enrichment Effects in Some Isotopic Exchange Equilibria Involving Carbon-14

BY D. R. STRANKS AND G. M. HARRIS

RECEIVED NOVEMBER 28, 1952

The equilibrium constants of a considerable number of isotopic exchange reactions have been predicted by the methods of statistical thermodynamics.[1,2] No data of this type have been reported in regard to carbon-14/carbon-12 exchanges. Concurrently with a recent experimental study of such an exchange,[3] it was found desirable to make a number of predictions of this nature. This note presents a brief summary of the results of these and of some additional computations, in the belief that they may prove of interest to others investigating carbon-14 isotope effects.

The procedure was as given by Urey,[1] utilizing the spectroscopic data referred to in the tabulation below. The vibrations for the corresponding carbon-14-containing compounds were determined by use of the harmonic oscillator approximation for diatomic molecules,[4] and of normal vibration equations (usually the valence-force-field approximation) for polyatomic molecules.[5] In certain indicated instances, earlier frequency assignments were checked or modified on the basis of the vibration equation treatment. The partition function ratios Q_{14}/Q_{12} at the three temperatures 273.16, 293.16 and 313.16°K., respectively, are given for each of the eighteen compounds treated. The equilibrium constant of any probable exchange reaction between a pair of these compounds at any of the temperatures given is then readily predicted

---

(1) H. C. Urey, *J. Chem. Soc.*, 562 (1947).

(2) A. P. Tudge and H. G. Thode, *Can. J. Research*, **B28**, 567 (1950).

(3) D. R. Stranks and G. M. Harris, *J. Phys. Chem.*, **56**, 906 (1952).

(4) G. Herzberg, "Molecular Spectra and Molecular Structure. I. Diatomic Molecules," D. Van Nostrand Co., Inc., New York, N. Y., 1950.

(5) G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Co., Inc., New York, N. Y., 1945.

TABLE OF RESULTS

Molecule	273.16°K.	Q_{14}/Q_{12} 293.16°K.	313.16°K.	Spectral data reference[a]	Remarks
HCHO	1.574	1.515	1.467	1, p. 300	
HCO_3^-	1.509	1.451	1.403	2	Freq. assgt. made on basis of VFF calcn. as $(OH)CO_2$
$CO_3^=$	1.478	1.424	1.378	1, p. 178	
CO_2	1.444	1.397	1.358	1, p. 276	Anharmonicity corrections applied
$CO(NH_2)_2$	1.418	1.372	1.333	3	ν_6 estd. by VFF calcn. and analogy to $COCl_2$
HCO_2^-	1.360	1.322	1.289	4	ν_6 estd. by VFF calcn. with k_Δ as for CH_2O
COS	1.355	1.317	1.286	1, p. 174	
$(C_2N_2)^{1/2}$	1.322	1.289	1.261	1. p. 294	
CNO^-	1.315	1.283	1.255	5	
ClCN	1.299	1.269	1.244	1, p. 174	
$COCl_2$	1.295	1.263	1.237	6	Frequency assgt. checked by VFF calculation
SCN^-	1.292	1.262	1.237	1, p. 174	
BrCN	1.282	1.254	1.230	1, p. 174	
HCN	1.281	1.256	1.233	1, p. 280	Anharmonicity corrections applied
ICN	1.265	1.239	1.216	1. p. 174	
CS_2	1.255	1.227	1.204	1, p. 173	
CO	1.216	1.196	1.179	7	Anharmonicity corrections applied
CN^-	1.192	1.174	1.159	1, p. 195	

[a] References: (1) G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. Van Nostrand Co., Inc., New York, N. Y.. 1945. (2) R. Duval, C. Duval and J. Lecomte, *Bull. soc. chim. France*, **5**, 517 (1943). (3) K. W. F. Kohlrausch and A. Pongratz, *Z. physik. Chem.*, **B27**, 176 (1934). (4) J. Lecomte, *et al.*, *Cahiers de Physique*, 17 (1943); *Ann. phys.*, **17,** 5 (1942); *Compt. rend.*, **208,** 1401 (1939). (5) J. Goubeau, *Ber.*, **68,** 912 (1935). (6) C. R. Bailey and J. B. Hale, *Phil. Mag.*, **25,** 98 (1938). (7) G. Herzberg, "Molecular Spectra and Molecular Structure. I. Diatomic Molecules." D. Van Nostrand Co., Inc., New York, N. Y., 1950, p. 522.

by the division of the required pair of partition function ratios.

Reactions involving species of great chemical similarity and which undergo rapid exchange show the expected small enrichment effects. Thus, in the case of the important biological equilibrium

$$HC^{12}O_3^- + C^{14}O_3^= \rightleftharpoons HC^{14}O_3^- + C^{12}O_3^=$$

at 293.16°K., $K = 1.451/1.424 = 1.019$. This represents but a 1.9% enrichment of carbon-14 in the bicarbonate. On the other hand, a number of probable exchanges, so far for the most part uninvestigated experimentally, should exhibit appreciable enrichments. There is the series involving cyanide ion—in addition to the CN^-/HCN system (well-known in carbon-13 studies) with a predicted 6.8% effect at 293.16°K., there are those comprising CN^- and CNO^- (9.2%), CNS^- (7.5%), C_2N_2 (9.8%), ClCN (8.1%), BrCN (6.8%) and ICN (5.5%). Additional particularly intriguing possibilities are the low-temperature catalytic equilibration (say on active MnO_2) of CO and CO_2 with a predicted enrichment of no less than 16.8% at 293.16°K., the photochemical exchange of CO with $COCl_2$ (6.5%), the very probable CO_2/COS exchange (6.1%), and the significant $CO(NH_2)_2$/CNO^- system (6.9%).

It will be noted that the predicted enrichments for certain of the systems studied here are somewhat greater than twice the values previously given in the literature for the corresponding carbon-13/carbon-12 systems. For example, Urey[1] reports a carbon-13 enrichment of 3.4% for the HCN/CN^- system at 273°K., while the carbon-14 value deduced from our table is 7.5% at the same temperature. Close examination shows that this apparent disagreement with theory stems from the vibrational frequencies used for the isotopic HCN molecules. Our method of calculation (using the VFF equations given by Herzberg[5]) gives for $HC^{13}N$ the frequencies 1969, 723 and 3431 cm.$^{-1}$, respectively, as compared to Urey's values of 1967, 723 and 3435 cm.$^{-1}$.

DEPARTMENTS OF CHEMISTRY
UNIVERSITY OF MELBOURNE
MELBOURNE, AUSTRALIA, AND
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN

Heats of Hydrolysis of Amide and Peptide Bonds[1]

BY JULIAN M. STURTEVANT

RECEIVED JANUARY 2, 1953

In recent publications,[2,3] a procedure for the calorimetric determination of the heats of hydrolysis of amide and peptide bonds has been described. The present note reports the application of the method to the hydrolysis of the amide bond of glycyl-L-phenylalanylamide and the peptide bond of carbobenzoxyglycyl-L-leucine.

Experimental

Glycyl-L-phenylalanylamide acetate, kindly supplied by Dr. J. S. Fruton of Yale University, was hydrolyzed by cathepsin C, also supplied by Dr. Fruton. Cysteine was added as activator. Kjeldahl analysis gave 14.79% nitrogen, as compared with the theoretical value of 14.94%. Carbobenzoxyglycyl-L-leucine, for which the author is indebted to Dr. R. Lumry of the University of Utah, was hydrolyzed by carboxypeptidase, purchased from the Worthington Biochemical Laboratory. Both reactions were carried out in buffered aqueous solution at 25°, and were accompanied by heat evolution which accurately followed in each case a first-order rate law to more than 90% completion. The former reaction was observed in the *p*H range 4.69 to 5.65; in this range no correction[4] for ionization heats is necessary, since the products are practically completely

---

[1] This research was aided by a grant from the Rockefeller Foundation. Presented at the Atlantic City Meeting of the American Chemical Society, September, 1952.

[2] A. Dobry and J. M. Sturtevant, *J. Biol. Chem.*, **195**, 141 (1952).

[3] A. Dobry, J. S. Fruton and J. M. Sturtevant, *ibid.*, **195**, 148 (1952).

ionized. The latter reaction was investigated in the pH range 6.46 to 7.45; the small ionization corrections were estimated using +800 and +10,800 cal. per mole for the second ionization heats of phosphoric acid[4] and leucine,[5] respectively, and pK_2' 9.60 for the second ionization of leucine.[5]

Results

The experimental results are summarized in Tables I and II. The notation adopted in previous work[2,3] has been followed. The rate constants given for each reaction have no absolute significance since it is known that the enzymes used were not highly purified preparations.

TABLE I

THE HYDROLYSIS OF GLYCYL-L-PHENYLALANYLAMIDE BY CATHEPSIN C AT 25°

Buffer concentration, 0.05 *M;* ionic strength, 0.3 *M;* P, sodium phosphate, A, sodium acetate

pH	Initial substrate concn., mole per l., × 10^3	Enzyme concn., mg. prot. nitrogen per ml.	Cysteine concn., moles per l., × 10^3	k, min.$^{-1}$	$-\Delta H_h$, cal. per mole	Buffer
4.69	0.587	0.0387	1.90	0.072	5900	P + A
4.69	.587	.0387	1.90	.066	5880	P + A
4.85	.453	.116	1.92	.088	6285	A
4.85	.439	.116	1.92	.086	6285	A
5.09	.453	.116	1.93	.107	6300	P
5.11	.694	.116	2.75	.137	6780	P
5.11	.453	.116	1.93	.115	6300	P
5.65	.342	.116	1.90	.095	5970	P
5.65	.342	.116	1.90	.093	6260	P
				Mean	6220 ± 150	

TABLE II

THE HYDROLYSIS OF CARBOBENZOXYGLYCYL-L-LEUCINE BY CARBOXYPEPTIDASE AT 25°

Sodium phosphate buffer, 0.05 *M;* ionic strength, 0.4 *M*

pH	Init. substrate concn., moles per l., × 10^3	Enzyme concn., mg. prot. nitrogen per ml.	$-\Delta H_{obsd.}$ cal. per mole	$-\alpha$ $(\Delta H_1 - \Delta H_p)$, cal. per mole	$-\Delta H_h$, cal. per mole	k_3/K_m
6.46	1.63	0.0321	2015	7	2022	0.89
6.46	1.63	.0321	2115	7	2122	1.01
6.77	1.49	.0391	2090	15	2105	1.03
6.77	1.49	.0391	2060	15	2075	0.99
6.81	2.35	.0414	2040	16	2056	1.34
6.81	2.35	.0414	2030	16	2046	1.27
7.24	1.87	.0413	2180	44	2224	1.92
7.24	1.87	.0413	2110	44	2154	1.85
7.44	1.14	.0413	2100	69	2169	2.21
7.45	1.14	.0321	2060	70	2130	2.55
				Mean	2110 ± 50	

Table III lists the heats of hydrolysis for the five compounds studied by our method. These values refer in each case to the formation of fully charged products, according to the equation

$$RCONHR' + H_2O = RCOO^- + {}^+NH_3R'$$

TABLE III

HEATS OF HYDROLYSIS OF SYNTHETIC PEPTIDES AT 25°

Substrate	Bond hydrolyzed	$-\Delta H_h$, cal. per mole
Benzoyl-L-tyrosinamide	Amide	5840 ± 220
Benzoyl-L-tyrosylglycinamide	Tyrosine–glycine	1550 ± 100
Carbobenzoxyglycyl-L-leucine	Glycine–leucine	2110 ± 50
Carbobenzoxyglycyl-L-phenylalanine	Glycine–phenylalanine	2550 ± 50
Glycyl-L-phenylalanylamide	Amide	6220 ± 150

The data are as yet not sufficiently extensive to permit tracing in detail the relation between peptide structure and heat of hydrolysis. However, it is evident that the amide hydrolyses are considerably more exothermic than the peptide hydrolyses. It should be noted that, since the heat of ionization of the ammonium ion is about 2000 cal. per mole more positive than the heat of the second ionization of most amino acids, the heat of hydrolysis of an amide bond to give *uncharged* products would be more nearly equal to that of the peptide bond to give *uncharged* products. A small structural change, such as replacement of the isobutyl side chain of leucine by the benzyl side chain of phenylalanine, produces a small but definite change in the heat of hydrolysis. It is perhaps significant that the smallest heat is observed in the hydrolysis of the neutral molecule benzoyltyrosylglycinamide; presumably this value will be found to be approximately characteristic of the hydrolysis of the majority of the peptide bonds in a protein which are located at considerable distances from charged groups.

CONTRIBUTION NUMBER 1141
STERLING CHEMISTRY LABORATORY
YALE UNIVERSITY
NEW HAVEN, CONNECTICUT

---

[4] H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 2nd Ed., Reinhold Publ. Corp., New York, N. Y., 1950, p. 514.

[5] E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943, pp. 80 and 84.

Antimetabolites of Uridine with Two Structural Alterations[1]

BY DONALD W. VISSER, GERALD BARRON AND RICHARD BELTZ

RECEIVED OCTOBER 6, 1952

A number of 5-substituted uridine derivatives competitively inhibit the growth response of *Neurospora* 1298 produced by uracil, uridine or cytidine[2,3,4] and several of these compounds also inhibit the propagation of Theilers GD VII encephalomyelitis virus *in vitro*.[5] Substitution of the hydrogen in the 3-position of uridine produces a similar antimetabolite, 3-methyluridine.[3,4] It was of interest, therefore, to prepare nucleosides which are substituted in both the 3- and 5-positions and compare the biological activity of these compounds with the corresponding derivatives having a single structural alteration. The new compounds are of interest not only because of their structural similarity to uridine and cytidine, which are utilized for nucleic acid biosynthesis, but also may be of value

---

[1] This work was aided by a grant from Research Corporation. Presented, in part, before the Biochemistry Division, at the April, 1952, Meeting of the American Chemical Society at Milwaukee, Wisconsin.

[2] T. K. Fukuhara and D. W. Visser, *J. Biol. Chem.*, **190**, 95 (1951).

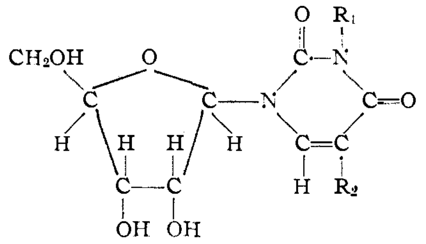
[3] M. Roberts and D. W. Visser, THIS JOURNAL, **74**, 668 (1952).

[4] M. Roberts and D. W. Visser, *J. Biol. Chem.*, **194**, 695 (1952).

[5] D. W. Visser, D. Langenborg and H. E. Pearson, *Proc. Soc. Exptl. Biol. Med.*, **79**, 571 (1952).

for extending knowledge concerning the relationship between structure and antimetabolite activity.

The doubly substituted nucleosides were prepared by prior methylation of uridine according to a modified procedure of Levene and Tipson,[6] and the hydrogen on carbon atom 5 of the resulting 3-methyluridine was substituted by a bromine (I), chlorine (II) or an amino group (III) by procedures similar to those described by Roberts and Visser.[3]



No.	R₁	R₂	Name. 3-methyl-5-
I	CH_3	Br	Bromouridine
II	CH_3	Cl	Chlorouridine
III	CH_3	NH_2	Aminouridine

Experimental[7]

3-Methyluridine.—Tritylation of uridine was eliminated from the procedure reported by Levene and Tipson.[6] Dry uridine (7.0 g., 0.029 mole) was dissolved slowly in 100 ml. of freshly-distilled acetic anhydride. The cloudy solution was allowed to stand overnight at room temperature, and then slowly concentrated at reduced pressure (4 mm.) at 20–25° to an amber sirup (about two days). The product crystallized into a solid cake upon seeding. The cake was washed with absolute ethanol and recrystallized from boiling absolute alcohol (9.5 g., 90%).

The triacetyluridine (19 g., 0.051 mole) was dissolved in a minimum amount of hot ethylene dichloride. The solution was cooled to 0°, and 5.3 g. of diazomethane in ether was added slowly with shaking. The solution, in a flask fitted with a stopper containing a drying tube, was allowed to stand overnight at room temperature. The yellow solution was taken to dryness under reduced pressure (4 mm.) at room temperature. Absolute methyl alcohol (50 ml.) was added and the solution was again taken to dryness at reduced pressure.

The residue, a white semi-crystalline product, was dissolved in a 5% solution of dry HCl in dry methyl alcohol (2.6 g. HCl/500 ml. methyl alcohol), refluxed slowly for 10 minutes, and left to stand overnight. The solution was then taken to dryness at reduced pressure (4 mm.) and room temperature. Methyl alcohol (10 ml.) was added and the solvent was again removed to eliminate most of the excess hydrochloric acid.

The semi-crystalline amber product was taken up in a minimum amount of cold distilled water, filtered, and passed through Amberlite IRA-400 (about 5 g.). The effluent (*p*H 5–7) was decolorized with carbon and lyophilized. The white residue was dissolved in an equal mixture of methyl alcohol and ethyl acetate, and crystallization induced by the addition of ethyl ether to opalescence. It was found that the compound crystallized best in the cold from a concentrated solution. The solution yielded 9.8 g. (74%) of white needles, melting at 122–123°. Levene and Tipson[6] reported a m.p. of 108–110° for 3-methyluridine (both compounds give an identical analysis). The lower melting compound has also been obtained in this Laboratory by the procedure outlined above. However, attempts to interconvert these compounds were not successful.

3-Methyl-5-bromouridine (I).—High-melting 3-methyluridine (2.6 g., 0.010 mole) was dissolved in water and bromine water was added at 5° until the solution remained colored. Air was then bubbled through the solution to remove excess bromine and the colorless solution was lyophilized. The sticky product was refluxed with absolute ethyl alcohol for two hours, and concentrated to a sirup on a water-bath. The product which crystallized upon cooling was recrystallized from absolute ethyl alcohol. The yield was 3.10 g. (91%) of a white crystalline compound, melting at 164–164.5°. *Anal.* Calcd. for $C_{10}H_{13}O_6N_2Br$: C, 35.63; H, 3.87; N, 8.31. Found: C, 35.99; H, 3.77; N, 8.54.

3-Methyl-5-chlorouridine (II).—3-Methyluridine (750 mg., 0.0029 mole) was suspended in 45 ml. of dry acetic acid and a 10% molar excess (0.32 g., 0.0045 mole) of dry chlorine dissolved in cold anhydrous carbon tetrachloride was added at room temperature and the resulting cloudy solution was allowed to stand overnight. After removal of solvent and acid the product was dissolved in a 1.0% solution of anhydrous HCl (0.44 g. in 44 ml.) in methyl alcohol. The solution was allowed to stand for two to five days. The acid was removed in the same manner as in the preparation of 3-methyluridine and the product crystallized from methyl alcohol. The crystallization which was favored by high concentration and cold yielded 300 mg. (35.3%) of white crystals melting at 158–159°. *Anal.* Calcd. for $C_{10}H_{13}O_6N_2Cl$: C, 41.02; N, 9.57; H, 4.48. Found: C, 40.93; N, 9.35; H, 4.85.

3-Methyl-5-aminouridine (III).—3-Methyl-5-bromouridine (1 g., 0.003 mole) was suspended in 30 ml. of absolute ethyl alcohol in a stainless steel bomb tube. The tube was cooled in a Dry Ice–acetone-bath and 8 ml. of liquid ammonia was added. The tube was sealed and allowed to come to room temperature and then heated at 55° for six days. The bomb was cooled in a Dry Ice–acetone mixture, opened, and the contents poured out. The ammonia and alcohol were removed from the amber solution under reduced pressure (aspirator) at room temperature. The product was taken up in a minimum of water and passed through 5 g. of IRA-120 ion exchange resin. The column was washed with 3 liters of water and the product was eluted with 500 ml. of 4 *N* aqueous ammonia. The ammonia was removed at reduced pressure and the solution lyophilized. The crystalline product was dissolved in a minimum amount of boiling ethyl alcohol, filtered, and allowed to crystallize in the cold. The yield was 500 mg. of fine, amber-tinted, semi-crystalline material melting at 159–168°. After crystallizations from absolute ethanol, 400 mg. (49%) of a white product was obtained, melting at 166–167°. *Anal.* Calcd. for $C_{10}H_{15}O_6N_3$: C, 43.96; N, 15.38, H, 5.53. Found: C, 44.24; N, 15.49; H, 5.40.

Microbiological.—The 3,5-substituted nucleosides were tested for growth-promoting or growth-inhibiting properties with a pyrimidine-requiring mutant of *Neurospora*, 1298, using a modification[8] of the basal medium of Horowitz and Beadle.[9] The mutant was incubated at 25° for three days in 50-ml. erlenmeyer flasks, each containing a total volume of 10 ml. of liquid medium.

The mutant was grown in the presence of given amounts of uracil, uridine or cytidine as the pyrimidine requirement and varying amounts of the 3,5-substituted nucleoside. The inhibition indices, the molar ratio of antimetabolite to metabolite which gives half-maximum growth, are summarized in Table I.

TABLE I

Inhibition indices[a]; *Neurospora* 1298

Antimetabolite, -uridine	Metabolite Uridine	Cytidine	Uracil
3-Methyl-5-bromo-	7.3[b]	1.2[b]	
3-Methyl-5-chloro-	6.4[b]	1.7[b]	
3-Methyl-5-amino-		9.1[b]	No inhib.[c]
3-Methyl-	4.0	0.47	No inhib.[c]
5-Chloro-	3.0	0.55	No inhib [c]
5-Amino-	14.0	3.0	0.2[d]

[a] Moles of antimetabolite per mole of metabolite giving 50% of maximum growth. Grown for three days at 25° in 50-ml. erlenmeyer flasks with a total volume of 10 ml. of medium. [b] Inhibition is competitive from a concentration range of 0.6 to 0.9 mg. substrate in 10 ml. of medium. [c] To 3.2 moles of antimetabolite per mole of metabolite. [d] Inhibition is not competitive.

---

(6) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **104**, 385 (1934).

(7) All melting points were taken on a Fisher–Johns melting point apparatus and are uncorrected.

(8) F. J. Ryan and E. Brand, *J. Biol. Chem.*, **154**, 161 (1944).

(9) N. H. Horowitz and G. W. Beadle, *ibid.*, **150**, 325 (1943).

Discussion

It is apparent that the 3,5-substituted nucleosides are less effective as antimetabolites than are the nucleosides in which only one of these structural changes exists. For example, 3-methyluridine or 5-chlorouridine have an inhibition index of approximately 0.5 when cytidine provides the pyrimidine requirement. When both structural changes are made on the same molecule, 3-methyl-5-chlorouridine, the inhibition index against cytidine is increased by a factor of about 3. A similar increase in the inhibition index obtained with the doubly substituted nucleosides is observed whether uridine, cytidine, or uracil provide the pyrimidine requirement. It is of interest to note that a methyl group in the 3-position of uridine decreases the activity of the antimetabolite whether the substituent on the 5-carbon is nucleophilic or electrophilic.

The results agree with the observation of Woolley and Pringle[10] who have demonstrated that as the structural difference between metabolite and analog increases, the degree of inhibition usually decreases. However, over the range of substrate concentration tested, the doubly substituted nucleosides retain their ability to inhibit in a competitive manner.

[10] D. W. Woolley and A. Pringle, *J. Biol. Chem.*, **194**, 729 (1952).

DEPARTMENT OF BIOCHEMISTRY AND NUTRITION
SCHOOL OF MEDICINE, AND
LABORATORIES OF THE ALLAN HANCOCK FOUNDATION
UNIVERSITY OF SOUTHERN CALIFORNIA
LOS ANGELES, CALIFORNIA

COMMUNICATIONS TO THE EDITOR

IONIC INHIBITION OF GROWTH IN LACTOBACILLUS LEICHMANNII 313 AND ITS REVERSAL WITH VITAMIN B_{12}

Sir:

Vitamin B_{12}, as a growth factor for *Lactobacillus Leichmannii* 313, can be replaced by thymidine[1] or other desoxyribosides.[2] It has been suggested[1,3] that vitamin B_{12} might function as a catalyst (coenzyme) in the formation of desoxyribosides. The experimental data presented here seem to offer some indirect evidence for the existence of a vitamin B_{12}-enzyme.

We found that slightly hypertonic concentrations of various inorganic salts inhibit the growth of *L. Leichmannii* 313, in a basal medium[4] supplemented with just sufficient (0.1 mγ per 5 ml.) vitamin B_{12} to allow full growth (in the absence of the salts). This inhibition can be reversed with an added excess of vitamin B_{12}. When the salt concentration is increased, the vitamin B_{12} requirement sharply increases. Through a narrow salt concentration range, which we will term the "reversible range" (*e.g.*, in the case of NaCl from 1.1 to 1.7%), the inhibition can be fully reversed by increasing the vitamin B_{12} level from the initial 0.1 mγ up to about 25 mγ (per 5 ml.); above this range, only partial reversal can be obtained during a standard, 16 hour, incubation period. Thymidine, throughout the "reversible range" supports full growth at slightly increasing (5–10 γ per 5 ml.) levels; above the "reversible range," the maximum growth response obtained with thymidine is the same as with excess vitamin B_{12} (see Table I).

TABLE I

Salt	Concentration %	Concentration M^a	μ^b	$(B_{12})_{1/2}$ max.^{c}	Thymidine^d
None	...	...	...	0.025^e	1.8
NaCl	1.4	0.239	0.239	1.0	
	1.5	.256	.256	1.5	2.0
	1.7	.291	.291	6.0	2.5
	1.9	.325	.325	(25.0)^f	(2.5)^f
KCl	1.62	.217	.217	0.50	1.8
	1.88	.252	.252	1.58	1.8
	2.13	.285	.285	7.5	2.0
	2.37	.318	.318	(25)^f	(2.2)^f
NH_4Cl	1.2	.224	.224	0.45	
	1.4	.262	.262	2.30	2.5
	1.6	.299	.299	5.0	
	1.8	.336	.336	(20)^f	
K_2SO_4	1.6	.092	.276	0.12	1.8
	1.8	.103	.309	0.40	1.8
	2.0	.115	.365	0.60	
	2.3	.132	.406	1.20	
	2.6	.149	.447	5.0	
	2.9	.166	.498	(15)^f	
$MgCl_2\cdot 6H_2O$	1.0	.049	.196	0.14	
	1.2	.059	.236	0.30	
	1.4	.069	.273	1.15	
$CaCl_2$	0.8	.073	.292	3.8	
	1.2	.109	.436	(25)^f	

[a] Gram moles per liter. [b] Ionic strength, $\mu = {}^1/_2\Sigma cv^2$, where c = gram ions per liter; v = valence, for each ion. [c] mγ per 5 ml.; amount of additional (in excess of 0.1) vitamin B_{12} needed for half maximum growth. [d] γ per 5 ml.; required for half maximum growth in vitamin B_{12}-free media. (We are indebted to Dr. W. Shive for a small sample of this substance.) [e] mγ per 5 ml. basal medium (vitamin B_{12} standard curve). [f] Salt concentration above "reversible range"; only partial growth obtained.

---

[1] W. Shive, J. M. Ravel and R. E. Eakin, THIS JOURNAL, **70**, 2614 (1948).

[2] E. Kitay, W. S. McNutt and E. E. Snell, *J. Biol. Chem.*, **177**, 993 (1949).

[3] E. Kitay, W. S. McNutt and E. E. Snell, *J. Bact.*, **59**, 727 (1950).

[4] Per 100 ml.: acid-hydrolyzed casein, 0.5 g.; L-cysteine hydrochloride, 10 mg.; DL-tryptophan, 20 mg.; L-asparagine, 10 mg.; DL-alanine, 20 mg.; adenine sulfate, 1 mg.; guanine hydrochloride, 1 mg.; uracil, 1 mg.; xanthine, 1 mg.; thiamin hydrochloride, 100 γ; pyridoxine, 200 γ; pyridoxamine, 60 γ; pyridoxal, 60 γ; calcium pantothenate, 100 γ; niacin, 200 γ; PABA, 20 γ; biotin, 0.2 γ; folic acid, 0.4 γ; riboflavin, 100 γ; ascorbic acid, 0.2 g.; dextrose, 2.0 g.; tween 80, 100 mg.; salts A, 1 ml.; salts B, 1 ml.; sodium acetate, 0.5 g. Incubation, 16 hours at 37°. Five ml. in each tube.