[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE AND THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF NOTRE DAME]

Studies on Amino Alcohols. I. The Preparation and Dehydration of Certain Aliphatic Tertiary Amino Alcohols[1]

BY BARBARA KNAPP CAMPBELL AND KENNETH N. CAMPBELL

Tertiary aliphatic alcohols, in general, undergo reactions in which the hydroxyl group is removed, such as dehydration and conversion to halides, more easily than do primary alcohols, but do not so readily enter into reactions in which the alcoholic hydrogen atom is replaced, such as esterification and etherification. In this connection, it seemed of interest to investigate the effect of an amino group on the properties of an alcoholic hydroxyl group.

If the amino group is considered to be electron-attracting,[2] then, because of the "inductive effect," the alcoholic hydrogen atom should be more loosely held. Tertiary amino alcohols in which the two functions are close together might, therefore, be expected to show some of the properties of primary alcohols, while, when the two functions are separated by a long carbon chain, the amino group should have little or no effect on the properties of the hydroxyl group.

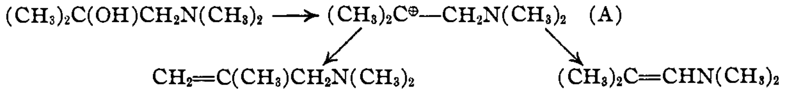
The object of the present investigation was to make a detailed study of the properties of the hydroxyl group in various types of amino alcohols. In this paper are reported the preparation and preliminary results on the dehydration of four aliphatic tertiary amino alcohols: 2-methyl-2-hydroxy-1-dimethylaminopropane (I), 2-methyl-2-hydroxy-4-dimethylaminobutane (II), 2-methyl-2-hydroxy-5-dimethylaminopentane (III), and 2-methyl-2-hydroxy-6-dimethylaminohexane (IV). The dimethylamino group was used in place of the unsubstituted amino group to minimize side reactions.

The first two members of the series (I and II) reacted instantly and vigorously at room temperature with benzoyl chloride in benzene solution to give the corresponding benzoate hydrochlorides. Compound III reacted only slowly under the same conditions, and compound IV not at all. A quantitative study of the ease of esterification of these and other amino alcohols is now in progress.

Comparative dehydration studies were made, using as nearly as possible the same conditions for the various amino alcohols. Although in general aliphatic tertiary alcohols are dehydrated readily by iodine,[3] the only member of the present series which was dehydrated by this reagent was compound IV. Compound I was not dehydrated by heating with anhydrous copper sulfate, a reagent which usually dehydrates aliphatic tertiary alcohols.[4] This reagent brought about dehydration of compounds II and III. Heating with potassium hydroxide did not dehydrate the first three amino alcohols.

Pyrolysis of the Grignard complex[3b] of 2-methyl-2-hydroxy-1-dimethylaminopropane (I) yielded 1-dimethylamino-2-methyl-1-propene, whose identity was established by the fact that its hydrochloride was readily hydrolyzed to isobutyraldehyde and dimethylamine in accordance with the usual behavior of vinyl amines.[5]

When this same amino alcohol (I) was treated with hot concentrated sulfuric acid, three products were isolated: dimethylamine, isobutyraldehyde and an unsaturated amine, $C_6H_{13}N$, which was not a vinyl amine since it resisted hydrolysis. Ozonization of this amine yielded formaldehyde but no acetone or acetaldehyde. From these results it seems probable that sulfuric acid dehydration of the amino alcohol gives both possible dehydration products, and that one of these, 2-methyl-1-dimethylamino-1-propene, is hydrolyzed during the process of isolation to isobutyraldehyde and dimethylamine.



$$\begin{tikzcd} (CH_3)_2C(OH)CH_2N(CH_3)_2 \arrow[r] & (CH_3)_2C^{\oplus}{-}CH_2N(CH_3)_2 \quad (A) \arrow[dl] \arrow[dr] & \\ CH_2{=}C(CH_3)CH_2N(CH_3)_2 & & (CH_3)_2C{=}CHN(CH_3)_2 \end{tikzcd}$$

The possibility that rearrangement of fragment A occurs is not, however, excluded. Further studies are in progress on the dehydration of amino alcohols.

Crystallographic studies were made on the

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[1] A part of this paper is abstracted from the thesis presented by B. K. Campbell in partial fulfilment of the requirements for the Ph.D. degree at Pennsylvania State College, August, 1937.

[2] Ingold, *Chem. Rev.*, **15**, 236 (1934).

[3] (a) Hibbert, THIS JOURNAL, **37**, 1748 (1915); (b) Church, Whitmore and McGrew, *ibid.*, **56**, 176 (1934).

[4] Meyer and Tuot, *Compt. rend.*, **196**, 1231 (1933).

[5] Meyer and Hopff, *Ber.*, **54**, 2274 (1921); Stach and König, *ibid.*, **63**, 88 (1930).

benzoate ester hydrochlorides, and will be reported elsewhere.

The authors wish to express their gratitude to Dean Frank C. Whitmore for suggesting the problem, and for much helpful advice, and to Professor Roger Adams and the Faculty of the University of Illinois for assistance and the use of their laboratories during 1935–36. The anhydrous dimethylamine used in this work was very kindly donated by the Röhm and Haas Co. of Philadelphia.

Experimental

2-Methyl-2-hydroxy-1-dimethylaminopropane (I)

Preparation.—This substance was prepared by a modification of the method of Fourneau.[6] A solution of 196 g. (1.8 moles) of methyl chloroacetate (b. p. 128° at 732 mm., $n^{20}{}_D$ 1.4211) in 800 cc. of dry ether was added dropwise, with cooling, over a period of seven hours to a Grignard reagent prepared from 120 g. (5 moles) of magnesium turnings, 1200 cc. of dry ether and methyl chloride gas. The reaction product was hydrolyzed with ice and hydrochloric acid, and extracted with ether. The ether solution, dried over anhydrous sodium sulfate, was concentrated under reduced pressure at room temperature until the residue showed $n^{20}{}_D$ about 1.433.

The crude isobutylene chlorohydrin (170–180 g., 1.6–1.7 moles) was heated in a 1-liter autoclave with 200 g. (4.4 moles) of anhydrous dimethylamine in 400 cc. of dry benzene at 135–140° for seven to eight hours. The maximum pressure developed was 150 pounds per square inch (10 atm.). The reaction product was filtered from solid dimethylamine hydrochloride, the benzene removed by distillation and the residue fractionated through column I[7] at 737 mm. to give ten fractions and a residue of 25 g. of a brown liquid. Fractions 4–9 inclusive, b. p. 127–128°, $n^{20}{}_D$ 1.4214–1.4215, weighed 81.3 g., a 40% yield, based on the ester used.

The pure amino alcohol had the following physical constants: b. p. (micro-Cottrell apparatus) 130.0–130.3° at 743 mm., $n^{20}{}_D$ 1.4215, $d^{20}{}_4$ 0.85881, MR_D obsd. 34.58, MR_D calcd. 35.49. It is miscible with water, alcohol, chloroform and ether, and is slightly soluble in ligroin. It decolorizes alkaline potassium permanganate and bromine in carbon tetrachloride, instantly, in the cold. It forms a chloroaurate, m. p. 126–128°.

Anal. Calcd. for $C_6H_{16}NOAuCl_4$: Au, 43.10. Found: Au, 42.80.

The alkamine hydrochloride, prepared by treating a solution of the alkamine in dry ether with dry hydrogen chloride, melted at 114.5–115.5° after recrystallization from chloroform–ligroin mixture.

Anal. Calcd. for $C_6H_{16}NOCl$: C, 46.90; H, 10.51; N, 9.13; Cl, 23.12. Found: C, 47.12; H, 10.28; N, 9.24; Cl, 23.36.

Benzoate Hydrochloride.—The amino alcohol was treated with benzoyl chloride in dry benzene according to the procedure of Fourneau.[6b] An immediate reaction took place, considerable heat was evolved and the ester hydrochloride precipitated. After two recrystallizations from alcohol and ether it was obtained as white monoclinic crystals which melted at 200°.[8]

Anal. Calcd. for $C_{13}H_{20}NO_2Cl$: N, 5.44; Cl, 13.80 Found: N, 5.44; Cl, 14.02.

Dehydration.—The apparatus used in these reactions was thoroughly dried by means of a current of hot, dry air before every reaction.

With Iodine.—Eight and six-tenths grams of the amino alcohol and a few crystals of iodine were refluxed for thirty minutes in a small flask attached to column II, and the mixture then distilled. No low-boiling material was obtained. Four grams of amino alcohol (b. p. 128°) was recovered, and 3 g. of a solid compound, m. p. 113°, was left in the flask. This solid, which was salt-like and contained ionizable iodine, was not identified.

With Potassium Hydroxide.—Twenty grams of solid potassium hydroxide was placed in a small two-necked flask attached to column II, and heated to 180°. Ten grams of amino alcohol was added dropwise to the hot alkali, the mixture heated under reflux for thirty minutes (oil-bath temperature 200°) and then slowly distilled. No low-boiling material was obtained, and 6.5 g. of amino alcohol, b. p. 125–128°, $n^{20}{}_D$ 1.4220, was recovered.

With Anhydrous Copper Sulfate.—Two grams of anhydrous copper sulfate was placed in a small two-necked flask attached to column II and heated to 200°. Ten grams of amino alcohol was added dropwise, the mixture heated under reflux for thirty minutes and then distilled. The distillate, b. p. 125–128°, $n^{20}{}_D$ 1.4210, weighed 7 g. No low-boiling material was obtained.

Pyrolysis of the Grignard Complex.—A solution of 60 g. (0.51 mole) of the amino alcohol in 120 cc. of ether was added at room temperature to a Grignard reagent prepared from 15 g. of magnesium turnings, 70 g. (0.64 mole) of ethyl bromide and 300 cc. of ether. The product was placed in a 1-liter Claisen flask and the ether removed by distillation from a water-bath. This bath was then replaced with one of Wood's metal, equipped with a pyrometer. Decomposition of the Grignard complex began when the bath temperature reached 280° and continued for thirty minutes, at the end of this time the temperature was 420°. The reaction flask contained considerable inorganic material mixed with tar. The main distillate, a yellow oil, was dissolved in dry ether and treated at 0° with dry hydrogen chloride. The solid hydrochloride so obtained was very unstable and quickly decomposed in moist air. It melted at 142–150°, and this melting point was not changed by attempts at purification. The yield was 10 g.

A portion of this hydrochloride was dissolved in water containing a few drops of hydrochloric acid, and the solution refluxed a few minutes. A strong aldehyde odor was observed. On treating a part of the solution with 2,4-dinitrophenylhydrazine a solid was obtained which melted at 180° after recrystallization. A mixture of this with the 2,4-dinitrophenylhydrazone of isobutyraldehyde (m. p.

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(6) (a) Fourneau, *Compt. rend.*, **138**, 766 (1904); (b) Fourneau, *J. pharm. chim.*, [7] **2**, 337 (1911).

(7) Two columns, packed with single-turn helices, were used in this work. Column I had a packed section of 13 × 400 mm., column II a packed section of 10 × 300 mm.

(8) Riedel, German Patent 169,746, records the melting point as 202°.

182°) melted at 180°. The rest of the solution was made alkaline with potassium hydroxide and boiled. A gas was evolved which turned red litmus blue and which had the odor of dimethylamine. A part of the gas was collected in dilute hydrochloric acid and treated with gold chloride. The product melted at 195°. Dimethylamine chloroaurate melts at 195–198°.[9]

Dehydration with Concentrated Sulfuric Acid.—A mixture of 70 g. of the amino alcohol and 200 g. of concentrated sulfuric acid was warmed on the steam-bath for ten hours and then was poured over an equal volume of crushed ice. Attempts were made to isolate the product by making the solution alkaline, extracting with ether and fractionating the extract, but no definite fractions could be isolated. The following method was adopted.

The aqueous solution was treated, with cooling, with solid potassium hydroxide until it was only slightly acid to litmus. It was then distilled until the boiling point reached 80°. The distillate, which came over largely at 60–70°, gave a 2,4-dinitrophenylhydrazone, m. p. 181°, which did not depress the melting point of an authentic sample of isobutyraldehyde 2,4-dinitrophenylhydrazone (m. p. 182°).

The residue from the above distillation was made strongly alkaline and distilled until the boiling point reached 100° (this will be referred to later as distillation 2). The distillate consisted of a yellow oil and a small aqueous layer. The oil was dried, dissolved in dry ether and converted to the hydrochloride. This salt, m. p. 142–144°, was perfectly stable in air and slightly hygroscopic. It did not decompose when boiled with dilute hydrochloric acid, and could be recovered unchanged by concentrating the solution. It formed a chloroaurate which melted at 116–118°.

Anal. Calcd. for $C_4H_{14}NAuCl_4$: Au, 44.87, Found: Au, 44.52.

Three grams of the hydrochloride was dissolved in 25 cc. of water[10] containing a few drops of hydrochloric acid, and treated with ozonized oxygen for four hours. The resulting solution was distilled under reduced pressure. The distillate gave positive tests for formaldehyde with resorcinol and gallic acid, a negative iodoform test and a negative Legal's test for acetone. Treatment with dimethyldihydroresorcinol gave a derivative, m. p. 187°, which did not depress the melting point of the methone derivative of formaldehyde (m. p. 187°). The basic fragment from the ozonization was not identified.

The aqueous mixture remaining from distillation 2 was acidified with hydrochloric acid and evaporated to a thick sirup, which yielded a chloroplatinate, m. p. 205°. A mixture of this with dimethylamine chloroplatinate (m. p. 206°) melted at 205°.

Anal. Calcd. for $C_4H_{16}N_2PtCl_6$: Pt, 39.00. Found: Pt, 38.50.

2-Methyl-2-hydroxy-4-dimethylaminobutane (II)

Methyl β-Bromopropionate.—A solution of 168 g. (1.1 moles) of crude β-bromopropionic acid,[11] in 500 cc. of absolute methyl alcohol was treated at 0° with a slow stream of dry hydrogen bromide for eight hours, and the mixture refluxed for ten hours. Excess alcohol was removed by distillation, the residue poured into cold water and worked up in the usual way. The crude ester was fractionated through column I to give 140 g. of material of b. p. 83° at 40 mm., n^{20}_D 1.4542. This is a 76% yield.

2-Methyl-2-hydroxy-4-dimethylaminobutane.—A solution of 320 g. (1.91 moles) of methyl β-bromopropionate in two volumes of dry ether was added, with cooling in an ice–salt bath, over a period of eight hours, to a Grignard reagent prepared from 144 g. (6 moles) of magnesium turnings, 1500 cc. of dry ether and excess methyl chloride gas. After standing for several hours at room temperature the reaction mixture was hydrolyzed with ice and hydrochloric acid and extracted with ether. The ether extract was dried over potassium carbonate and concentrated under reduced pressure at room temperature until the residue showed n^{20}_D 1.452.

The crude bromohydrin (270 g., about 1.6 moles) and a solution of 155 g. (3.5 moles) of anhydrous dimethylamine in 400 cc. of benzene were heated in an autoclave at 140–150° for eight hours. The product was worked up as described above. Eighty-five grams (a 34% yield) of the amino alcohol, b. p. 81° at 50 mm., n^{20}_D 1.4285–1.4295, was obtained.

The alkamine is a colorless viscous liquid with a disagreeable odor. It shows the same solubilities and reactions with permanganate and bromine as its lower homolog. Purified samples showed the following physical constants: b. p. (micro-Cottrell apparatus) 160.1–160.5° at 743 mm., n^{20}_D 1.4295, d^{20}_4 0.8602, *MR*D obsd. 39.30, *MR*D calcd. 38.60.

The hydrochloride melted at 141–141.5° after several recrystallizations from chloroform–ligroin and alcohol–ether mixtures.

Anal. Calcd. for $C_7H_{18}NOCl$: C, 50.08; H, 10.81; N, 8.35; Cl, 21.17. Found: C, 49.98; H, 10.61; N, 8.31; Cl, 21.19.

Benzoate Hydrochloride.—Ten grams of the amino alcohol in 30 cc. of dry benzene was added to a solution of 20 g. of benzoyl chloride in 20 cc. of benzene. The mixture immediately became hot and solidified. The product, after recrystallization from alcohol–ether, was obtained as white monoclinic crystals which melted at 165–166°. This ester hydrochloride is more hygroscopic than the preceding one.

Anal. Calcd. for $C_{14}H_{22}NO_2Cl$: N, 5.16; Cl, 13.07. Found: N, 5.17; Cl, 13.10.

Dehydration.—The dehydration experiments were carried out as described for the lower homolog. When 10 g. of alkamine was treated with iodine, 8 g. was recovered (b. p. 155–160°, n^{20}_D 1.4295) and no low-boiling material was obtained. The distillate gave a negative test for water with anhydrous copper sulfate. No dehydration occurred when 4 g. of alkamine was heated with 10 g. of solid potassium hydroxide, and 2.25 g. of the amino alcohol (b. p. 158–160°, n^{20}_D 1.4300) was recovered.

Treatment of 4.5 g. of the amino alcohol with 3 g. of anhydrous copper sulfate resulted in a distillate which boiled largely at 70–74°, contained a lower, aqueous layer and had an odor and refractive index (n^{20}_D 1.378) very different from those of the original alkamine. No attempt was made to identify this dehydration product.

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[9] Straus, *Ann.*, **401**, 375 (1913).

[10] Harries and Reichard, *Ber.*, **37**, 613 (1904).

[11] *Org. Syntheses*, **3**, 25 (1923).

Pyrolysis of the Grignard Complex.—The Grignard complex from 53 g. of amino alcohol and 0.5 mole of ethylmagnesium bromide was heated in a Wood's metal bath. Decomposition began suddenly at 300°. Practically no volatile material was obtained, and most of the product remained in the distilling flask as a thick tar, from which nothing could be extracted with ether.

2-Methyl-2-hydroxy-5-dimethylaminopentane, (III)

Methyl γ-Chlorobutyrate.—This ester was made from γ-chlorobutyronitrile (prepared by the method in "Organic Syntheses"[12]) by a modification of the procedure of Henry.[13] A solution of 192 g. (1.87 moles) of the nitrile (b. p. 84–85° at 15 mm., $n^{20}\text{D}$ 1.4463) in 500 cc. of absolute methanol was treated with a rapid stream of hydrogen chloride gas for three hours and the solution then refluxed for twelve hours. The precipitate was removed, the filtrate poured into cold water and the organic layer washed, dried and distilled. There was obtained 200 g. of ester of b. p. 90° at 45 mm., $n^{20}\text{D}$ 1.4318–1.4320. This is an 80% yield.

2-Methyl-2-hydroxy-5-dimethylaminopentane.—A solution of 200 g. of methyl γ-chlorobutyrate in 800 cc. of ether was added dropwise, over a period of six hours, to 4 moles of methylmagnesium chloride, cooled in an ice–salt bath. The mixture, after standing at room temperature for several hours, was hydrolyzed with ice and hydrochloric acid, and extracted with ether. The ether extract, dried over potassium carbonate, was concentrated at room temperature under reduced pressure until the residue showed $n^{20}\text{D}$ 1.436.

The crude chlorohydrin (200 g.) and a solution of 155 g. of dimethylamine in 400 cc. of benzene were heated in an autoclave at 140–150° for nine hours. Fractionation of the liquid product through column I gave 73 g. of a colorless, viscous liquid of b. p. 99° at 30 mm., $n^{20}\text{D}$ 1.4400, d^{20}_4 0.8644, *MR*D obsd. 44.22, *MR*D calcd. 44.61. The yield of amino alcohol was 34%, based on the ester used. The amino alcohol is soluble in water and organic solvents. It reacts with alkaline potassium permanganate and with bromine in carbon tetrachloride, in the cold.

The hydrochloride melted at 153–154° after several recrystallizations from chloroform–ligroin. It is very hygroscopic.

Anal. Calcd. for $C_8H_{20}NOCl$: C, 52.83; H, 11.10; N, 7.71; Cl, 19.54. Found: C, 52.70; H, 11.26; N, 7.53; Cl, 19.80.

Benzoate Hydrochloride.—A solution of 20 g. of amino alcohol in 60 cc. of benzene was added to a solution of 40 g. of benzoyl chloride in 40 cc. of benzene. No solid formed, and very little heat was evolved. After the mixture had stood at room temperature for three days, a fairly voluminous precipitate had collected. This material, after several recrystallizations, was obtained as white, monoclinic crystals which melted at 114°. This ester hydrochloride is much more hygroscopic than the two preceding ones.

Anal. Calcd. for $C_{15}H_{24}NO_2Cl$: N, 4.91. Found: N, 5.21.

Dehydration.—Since this amino alcohol has a high boiling point, and since the distillations were carried out very slowly, the refractive indices of the products, rather than the boiling points, were used as indications of dehydration.

When 10 g. of the amino alcohol ($n^{20}\text{D}$ 1.4400) was treated with iodine, the entire distillate, 8.5 g., showed $n^{24}\text{D}$ 1.4390–1.4400, gave a negative test for water with anhydrous copper sulfate, and in every way resembled the original amino alcohol. Ten grams of alkamine and 15 g. of solid potassium hydroxide gave 8.76 g. of distillate of $n^{20}\text{D}$ 1.4390–1.4400. This material gave a negative test for water.

Ten grams of amino alcohol and 6 g. of anhydrous copper sulfate yielded 3 g. of distillate of b. p. 67–69°, $n^{20}\text{D}$ 1.3710 and 5 g. of distillate of $n^{20}\text{D}$ 1.4390–1.4400, which proved to be identical with the original amino alcohol. The lower-boiling fraction gave a positive test for water with anhydrous copper sulfate and had an odor very different from that of the alkamine.

2-Methyl-2-hydroxy-6-dimethylaminohexane (IV)

Preparation.—Methyl δ-bromopentanoate was prepared from 162 g. (0.9 mole) of the bromo acid,[14] 800 cc. of absolute methanol and 20 g. of concentrated sulfuric acid by the usual procedure. The product on fractionation through column I gave 125 g. of ester of b. p. 95–96° at 13 mm., $n^{20}\text{D}$ 1.4615–1.4620.

A solution of 120 g. (0.61 mole) of methyl δ-bromopentanoate in 300 cc. of ether was added dropwise to a Grignard reagent prepared from 50 g. of magnesium, 750 cc. of dry ether and excess methyl bromide gas. The reaction mixture was packed in an ice–salt bath during this process, which required ten hours. The product was hydrolyzed with ice and hydrochloric acid and extracted with ether. The extract was concentrated under reduced pressure at room temperature until the residue did not change appreciably in weight on thirty minutes' additional concentration. This material (*ca.* 140 g.) was heated with a solution of 70 g. of anhydrous dimethylamine in 300 cc. of benzene in an autoclave at 140° for twelve hours. The liquid reaction product was fractionated through column I to give 76.3 g. of amino alcohol of b. p. 118–118.5° at 30 mm., $n^{20}\text{D}$ 1.4462, d^{20}_4 0.8664, *MR*D obsd. 48.96, *MR*D calcd. 49.35. The yield was 78%, based on the ester used.

The alkamine hydrochloride, which is much more hygroscopic than any of the others, melted at 100–101° after several recrystallizations.

Anal. Calcd. for $C_9H_{22}NOCl$: N, 7.16; Cl, 18.20. Found: N, 7.14; Cl, 18.48.

Esterification.—Ten grams of amino alcohol in 20 cc. of benzene was added to a solution of 20 g. of benzoyl chloride in 20 cc. of benzene. No reaction occurred, and no heat was evolved. The mixture was allowed to stand at room temperature for five days, and then the small amount of solid that had formed was removed. It was shown to be, not the expected benzoate hydrochloride, but the hydrochloride of the amino alcohol, by its melting point (101–103°), the melting point (101°) of a mixture with known amino alcohol hydrochloride (m. p. 100–101°), and by analysis.

Anal. Calcd. for $C_{16}H_{26}NO_2Cl$: Cl, 11.85. Calcd. for $C_9H_{22}NOCl$: Cl, 18.20. Found: Cl, 18.23.

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[12] *Org. Syntheses*, **8**, 52 (1928).

[13] Henry, *Bull. soc. chim.*, **45**, 341 (1886).

[14] Marvel, *et al.*, THIS JOURNAL, **49**, 1828 (1927).

Dehydration with Iodine.—Five grams of amino alcohol and a few crystals of iodine were heated at 200° for thirty minutes, and the mixture then distilled. The first fraction (2 g.) was much less viscous than the original alkamine, had a lower index of refraction (n^{20}_D 1.3650) and contained a slight aqueous layer. The second fraction was unreacted amino alcohol (n^{20}_D 1.4450).

Summary

The preparation and properties of four aliphatic tertiary amino alcohols, 2-methyl-2-hydroxy-1-dimethylaminopropane, 2-methyl-2-hydroxy-4-dimethylaminobutane, 2-methyl-2-hydroxy-5-dimethylaminopentane and 2-methyl-2-hydroxy-6-dimethylaminohexane, have been described.

Dehydration studies carried out with iodine, copper sulfate and potassium hydroxide on these amino alcohols indicate that when the amino group is adjacent to the hydroxyl group dehydration does not occur as easily as with ordinary tertiary alcohols. When the amino group is removed farther from the hydroxyl group, dehydration becomes easier.

The products formed by sulfuric acid dehydration, and by pyrolysis of the Grignard complex of 2-methyl-2-hydroxy-1-dimethylaminopropane, have been studied.

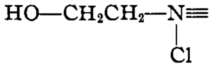
NOTRE DAME, INDIANA RECEIVED FEBRUARY 28, 1938

[CONTRIBUTION FROM MELLON INSTITUTE OF INDUSTRIAL RESEARCH, AND E. R. SQUIBB & SONS]

Halogeno-alkyl Glycosides. III. Quaternary Salts. Glucosamine Quaternary Derivative

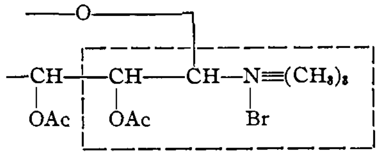
BY HAROLD W. COLES[1] AND FRANK H. BERGEIM[2]

It is known that alterations in the structure of the alkanol group attached to the quaternary nitrogen in choline chloride (I)[3] or other changes such as acylation[4] of this group affect the activity and behavior of this compound. It therefore seemed of interest to us to determine how the choline action would be affected by replacing the alkanol group with sugar residues so as to have the latter attached directly to the quaternary nitrogen and by etherifying the alkanol group with sugar residues so as to have the latter attached to the quaternary nitrogen indirectly. Besides contributing to the solubility of the active principles attached to the sugars the combinations, by gradual decomposition, would tend to give a milder and more general reaction instead of a more local toxic effect. It was therefore anticipated that the sugar residues might abolish or at least greatly diminish the toxicity of the quaternary group.



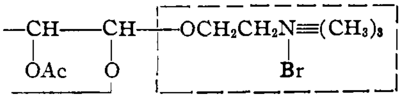
$HO{-}CH_2CH_2{-}N{\equiv}(CH_3)_3{-}Cl$

I



II

There are few literature references to pharmacological tests on choline derivatives of the carbohydrates. It was decided to prepare and test three different types. The first type is illustrated by (II). The acetylcholine part of the formula will be recognized within the broken line. It is at the same time a cyclic ether and an acetic ester, both linkages of which enhance the muscarine action of choline. It was considered also possible that the sugar part of the molecule would cause the product to be absorbed in parts of the body where choline is not ordinarily absorbed. Numerous quaternary derivatives of this type have been prepared by earlier workers. The two representatives of this first type prepared by the authors were (tetraacetyl-β-*d*-glucosido)-1-trimethylammonium bromide and (β-*d*-glucosido)-1-trimethylammonium bromide.



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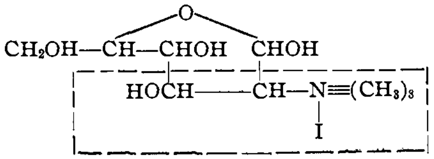

IV

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[1] Senior Industrial Fellow, E. R. Squibb & Sons Industrial Fellowship, Mellon Institute.

[2] Research Laboratories, E. R. Squibb & Sons, Brooklyn, N. Y.

[3] Dyson, "The Chemistry of Chemotherapy," Ernest Benn, Limited, London, 1928, pp. 105–120.

[4] Dale, *J. Physiol.*, **48**, 111 (1914).