Summary

The preparation of a new type of sugar derivative is described. The heating of a suspension of phenyl-D-glucosazone with an aqueous solution of copper sulfate causes the production of aniline and a very stable substance which proves to be a substituted osotriazole, now named phenyl-D-glucosotriazole. Proof of the structure of the substance has been obtained through the oxidation by sodium periodate to yield v. Pechmann's 2-phenyl-4-formyl-osotriazole. The role played by the copper sulfate apparently concerns an osazone-copper ion complex, of deep red color, the formation of which is readily observable in the case of easily soluble osazones. Phenyllactosotriazole is hydrolyzed by mineral acids at nearly as fast a rate as lactose and yields phenyl-D-glucosotriazole and D-galactose. The phenylosotriazoles from several other sugars are mentioned, in advance of later full publication; the reaction is a general one for sugar phenylosazones and the yields are good. Owing to the very low solubility of phenyl-D-glucosotriazole and its high tendency to crystallize, its production from phenyl-D-glucosazone is a useful confirmatory test for the latter substance, especially for small quantities of it.

BETHESDA, MARYLAND RECEIVED FEBRUARY 16, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Hydrolysis of Trimethylethylene Bromide. Mechanism of Ketone Formation

BY C. M. SUTER[1a] AND HARRY D. ZOOK[1b]

It has long been known that the hydrolysis of certain olefin bromides results in the formation of carbonyl compounds. Eltekoff[2] obtained acetaldehyde and ethylene glycol from ethylene bromide or chloride, acetone and propionaldehyde from the propylene halides, isobutyraldehyde from isobutylene bromide and methyl isopropyl ketone from trimethylethylene bromide. His procedure consisted in heating the halide with lead oxide and water to 140-150°. The formation of methyl isopropyl ketone also has been studied by Ipatieff[3a] and more recently by Whitmore and Evers,[3b] who found the use of lead oxide or a high temperature unnecessary. This reaction is now the most convenient source of the ketone.[4] Some other olefin bromides give aldehydes or ketones on hydrolysis but the yields are not large.[5]

Little consideration has been given to the mechanism by which the olefin halides are converted to the carbonyl compounds. Eltekoff[2] found that the longer a halide was heated with water and lead oxide the larger the yield of aldehyde or ketone and the smaller the amount of glycol. He concluded, therefore, that the dehydration of the glycol in the slightly acidic solution was the source of the carbonyl compound. He further found that trimethylethylene glycol was converted to the ketone when its aqueous solution was heated to 220°. Ayres[6] has shown that tetramethylethylene bromohydrin when heated to 100° in the dry state or when shaken with aqueous silver nitrate or oxide yields pinacolone directly without intervention of the glycol. Some time ago Whitmore[7] suggested that ketone formation from a dibromide occurred without involving either a bromohydrin or glycol as an intermediate.

$$(CH_3)_2CBrCHBrCH_3 \xrightarrow{H_2O} [(CH_3)_2C^+CHBrCH_3] \longrightarrow$$
$$[(CH_3)_2CHC^+BrCH_3] \xrightarrow{H_2O} (CH_3)_2CHCOCH_3$$

However, behavior of indene bromide where the halogen adjacent to the benzene ring shows about the same activity as that of a tertiary alkyl halide, is not in accord with this mechanism.[8] Here indene bromohydrin is the primary hydrolysis product and this may be converted to 1-indanone or through the glycol to 2-indanone. If the bromohydrin were an intermediate in the hydrolysis of trimethylethylene bromide, ketone formation could occur either directly with the shift of a methyl group or indirectly by way of the glycol, but in the case of isobutylene bromide, the bromohydrin should give methyl ethyl ketone, whereas only isobutyraldehyde has been observed. Here, at least, it seemed clear that if the bromohydrin is an intermediate, so also is the glycol. In the present investigation a detailed study has been made of the hydrolysis of trimethylethylene and isobutylene bromides, mostly in dioxane-water mixtures.

As was pointed out recently by Vaughan and Rust,[9] pure trimethylethylene bromide has not been described. The action of bromine upon *t*-amyl alcohol gives a product from which a mix-

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(2) Eltekoff, *J. Russ. Phys.-Chem. Soc.*, **10**, 215 (1878); *Ber.*, **11**, 989 (1878).

(3) (a) Ipatieff, *J. prakt. Chem.*, (2) **53**, 266 (1896); (b) Whitmore and Evers, THIS JOURNAL, **55**, 812 (1933).

(4) Whitmore, Evers and Rothrock, "Organic Syntheses," **13**, 68 (1933); Calonge, *Bull. soc. chim.*, [5] **3**, 501 (1936).

(5) Froebe and Hochstetter, *Monatsh.*, **23**, 1082 (1902); Evers, Rothrock, Woodburn, Stahly and Whitmore, THIS JOURNAL, **55**, 1136 (1933).

(6) Ayres, *ibid.*, **60**, 2956 (1938).

(7) Whitmore, *ibid.*, **54**, 3274 (1932).

(8) Porter and Suter, *ibid.*, **57**, 2022 (1935).

(9) Vaughan and Rust, *ibid.*, **61**, 215 (1939); Conn, Kistiakowsky and Smith, *ibid.*, **61**, 216 (1939).

ture of isomeric dibromides may be separated by distillation but these resist further purification by this means. The bromination of trimethylethylene gives a mixture of substitution and addition products from which by fractional distillation and crystallization the dibromide has now been isolated in a state of satisfactory purity. To get an equally pure product from the isomeric dibromides obtained directly from *t*-amyl alcohol required some thirty crystallizations and gave a low yield.

In a preliminary experiment involving 0.058 *M* trimethylethylene bromide in 50% by volume aqueous dioxane at 80°, it was found that over 90% of the theoretical amount of hydrobromic acid was formed in twenty-five minutes but that no appreciable amount of ketone had appeared. After ten hours ketone formation still amounted to less than 20% of the theoretical amount. This at once indicated that the hydrolysis of the bromides was in no way directly related to the formation of methyl isopropyl ketone. That the ketone arises from trimethylethylene glycol through the catalytic action of the hydrogen ions in the solution was confirmed by preparing the pure glycol and measuring the rate at which it was converted to the ketone under various conditions. In dilute (0.11 *M*) sodium carbonate solution at reflux temperature no detectable amount of ketone resulted in thirteen hours. In distilled water the odor of ketone became noticeable within an hour and at the end of six hours, the ketone present corresponded to 1.2% of the theoretical amount. The solution had, however, become slightly acidic due to some side reaction and it appears that some decomposition with formation of a trace of acid preceded ketone formation. Measurements in sulfuric and hydrobromic acid solutions showed that the reaction rate was dependent upon the hydrogen ion activity. The rate of ketone formation in a solution made by dissolving trimethylethylene bromide in water by stirring for some time at 80° was in agreement with that in a solution obtained by adding the glycol to hydrobromic acid. The value of K, the first order constant, showed some decrease as the reaction progressed, probably due to side reactions among which was the formation of the unidentified acidic substance already mentioned. At 80° the initial value of K was 0.20 hours^{-1} decreasing to 0.18 hours^{-1} at half reaction where

$$K = \frac{2.3}{t\gamma[\mathrm{H}^+]} \log \frac{a}{a - x}$$

Several methods of estimating methyl isopropyl ketone were investigated in some detail.[10] It was found that precipitation with 2,4-dinitrophenylhydrazine was unsatisfactory since ketone solutions less than 0.01 *M* in 3:2 dioxane–water mixtures gave negative tests. Messinger's iodoform method[11] which works well for acetone gave somewhat variable results. The amount of iodine consumed in 3:2 dioxane–water solutions for ketone concentrations ranging from 0.01 *M* to 0.1 *M* corresponded to 50 ± 5% of the theoretical amount based upon the equation

$$\mathrm{C_5H_{10}O + 4I_2 + 5NaOH \longrightarrow}$$
$$\mathrm{(CH_3)_2CICOONa + CHI_3 + 4H_2O + 4NaI}$$

The analytical method finally adopted was based upon that of Marasco[12] for acetone. The reaction of the ketone with hydroxylamine hydrochloride was found to be 66 ± 3% complete for ketone solutions of concentrations ranging from 0.01 *M* to 0.1 *M* made up in 3:2 dioxane–water solution. In distilled water the reaction was 58 ± 2% complete. In both cases the percentage decreased rapidly for lower concentrations being 51% for 0.005 *M* ketone in water.

The formation of hydrogen bromide from trimethylethylene bromide occurred at a convenient rate at 45° and most of the hydrolysis measurements were made at this temperature. It was first found that acid formation occurred by a first order reaction since changing the initial concentration did not change k_1. This is a characteristic of the halogen in simple tertiary alkyl halides.[13] Under some circumstances olefin formation is known[14] to accompany hydrolysis but this was unimportant for the dibromide.[15] However, when the value of k_1 for the hydrolysis of the dibromide to the bromohydrin was determined for various time intervals on the assumption that no other reaction was taking place, the value increased regularly with time. This is what would be expected if the bromohydrin were undergoing conversion to the glycol at a rate comparable to that of the first reaction. A satisfactory value was obtained for k_1 by plotting its apparent value against time and extrapolating to zero time.

$$\mathrm{(CH_3)_2CBrCHBrCH_3} \xrightarrow[\mathrm{H_2O}]{k_1} \mathrm{(CH_3)_2COHCHBrCH_3} \xrightarrow[\mathrm{H_2O}]{k_2}$$
$$\mathrm{(CH_3)_2COHCHOHCH_3}$$

With k_1 known, the quantity of hydrobromic acid formed at a given time from the first hy-

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(10) It is interesting to note that although methyl isopropyl ketone is the only carbonyl compound that has been isolated from this hydrolysis, 2,3-dihydroxybutane gives some dimethylacetaldehyde along with methyl ethyl ketone when heated with aqueous sulfuric acid. The former compound is formed by a methyl rearrangement of the pinacol–pinacolone type. Akabori, *J. Chem. Soc. Japan*, **59**, 1132 (1938); *Chem. Abs.*, **33**, 2106 (1939). Note Added in Proof: Cook, Krimmel and Whitmore have just reported (A. C. S. meeting at Cleveland) that up to 1% of trimethylacetaldehyde is formed in the hydrolysis of trimethylethylene bromide.

(11) Scott, "Standard Methods of Chemical Analysis," D. Van Nostrand Co., New York, N. Y., 1927, p. 1759.

(12) Marasco, *Ind. Eng. Chem.*, **18**, 701 (1926).

(13) Cooper and Hughes, *J. Chem. Soc.*, 1183 (1937); Bateman, Hughes and Ingold, This Journal, **60**, 3080 (1938); Olson and Halford, *ibid.*, **59**, 2644 (1937). These references mention earlier work.

(14) Bateman, Hughes and Ingold, *J. Chem. Soc.*, 881 (1938); French, McShaw and Johler, This Journal, **56**, 1346 (1934); Woodburn and Whitmore, *ibid.*, **56**, 1394 (1934).

(15) This was evident since heating trimethylethylene bromide with water gave only water soluble products and gave also the theoretical amount of hydrobromic acid. 2-Methyl-3-bromo-2-butene would be water insoluble and inert to further hydrolysis. Ipatieff[3] has shown that alcoholic potassium hydroxide acts with the dibromide to produce this unsaturated compound.

drolysis was calculated and subtracted from the quantity found by titration. The excess was a measure of the extent to which the bromohydrin had hydrolyzed and the difference between the concentration of acid from the first reaction and that of the second gave the concentration of bromohydrin. The value of k_2 was then obtained by a graphical method[16] from the equation for two consecutive first order reactions

$$y = a + \frac{ak_1}{k_1 - k_2}e^{-k_1t} - \frac{ak_1}{k_1 - k_2}e^{-k_2t}$$

Here y is the concentration of hydrobromic acid from the second reaction at time t and a is the initial dibromide concentration. The calculation of k_2 for various time intervals showed a decrease with time but the initial value corresponded approximately to that of k_1.

The decrease of k_2 with time led us to consider another mechanism for the formation of glycol from dibromide. If it is assumed that the second bromine hydrolyzes at the same time as the first or that the second reaction occurs with great rapidity compared with the first, the hydrolysis data could be expressed by $k^*t = 2.3 \log a/(a - 0.5\,z)$, where a is the initial concentration of dibromide and z is the concentration of hydrobromic acid. As may be seen in Table I this hypothesis fits the experimental results with considerable accuracy.

TABLE I

Time, min.	$k_1 \times 10^4$ (apparent value)[a]	$k_2 \times 10^4$	$k^* \times 10^4$
60	23	..	11.0
120	25	..	11.6
170	27	..	12.1
290	30	..	11.9
470	42	..	12.0
680	..	16	12.0
890	..	15	11.9
1220	..	14	11.7
1490	..	13	11.7

[a] Extrapolation to zero time in this and other experiments gave $k_1 = 0.0021$ at 45°.

Trimethylethylene bromohydrin was then prepared and its hydrolysis studied. In brief, its hydrolysis rate was in agreement with that deduced from the experiments on dibromide hydrolysis, the rate exhibiting the same decrease with time. It was therefore necessary to decide experimentally between the two mechanisms. If k_1 and k_2 were approximately equal, the concentration of bromohydrin in the solution would reach an appreciable value whereas if the glycol were formed directly, the bromohydrin's concentration would be negligible. A method for determining the bromohydrin was therefore devised. In separate experiments it was found (1) that a bromohydrin could be titrated with standard alkali in hot solution using phenolphthalein as the indicator and (2) the distribution ratio of the bromohydrin between the two phases of a system containing water, dioxane and carbon tetrachloride was convenient for analysis of the aqueous layer. It was necessary to add the carbon tetrachloride to remove any unreacted dibromide, as this also reacts with hot dilute alkali. The distribution ratio of trimethylethylene bromohydrin was determined by shaking the carbon tetrachloride layer after the first separation again with a dioxane–water mixture and titrating a second time for bromohydrin. From these data both the total amount of bromohydrin present and the distribution ratio were readily calculated. The ratio for the isobutylene bromohydrin mentioned later was obtained by starting with a known quantity of pure compound. Application of this procedure to a sample of a hydrolysis mixture of trimethylethylene bromide showed that the bromohydrin was actually present and the quantity was in fair agreement with that calculated from the value of k_1. The approximate equality of k_1 and k_2 was therefore a coincidence. As a further check on this, the hydrolysis rates of isobutylene bromide and isobutylene bromohydrin were investigated. These compounds reacted at a much lower rate than the trimethylethylene homologs, k_1 being 12×10^{-5} compared with 21×10^{-4} and k_2 3×10^{-5} as compared with 16×10^{-4}. It is to be noted that here the bromohydrin hydrolyzes much more slowly than the dibromide. The rate of aldehyde formation from isobutylene glycol was not investigated.

Since the hydrolysis rate of a tertiary alkyl halide is not modified by either hydrogen or hydroxyl ions, it was of interest to determine the behavior of the trimethylethylene bromide in this respect. While the values of k_1 and k_2 both remained unchanged in acid solution, in alkaline solution the dibromide hydrolyzed at a much more rapid rate. This was not investigated in detail. The rapid action of alkali with the bromohydrin has already been mentioned.

The first rate determinations made on the hydrolysis of the bromohydrins were later found to be seriously in error. This was caused by the fact that when 0.1 *N* sodium hydroxide is added to a solution containing hydrogen ions and a bromohydrin, the latter reacts to a marked extent before neutralization of the alkali has taken place. This was not at all obvious in carrying out the titration since with methyl red–methylene blue indicator a sharp end-point was obtained. However, when 0.01 *N* or 0.001 *N* alkali was employed and the titration conducted at 0° a quite different curve resulted. The values obtained with 0.1 *N* alkali fell on a smooth curve so long as a standard titration procedure was used. Variation in the rate of adding the alkali or in stirring the solution gave erratic results. Titration of the hydrolysis mixtures from the dibromides gave less trouble

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(16) Hitchcock and Robinson, "Differential Equations in Applied Chemistry," John Wiley and Sons, New York, N. Y., 1923, p. 56.

as here the bromohydrin concentration was apparently low enough to reduce the alkali reaction to a minor factor.

Experimental

Preparation of Olefin Bromides.—The isobutylene bromide was prepared by fractionation of the product obtained by bromination of *t*-butyl alcohol. The sample used for rate determinations distilled constantly at 61° (40 mm.) and had n^{25}_{D} 1.5070.

Bromination of 435 ml. (4 moles) of *t*-amyl alcohol[4] and fractionation of the product through a 150 cm. column packed with glass helices gave 192 ml. of product distilling at 55° (17 mm.) and having a m. p. of −3 to +5° along with lower and higher boiling fractions that could not be solidified at −12°. Fractional crystallization involving thirty crystallizations gave 30 ml. of dibromide, m. p. 9–12°.

To 165 g. (2.36 moles) of trimethylethylene (obtained by fractionation of the olefins resulting from the dehydration of *t*-amyl alcohol with oxalic acid[17]) dissolved in 200 ml. of carbon tetrachloride was added slowly with stirring at 10–20° during two hours 124 ml. (2.3 moles) of bromine dissolved in 150 ml. of carbon tetrachloride. Fractionation gave 195 g. (125 ml.) of product distilling at 59.5–61° (19 mm.) and melting at 3–7°. Refractionation through a 60 cm. packed column gave 14 ml., m. p. 9–12° and other fractions with lower melting points. Systematic fractional crystallization of these gave 23 ml., m. p. 12–13°, n^{25}_{D} 1.5078, d^{25}_{4} 1.663 and 32 ml., m. p. 9–12°. The fraction melting at 12–13° was used for rate studies. The highest melting point previously reported[18] is 7°. Recently, a very pure product has been obtained directly by more careful fractionation of both the trimethylethylene and the dibromide. Twenty-three fractions boiled constant at 63°, n^{20}_{D} 1.5090, m. p. 14–16°.

Preparation of Olefin Bromohydrins.—Trimethylethylene bromohydrin has been prepared previously[19] in an impure state but isobutylene bromohydrin has not been described.

To a vigorously stirred mixture of 232 g. of trimethylethylene in 7 liters of water was added 200 ml. of bromine dissolved in 8 liters of water containing 600 g. of potassium bromide. The water layer was removed from 100 ml. of heavy oil (found later to be 76% dibromide) and subjected to a continuous ether extraction for eight hours. When the oily layer containing dibromide was not separated, it was found impossible to get pure bromohydrin, probably due to the formation of a constant boiling mixture. Distillation of the residue remaining after evaporation of the ether gave eight fractions of material all distilling at 48° (14 mm.) but ranging in refractive index from n^{25}_{D} 1.4680 to 1.4710. The last two fractions, n^{25}_{D} 1.4710, amounting to 46 ml. were combined and analyzed.

Anal. Calcd. for $C_5H_{11}OBr$: Br, 47.87. Found: Br, 47.70.

The pure bromohydrin proved to be unstable, a brown color developing within a few days and after thirty days a dark green mixture remained which upon distillation gave fractions apparently containing methyl isopropyl ketone, bromohydrin and dibromide. There remained a dark green water-insoluble residue. Redistillation of the bromohydrin before the green color developed regained the pure compound. It was necessary to keep the temperature below 60° during distillation or decomposition became appreciable. When heated at 100°, the characteristic odor of methyl isopropyl ketone became evident.

In the preparation of isobutylene bromohydrin, isobutylene from 600 ml. of *t*-butyl alcohol was passed through a flask containing 1500 ml. of water. A solution of 150 ml. of bromine and 400 g. of potassium bromide in 8 liters of water was added as fast as reaction took place as was indicated by the disappearance of the bromine color. The contents of the flask were stirred vigorously during the reaction. The aqueous solution of bromohydrin was decanted from an oily layer of 95 ml. and extracted three times with ether using 1 liter each time. The ether solution was dried over anhydrous magnesium sulfate and fractionated. Obtained were: fractions 2–4, 62 g., b. p. 48–49.5° (17 mm.), n^{25}_{D} 1.4680–1.4705; fractions 5–8, 164 g., b. p. 49.5° (16 mm.), n^{25}_{D} 1.4710, d^{25}_{4} 1.437. In contrast to trimethylethlene and tetramethylethylene[6] bromohydrins this material was stable almost indefinitely.

Trimethylethylene Glycol.—The following procedure was based upon the patented method of Schering.[20] Trimethylethylene bromide (62 ml., m. p. 9–12°) was stirred for three days at 50° with 1.5 liters of water containing 45 g. of sodium hydroxide. The water layer was separated from 5 ml. of a heavy oil and saturated with potassium carbonate (approximately 1 kg.). The glycol layer was taken up in ether and the salt solution continuously extracted with ether for five hours. From the combined ether solutions was obtained after distillation 21.5 g. (57%) of glycol, b. p. 75–76° (14 mm.), n^{25}_{D} 1.4375.

Purification of Dioxane.—The dioxane purified by the method of Eigenberger[21] after careful fractionation distilled at 100.3° (750 mm.) but still had appreciable iodine consumption.[11] This was reduced by fractional crystallization. It was noted that the crystals were white and translucent until the iodine consumption fell to zero when they became transparent.

Estimation of Methyl Isopropyl Ketone.—Solutions containing known concentrations of methyl isopropyl ketone in water and in water–dioxane mixtures were prepared. The acid liberated when 25-ml. samples of each of these solutions reacted with 400 ml. of neutralized hydroxylamine hydrochloride solution[12] was then determined by titration and the per cent. reaction plotted against concentration of ketone. The acid liberated amounted to 66 ± 3% for ketone solutions ranging from 0.01 to 0.1 *M* in 3:2 dioxane–water mixtures, decreasing to 54% for a 0.005 *M* solution. For ketone solutions in water the percentages were 58 ± 2% and 51%. The dioxane employed in making up the solutions had no iodine consumption and gave no test for carbonyl compounds with dinitrophenylhydrazine reagent. Making use of these data the extent of ketone formation in various reaction mixtures was determined.[10]

Ketone Formation from Trimethylethylene Bromide and Glycol.—A preliminary hydrolysis of the dibromide in dioxane–water solution at 79.8° showed practically quantitative formation of hydrobromic acid in one hour while ketone formation amounted to 10.3%. In a second experiment 2 ml. of the dibromide was added to 248 ml. of water at 79.8° and stirred until solution was complete. Then 25 ml. (24.4 ml. at 25°) samples were analyzed at various time intervals for ketone. In Table II $K = \frac{2.303}{t\gamma[\mathrm{H}^+]} \log \frac{a}{a - x}$ where $\gamma = 0.812$[22] and $[\mathrm{H}^+] = 0.113$. In a similar experiment in sulfuric acid solution in which 1.91 g. (2 ml.) of trimethylethylene glycol was added to 248 ml. of 0.119 *N* acid the average value of *K* to 50% reaction time (ninety-five hours) was 0.21 hours^{-1}. Here $\gamma = 0.341$.[23] In a solution made in the same way from 0.117 *N* hydro-

TABLE II

Time, hours	24	52.5	73	92	
x (ketone concn.)	0.0202	0.0322	0.0393	0.0413	0.0565
K, hours^{-1}	0.20	0.18	0.18	0.16	

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[17] Sherrill and Walter, THIS JOURNAL, **58**, 742 (1936); Thompson and Sherrill, *ibid.*, **58**, 745 (1936).

[18] Blaise and Courtot, *Bull. soc. chim.*, [3] **35**, 583 (1906).

[19] Read and Reid, *J. Chem. Soc.*, 1487 (1928).

[20] Schering, German Patent 246,572, *Frdl.*, **10**, 1010; *Chem. Zentr.*, **83**, I, 1874 (1912).

[21] Eigenberger, *J. prakt. Chem.*, **130**, 75 (1931).

[22] Livingston, THIS JOURNAL, **48**, 46 (1926).

[23] Randall and Scott, *ibid.*, **49**, 654 (1927).

bromic acid the value of K decreased markedly with time from 0.20 to 0.14 hour^{-1} at 36% ketone formation.

A solution containing 4.78 g. (5 ml.) of glycol in 100 ml. of water was refluxed for 5.75 hours. The characteristic odor of methyl isopropyl ketone became evident within one hour. A 25-ml. sample of the solution required 0.45 ml. of 0.141 N sodium hydroxide to neutralize the acid produced. Analysis for ketone indicated a yield of 1.2%. In another experiment where 1.2 g. of sodium carbonate was added at first, no ketone was formed.

Refluxing and stirring 16.63 g. (10 ml.) of trimethylethylene bromide with 200 ml. of water and 10 g. of sodium carbonate for six hours gave no detectable amount of ketone. The dibromide phase, however, disappeared in two hours.

Summary

The mechanism by which trimethylethylene bromide is converted into methyl isopropyl ketone has been studied. The reaction proceeds in steps through trimethylethylene bromohydrin and trimethylethylene glycol as evidenced by rate measurements on the hydrolysis of the bromide and bromohydrin and on the conversion of glycol to ketone.

Preliminary experiments with isobutylene bromide indicate that a similar mechanism holds for the hydrolysis of this compound.

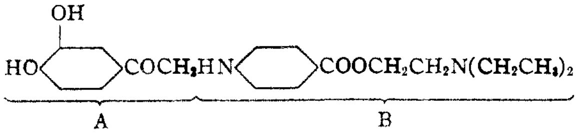
EVANSTON, ILLINOIS RECEIVED DECEMBER 22, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Amines Related to Epinephrine. I. Some Amines of the "Eprocaine" Type[1]

BY RALPH HILL[1] AND GARFIELD POWELL

Among local anesthetics which have pressor action, a compound appears[2] under the name of "Eprocaine." It is a particularly simple combination of a well-known pressor residue (A) and an anesthetic residue (B), and is reported to have pressor and anesthetic activity.[2]



We have sought, in the work described below, a confirmation of the preparation and properties of "eprocaine" itself, and the synthesis of other compounds in which the residue A is unchanged and the residue B is varied to include other anesthetic residues which have been subjected to some physiological testing. "Eprocaine" itself has been studied, and also the di-*n*-propyl, di-isopropyl, di-*n*-butyl homologs on the aliphatic amino group. We have also prepared, for comparison, the compounds in which B is the "benzocaine" residue (ethyl *p*-aminobenzoate) and the homologs of this having *n*-propyl and *n*-butyl ester groups, together with derivatives. The ethyl ester[3] has previously been described (with a much lower melting point) but no mention has been made of derivatives or physiological testing.

"Eprocaine" was found to give a definite rise in blood pressure when injected intravenously into a pithed decerebrate cat anesthetized with nembutal. A 1% solution gave definite anesthesia, administered intracutaneously to the guinea pig, with evidence the next day of severe tissue damage at the point of injection.[4] On the second group of amines (with B as benzocaine and related residues), anesthetic testing was limited (because of the low solubility of the salts in water) to dusting on the exposed sciatic nerve of the frog. With benzocaine as control, absence of activity was indicated.[5]

Experimental

β-Diethylaminoethyl *p*-(3,4-Dihydroxyphenacylamino)-benzoate Hydrochloride, "Eprocaine."—Fifteen grams of procaine was dissolved in 75 cc. of boiling water and 11.8 g. of chloroacetylcatechol added. The mixture was refluxed for two hours and then concentrated *in vacuo* nearly to dryness. On addition of 75 cc. of alcohol the residue crystallized. Recrystallized from 85% alcohol it melted at about 205° with darkening; yield 73% from procaine.

Anal.[6] Calcd. for $C_{21}H_{27}O_5N_2Cl$: C, 59.9; H, 6.5; N, 6.6; Cl, 8.4. Found: C, 59.8; H, 6.4; N, 6.9; Cl, 8.7.

"Eprocaine" is only slightly soluble in hot alcohol, but quite soluble in water. With ferric chloride solution it gives an emerald green color, turning violet on careful addition of sodium carbonate solution. All compounds described in this paper derived from 3,4-dihydroxyphenacyl halides responded to this test, with addition of alcohol when needed for solubility purposes. The free base is precipitated by sodium hydroxide and is dissolved in excess. The base is soluble in alcohol, acetone, and hot water, insoluble in cold water and benzene.

Table I shows the results obtained in the preparation of homologs by the following general procedure, in each case using a corresponding amount of the proper ester. Four grams of ethyl *p*-aminobenzoate was dissolved in about 500 cc. of boiling water and 4.5 g. of chloroacetylcatechol added. The clear solution was boiled for four hours, keeping the volume constant by the addition of water. During this process the product separated out as white flocculent crystals. The crystals were filtered hot, washed with hot water, and recrystallized from alcohol.

Dibenzoate of β-Diethylaminoethyl *p*-(3,4-Dihydroxyphenacylamino)-benzoate.—A solution of 0.5 cc. of benzoyl chloride in 3 cc. of benzene was added to 0.5 g. of "eprocaine" dissolved in 20 cc. of water. One-half gram of sodium carbonate was added in portions with shaking and cooling. The product separated as a gummy mass which

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(1) From a dissertation submitted by Ralph Hill in partial fulfillment of the requirements for the Ph.D. degree at Columbia University. Original manuscript received January 15, 1943.

(2) Osborne, *Science*, **85**, 105 (1935).

(3) Ishiwara, *Ber.*, **57**, 1126 (1924).

(4) Private report of M. G. Mulinos, Columbia University.

(5) Private report of Edwin J. Fellows, Temple University.

(6) For analyses reported in this paper we are indebted to Mr. Saul Gottlieb.