with the Beckmann spectrophotometer. The absorption maxima are given in Table I, together with those of xanthopterin and isoxanthopterin determined in the same way.

The authors wish to express their gratitude to Mr. Samuel W. Blackman for the microanalyses recorded here.

THE WELLCOME RESEARCH LABORATORIES
TUCKAHOE 7, NEW YORK
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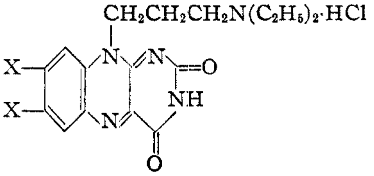
Basically-substituted Isoalloxazines

BY HOWARD BURKETT

The structural similarity of atebrin to riboflavin suggested the synthesis of basically-substituted isoalloxazine derivatives, such as I, II and III, as possible antimalarials.



I, X = CH_3—
II, X = CH_3O—
III, X = Cl—

After this work was begun, other series of compounds very closely related to these were reported.[1,2,3] As a result the preparation of related compounds which had been planned was not carried out. The synthesis of compound III was attempted using a procedure similar to that employed for I and II and also according to the method of Kuhn and Weygand,[4] in which acetic acid served as the solvent and boric acid as the catalyst. That the product in very dilute solution gave a yellow-green fluorescence, typical of isoalloxazines, would indicate that the desired product was present, but the analyses indicated considerable contamination and cast some doubt that the expected compound was obtained. Consequently, this product was not submitted for biological testing and it is not reported in this note.

Compounds I and II were devoid of antimalarial activity, when tested on ducks infected with *Plasmodium lophurae.*

The author thanks Dr. K. K. Chen and Dr. C. L. Rose of Eli Lilly and Company for the pharmacological tests, Mr. Howard Hunter also of Eli Lilly and Company for the microanalyses and Eli Lilly and Company for financial assistance.

Experimental

7,8-Dimethoxy-10-(γ-diethylaminopropyl)-isoalloxazine Hydrochloride.—Four grams of 4,5-dinitroveratrole[5] was mixed with 4 ml. of γ-diethylaminopropylamine and 5 ml. of ethanol. After the mixture had refluxed for twenty hours, it was poured into water and acidified with hydrochloric acid. This solution was extracted with ether. The aqueous solution was made basic with sodium hydroxide and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate, filtered and saturated with anhydrous hydrogen chloride, forming an oily precipitate of crude 4-nitro-5-(γ-diethylaminopropylamino)-veratrole hydrochloride,[6] which could not be made to crystallize. The hydrobromide, sulfate and free-base could not be obtained in solid form and the base could not be distilled. Consequently, the oily hydrochloride was dissolved in 40 ml. of methanol and hydrogenated at atmospheric pressure and room temperature, using 0.10 g. of Adams platinum oxide catalyst. After the catalyst had been removed by filtration, the methanol was evaporated under reduced pressure with slight warming. Twenty milliliters of methanol was added and again evaporated. Ether was added to the residue and the mixture was saturated with anhydrous hydrogen chloride. After the ether had been decanted, the oil which remained was dissolved in 40 ml. of boiling methanol and 2.5 g. of alloxan monohydrate in 15 ml. of methanol was added. After refluxing for thirty minutes, the mixture was cooled and filtered. Recrystallization of the yellow solid from a water–acetone solution gave 1.04 g. (13.1%) of product melting at 220–222° with decomposition.

Anal. Calcd. for $C_{19}H_{25}N_5O_4 \cdot HCl \cdot 2H_2O$: C, 49.70; H, 6.58; N, 15.25. Found: C, 49.76; H, 6.22; N, 15.70.

4-Nitro-5-(γ-diethylaminopropylamino)-*o*-xylene.—Three grams of 4,5-dinitro-*o*-xylene,[7] 4 ml. of γ-diethylaminopropylamine and 8 ml. of ethanol were refluxed on the steam-bath for four days. The reaction mixture was cooled, poured into water, acidified with concentrated hydrochloric acid and extracted with ether. In a short time, as the dissolved ether evaporated spontaneously from the aqueous solution, yellow needles precipitated. Filtering and washing with a small amount of water yielded 2.89 g. of product melting at 211–212.5°.

Anal. Calcd. for $C_{15}H_{25}N_3O_2$: C, 57.00; H, 7.99; N, 13.33. Found: C, 56.73; H, 8.03; N, 13.17.

Evaporation of the filtrate to two-thirds of its original volume and cooling yielded an additional 0.4 g. of slightly less pure product, making the total yield 3.29 g. (77%).

7,8-Dimethyl-10-(γ-diethylaminopropyl)-isoalloxazine Hydrochloride.—Treatment of the 4-nitro-5-(γ-diethylaminopropylamino)-*o*-xylene in the same way as the 4-nitro-5-(γ-diethylaminopropylamino)-veratrole hydrochloride was treated above, yielded 37.5% of a yellow, crystalline product melting at 289–289.5° with decomposition.

Anal. Calcd. for $C_{19}H_{25}N_5O_2 \cdot HCl \cdot 2.5H_2O$: C, 52.20; H, 6.86; N, 16.01. Found: C, 52.26; H, 6.66; N, 16.23.

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[1] Adams, Weisel and Mosher, THIS JOURNAL, **68**, 883 (1946).

[2] King and Acheson, *J. Chem. Soc.*, 681 (1946).

[3] Kipnis, Weiner and Spoerri, THIS JOURNAL, **69**, 799 (1947).

[4] Kuhn and Weygand, *Ber.*, **68**, 1282 (1935).

[5] Prepared according to the method of Vermeulen, *Rec. trav. chim.*, **48**, 969 (1929).

[6] The procedure for the synthesis of this compound has been discussed by Parijs, *Rec. trav. chim.*, **49**, 45 (1930), and by Kipnis, Weiner and Spoerri, THIS JOURNAL, **66**, 1446 (1944). The latter authors give other references to applications of this reaction.

[7] Prepared according to the method of Crossley and Renouf, *J. Chem. Soc.*, **95**, 212 (1909).

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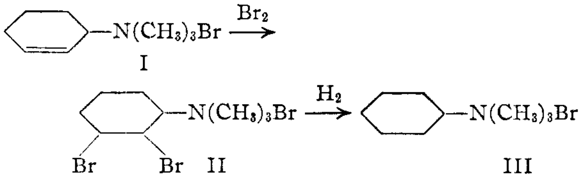
The Reduction of Allylic Quaternary Ammonium Bromides

BY DAVID R. HOWTON

In connection with other work, we have studied the reduction of 2-cyclohexenyltrimethylammonium bromide (I). The catalytic hydrogenation of I at room temperature and atmospheric pressure over Adams platinum, Raney nickel, palladium-on-barium-sulfate, or palladium-on-charcoal proceeds with the uptake of more than one molecular equivalent of hydrogen and the formation of trimethylamine hydrobromide. With the palladium catalysts, small amounts of the intact reduction product (III) are formed.[1]

We wish to report that the reduction I → III can be accomplished smoothly by addition of bromine to I[2] followed by hydrogenation of the intermediate dibromoquaternary bromide (II) at room temperature and pressure over palladium-on-barium sulfate.[3]



We have also applied this procedure, which is presumably of general applicability, to the conversion of allyltrimethylammonium bromide into *n*-propyltrimethylammonium bromide; further examples of its use[4] will be published in the near future.

The author wishes to thank Dr. Edwin R. Buchman for his interest in, and The Research Corporation for its financial support of, this work.

Experimental[5]

2-Cyclohexenyltrimethylammonium bromide (I) was prepared in 82% yield by adding somewhat more than the theoretical amount of an 18% solution of trimethylamine in benzene to 3-bromocyclohexene[6] and allowing the mixture to stand overnight at room temperature. Recrystallized from ethyl acetate–ethanol or by rapidly diluting a concentrated methanol solution with acetone, I formed colorless needles or flat blades, m. p. 179.5–180.0° dec. Harries,[7] who prepared this salt by another method, gives m. p. 181°. The quaternary picrate corresponding to I formed long bright yellow needles from ethanol, m. p. 129.7–130.1°.

Anal. Calcd. for $C_{15}H_{20}N_4O_7$: C, 48.91; H, 5.47. Found: C, 49.12; H, 5.53.

Direct catalytic hydrogenation of I over pre-reduced platinum oxide resulted in the absorption of 1.62 molecular equivalents of hydrogen; trimethylamine hydrobromide (identified by m. p. and mixed m. p. with an authentic sample) was isolated in good yield from the reaction mixture. The use of Raney nickel as a catalyst in the hydrogenation gave very similar results. The principal product of an experiment using palladium-on-charcoal was again trimethylamine hydrobromide; by virtue of the volatility of free trimethylamine, a 6% yield of III (identified by m. p. and mixed m. p. of the picrate double salt described below) was also obtained; hydrogenation over palladium-on-barium sulfate[8] also gave small amounts of III.

(2,3-Dibromocyclohexyl)-trimethylammonium Bromide (II).—A solution of 1.10 g. (0.005 mole) of I in about 5 ml. of chloroform was treated with one molecular equivalent (0.80 g.) of bromine. On standing overnight at room temperature, the initially-precipitated heavy orange oil lost most of its color and redissolved. After removing the chloroform on a steam-bath, the solid residue was taken up in a little warm ethanol and diluted with acetone, giving 1.54 g. (81%)[9] of II, crude m. p. 144–149° dec.; recrystallization from methanol diluted with acetone gave well-formed colorless rhombs, m. p. 152° dec.

Anal. Calcd. for $C_9H_{18}Br_3N$: N, 3.69. Found: N, 3.26.

The picrate of II, after two recrystallizations from ethanol–water, formed glistening aggregates of yellow needles, m. p. 148.9–149.2°.

Anal. Calcd. for $C_{15}H_{20}Br_2N_4O_7$: C, 34.11; H, 3.82. Found: C, 34.38; H, 4.16.

Hydrogenation of II.—Shaking a solution of 0.91 g. of II in 10 ml. of water with 0.50 g. of palladium-on-barium-sulfate[8] and moist hydrogen resulted in the absorption of 113.6 ml. (calcd. for two mole-equivalents, 123 ml.) of the gas in about two hours. Two recrystallizations of the crude product (0.47 g., calcd. 0.53 g.) from acetone–methanol gave sparse clusters of colorless needles (III), m. p. 281° dec., in good yield.

Anal. Calcd. for $C_9H_{20}BrN$: N, 6.30. Found: N, 6.47.

Treatment of this salt with sodium picrate gave a product identical (m. p. and mixed m. p.) with that prepared in the same way from an authentic sample of cyclohexyltrimethylammonium iodide[10]; analysis of this derivative (clusters of long orange-yellow needles from ethanol, m. p. 188.2–188.5°) indicated that it was a hydrated double salt composed of cyclohexyltrimethylammonium picrate and sodium picrate.

Anal. Calcd. for $C_{15}H_{22}N_4O_7 \cdot C_6H_2N_3O_7Na \cdot 1.5H_2O$: C, 38.89; H, 4.20; N, 15.12; Na, 3.55. Found: C, 38.87; H, 4.27; N, 15.33; Na, 3.68.

The sodium-free picrate corresponding to III was obtained by shaking an aqueous solution of the iodide with silver oxide and adding an equivalent amount of picric

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[1] Emde and Kull (*Congr. intern. quim. pura aplicada*, **4**, 290 (1934) [*C. A.*, **30**, 2932 (1936)]; *Arch. Pharm.*, **274**, 173 (1936) [*C. A.*, **30**, 4829 (1936)]) have observed similar results in the hydrogenation of other allylic trimethylammonium halides; apparently Raney nickel has not been shown previously to cause this type of hydrogenolytic fission of the carbon–nitrogen bond.

[2] Brominations of this type have been carried out by Partheil (*Ann.*, **268**, 155 (1892)) and others; the statement by Robertson, Clare, McNaught and Paul (*J. Chem. Soc.*, 335 (1937); cited by Williams, *Trans. Faraday Soc.*, **37**, 750 (1941)) that allylammonium ions are unreactive toward bromine is unqualified and unsupported by any evidence in their paper.

[3] These conditions have been used by Rosenmund and Zetzsche (*Ber.*, **51**, 578 (1918)) to replace halogen with hydrogen in vicinal dihalides of another type.

[4] Buchman and Howton, work in progress; an allylic rearrangement has been observed to take place during one bromination of this type.

[5] All melting points are corrected. Microanalytical work was done by Dr. G. Oppenheimer and G. A. Swinehart. Except as described otherwise, quaternary picrates reported in this paper were prepared by addition of a hot 10% aqueous solution of sodium picrate to a concentrated solution of the corresponding quaternary halide in water. Occasionally we have noted that picrates prepared in this way are apparently double salts containing, in addition to the expected quaternary picrate, an equivalent amount of sodium picrate. In order to detect these anomalies, salts prepared by this method should be subjected to carbon–hydrogen analysis to reveal any ash content; nitrogen analyses may not discern such anomalies in some cases.

[6] Ziegler, Späth, Schaaf, Schumann and Winkelmann, *Ann.*, **551**, 80 (1942); see also Howton, THIS JOURNAL, **69**, 2060 (1947).

[7] Harries, *Ber.*, **45**, 813 (1912).

[8] Catalyst prepared according to Schmidt, *Ber.*, **52**, 409 (1919).

[9] An experiment of the same size in which bromine was added until it was no longer taken up and the excess bromine destroyed almost at once by heating with ethanol gave a 66% yield of II and 13% of recovered I.

[10] Obtained in 85% yield by the exhaustive methylation of cyclohexylamine, massive striated colorless bars from acetone–methanol, m. p. 271.5–271.8° dec., Wallach, *Ann.*, **340**, 46 (1905), gives m. p. 260°; Breuer and Schnitzer, *Monatsh.*, **68**, 301 (1936), m. p. 263°. Catalytic (platinum) hydrogenation of the methobromide of N,N-dimethylaniline (from the base plus methyl bromide in benzene, pale blue jagged clusters from ethyl acetate–ethanol, m. p. 212° dec.; Vorländer and Siebert, *Ber.*, **52**, 283 (1919), give m. p. *ca.* 214°, gave an almost quantitative yield of trimethylamine hydrobromide, as reported in a similar case by Emde and Kull (*cf.* ref. 1).

acid to the resulting solution of the quaternary hydroxide, clusters of yellow needles from ethanol, m. p. 125.4°.

Anal. Calcd. for $C_{15}H_{22}N_4O_7$: C, 48.64; H, 5.99; N, 15.13. Found: C, 48.92; H, 5.98; N, 15.04.

Mixing an aqueous solution of this salt with another of sodium picrate gave the mixed salt, m. p. 188°.

Allyltrimethylammonium bromide (IV), obtained by the method used to prepare I, formed a picrate, long yellow needles from ethanol–water, m. p. 220.3–220.5° dec.

Anal. Calcd. for $C_{12}H_{16}N_4O_7$: C, 43.90; H, 4.91. Found: C, 43.92; H, 4.71.

The action of sodium styphnate on IV in aqueous solution gave a styphnate, long slender yellow bars from water, m. p. *ca.* 155° dec.

(2,3-Dibromo-*n*-propyl)-trimethylammonium bromide (V) was prepared from IV as described above in the preparation of II, colorless flossy sheaves from ethanol, m. p. 178° dec. (Partheil (see ref. 2) gives m. p. 173°). The picrate was recrystallized from ethanol, brilliant yellow needles, m. p. 127.5–128.5°.

Anal. Calcd. for $C_{12}H_{16}Br_2N_4O_7$: C, 29.53; H, 3.30. Found: C, 29.56; H, 3.31.

Hydrogenation of V (0.68 g.) was carried out as with II. After one hour, the hydrogen-uptake was negligible and 109.6 ml. had been absorbed (theory 103.5 ml.). The light brown crystalline residue obtained by evaporation of the catalyst-freed solution weighed 0.36 g. (calcd. 0.36 g.). The picrate prepared from this crude product was identical with an authentic sample of *n*-propyltrimethylammonium picrate (m. p. and mixed m. p., see below).

Authentic *n*-propyltrimethylammonium bromide was prepared from *n*-propyl bromide by the action of trimethylamine in benzene; the crude product was dissolved in a small amount of warm ethanol and diluted with acetone, irregular etched colorless bars or parallelopiped plates, m. p. 242.5–243.0° dec.

Anal. Calcd. for $C_6H_{16}BrN$: C, 39.57; H, 8.86; N, 7.69. Found: C, 39.42; H, 8.73; N, 7.77.

The corresponding picrate formed opaque yellow striated bars from water, m. p. 200–201°.[11]

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[11] Hanhart and Ingold, *J. Chem. Soc.*, 1014 (1927), give m. p. 195–196°; Ries, *Z. Kryst. und Min.*, **55**, 485 (1915–1920), m. p. 207°.

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RECEIVED JUNE 3, 1947

Diffusion Coefficients and Molecular Radii of Hydrogen Cyanide, Cyanogen Chloride, Phosgene and Chloropicrin[1]

BY I. M. KLOTZ AND D. K. MILLER

In studies of the mechanism of removal of gases by porous adsorbents such as charcoal, it is necessary to have information on the diffusion coefficients of these molecules in air.[2] While approximate methods are available for estimating these coefficients[3] it was considered desirable to obtain accurate information for a number of substances of historical interest as toxic agents. Since classical kinetic theory correlates the molecular radius with the diffusion coefficient of a gas, it is also possible to use the data obtained to calculate radii for the substances investigated. These radii may be of particular interest in connection with the determination of surface areas from adsorption methods.

Experimental

The rate of evaporation of the substance in the liquid state was measured with an apparatus which is essentially the Winkelmann modification of Stefan's method.[4] In brief the diffusion coefficient is determined by following the rate of fall of the meniscus of a column of the liquid in a small glass tube across the top of which a current of fresh air is blown. Experiments were carried out at a number of different rates of flow in order to be certain that zero concentration of toxic gas was maintained at the open end of the small glass tube. All experiments were carried out in duplicate. Temperatures were constant within ±0.05°.

Results and Calculations

The diffusion coefficient, D, was calculated from the equation

$$D = \frac{x \Delta x \rho RT}{Mtp} \frac{1}{\ln[p/(p - p_s)]} \qquad (1)$$

where

x = average distance, in cm., from the level of the meniscus to the top of the tube during the experiment
Δx = change in the level of the meniscus in the time t
ρ = density of the liquid
R = gas constant
T = absolute temperature
M = molecular weight of the vapor
p = total pressure
p_s = saturation pressure of the vapor at the temperature T

The results obtained are summarized in Table I.

TABLE I

DIFFUSION COEFFICIENTS

Vapor	Temperature, °C.	D (sq. cm./sec.)
CCl_3NO_2	25	0.088
$COCl_2$	0	.095
CNCl	0	.111
HCN	0	.173

From Table I, it is evident that the diffusion coefficient rises with decreasing molecular weight, as would be expected from the kinetic theory of gases. It is also of interest to note that the values obtained fall quite close to the approximate curve used previously for general calculations.[2]

Estimates of the radii of these vapor molecules have been made from the measured diffusion coefficients with the aid of the equation[5,6]

$$(r + 1.54 \times 10^{-8})^2 = \frac{\sqrt{\bar{C}_1^2 + \bar{C}_2^2}}{3\pi Dn\,(1 + \alpha)} \qquad (2)$$

where

r = the radius of the vapor molecule
$\bar{C}_1$ = the mean velocity of the vapor molecule
$\bar{C}_2$ = the mean velocity of an air molecule
$\bar{C}$ = $0.921\sqrt{3RT/M}$
n = the number of molecules in one cc. of air at 760 mm. and the temperature T
α = a correction factor depending on the relative masses of the vapor and air molecules[5,6]

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[1] This work was performed under OSRD contract OEMsr-282 between Northwestern University and the Office of Scientific Research and Development, Washington, D. C.

[2] I. M. Klotz, *Chem. Rev.*, **39**, 241 (1946).

[3] E. R. Gilliland, *Ind. Eng. Chem.*, **26**, 681 (1934).

[4] K. Jellinek, "Lehrbuch der physikalischen Chemie," Vol. II, 2nd ed., F. Enke, Stuttgart, 1928, pp. 615–618.

[5] J. H. Jeans, "The Dynamical Theory of Gases," Cambridge University Press, Cambridge, 1921, p. 316.

[6] E. Mack, Jr., THIS JOURNAL, **47**, 2468 (1925).