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The Preparation of Geminally Substituted 4-Bromobutylamines. I. 4-Bromobutylamine and 4-Bromo-1,1-dimethylbutylamine[1]

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The preparation and properties of the hydrobromides of 4-bromobutylamine and 4-bromo-1,1-dimethylbutylamine are described. Alternate synthetic routes were explored. The usual characterization tests for these amines and for some of analogous hydroxy, ethoxy and phenoxy amines fail because of facile cyclization, the products of which were characterized.

In order to study the effect of *gem*-substituents on the rate of ring closure of 4-bromobutylamines to pyrrolidines, the effect of position of substituents required the preparation of the hydrobromides of 4-bromobutylamine (I), 4-bromo-1,1-dimethylbutylamine (II), 4-bromo-2,2-dimethylbutylamine and 4-bromo-3,3-dimethylbutylamine. Reported here is the work on I and II. Later papers will describe the other compounds and the rate studies.

Surprisingly, Freundlich,[2] who studied the rate of cyclization of the parent compound I, never described the method of preparation nor the properties of the material which he used. However, both Blank[3] and von Braun[4] prepared I from 4-phenoxybutylamine by cleavage with hydrobromic acid. In both cases the product was described only as a "hygroscopic solid." Repetition of this sequence from 3-phenoxypropyl bromide through the nitrile and reduction to the phenoxyamine afforded a good yield of I. Another possible sequence tried was from methyl acrylate by the addition of hydrogen cyanide, reduction of the cyano ester to 4-hydroxybutylamine, and conversion to I with hydrobromic acid. Unfortunately, a low yield of 20% in the reduction (done early in the work) caused the method to be abandoned. The low yield apparently was due to isolation difficulties since the amino alcohol proved to be so water soluble that it could not be extracted conveniently from aqueous systems. In view of our development of a technique for decomposing lithium aluminum hydride reduction mixtures with a limited quantity of saturated aqueous sodium chloride solution to give high yields of amino alcohols, it would seem that this sequence starting from readily available methyl acrylate is superior to the method of Blank.

The Delépine[5] method for the preparation of amines by hydrolysis of the adducts formed from alkyl halides and hexamethylenetetramine suggested a short and simple synthesis of I from tetramethylene bromide. Although the quaternary adduct was obtained in quantitative yield by allowing a chloroform slurry of the reactants to stand for a week at room temperature, so much difficulty was experienced in the subsequent hydrolysis that this synthesis failed.

II was prepared successfully by the Michael addition of 2-nitropropane to methyl acrylate followed by reduction to the amino alcohol which with hydrobromic acid gave the product. The structure of II was inferred as correct by comparison of the melting points of several derivatives of the cyclized product, 2,2-dimethylpyrrolidine, with literature values. A possible scheme for the structure proof was based upon a free radical cyclization reaction of N-bromobutylamine derivatives discovered by Coleman.[6] Bromination of the benzenesulfonamide of the *t*-alkylamine was attempted in the presence of bases such as sodium acetate, sodium hydroxide and potassium *t*-butoxide. In none of the cases was the N-bromo derivative isolated, and the effort was dropped.

A method successfully used for the preparation of 4-ethoxy-1,1-dimethylbutylamine, a precursor of II, was the addition of 3-ethoxypropylmagnesium bromide to acetone, treatment of the tertiary alcohol with sodium cyanide and sulfuric acid to give

(1) Generously supported in part by the Office of Naval Research under Contract No. Nonr-723(00).

(2) H. Freundlich and H. Kroepelin, *Z. physik. Chem.*, **122**, 39 (1926).

(3) P. Blank, *Ber.*, **25**, 3040 (1892).

(4) J. von Braun and E. Beschke, *ibid.*, **39**, 4119 (1906).

(5) M. Delépine, *Compt. rend.*, **120**, 197 (1895).

(6) G. H. Coleman, *Proc. Iowa Acad. Sci.*, **46**, 217 (1939).

the formamide which was hydrolyzed to the product.

Steps two and three represent an extension of the excellent Ritter and Kalish[7] method for the conversion of tertiary alcohols to *t*-alkylamines. The yield of 55% was unusually low for this method and could be due to hydrolysis of the ethoxy group in the highly acidic medium or to steric factors. The structure of the ethoxy amine was correct, since cleavage with hydriodic acid and subsequent treatment with benzenesulfonyl chloride produced N-phenylsulfonyl-2,2-dimethylpyrrolidine, identical with authentic material.

The classification tests for amines must be applied with caution in the series reported here. Thus, the product of the Hinsberg test with I was N-phenylsulfonylpyrrolidine. Cyclization presumably occurred before the substitution since 4-bromobutylamine in the free state has a half-life of approximately one second.[2] The nickel tests for distinguishing among primary, secondary and tertiary amines[8] were also misleading. The nickel test for primary amines depends upon the fact that primary amines react instantly with an aqueous triethanolamine solution of nickel chloride and 5-nitrosalicylaldehyde to give insoluble complexes. Secondary amines, but not primary or tertiary amines, react instantly with an aqueous ammoniacal solution of nickel chloride saturated with carbon disulfide to give insoluble nickel dithiocarbamates. These tests are considered general and reliable, but since the test media were alkaline, they failed to give conclusive results here. Thus, 4-bromobutylamine hydrobromide gave an instantaneous test for a primary amine and a slow (one hour) test for a secondary amine. 4-Hydroxy-1,1-dimethylbutylamine gave anomalous negative tests with both nickel reagents. The Hinsberg test gave both the expected product, N-(4-hydroxy-1,1-dimethylbutyl)-benzenesulfonamide, and also N-phenylsulfonyl-2,2-dimethylpyrrolidine. The cyclic derivative most likely arose by cyclization of 4-phenylsulfonamido-4-methylpentyl benzenesulfonate. It is well known that alkyl toluenesulfonates are as reactive as alkyl bromides in displacement reactions.[9] With 4-ethoxy-1,1-dimethylbutylamine the Hinsberg test indicated a secondary amine and the nickel tests for both primary and secondary amines were negative. This behavior was identical to that of the parent substance 1,1-dimethylbutylamine which gave a benzenesulfonamide which was found to be insoluble in both aqueous sodium and potassium hydroxide solutions, even above the melting point of the benzenesulfonamide, whereas the lower homolog, N-*t*-butylbenzenesulfonamide, was found to be freely soluble in cold aqueous base. II gave a negative primary amine test and a slow positive secondary amine test with the nickel reagents. The Hinsberg reaction gave N-phenylsulfonyl-2,2-dimethylpyrrolidine identical with that from the amino alcohol.

II was stable in the solid state and when dissolved in non-hydroxylic solvents, but some cyclization with concomitant loss of hydrogen bromide occurred in aqueous solution. Thus, the *p*H of a 0.02 *M* solution dropped from 4.6 to 3.0 over a period of two days, about 5% reaction. Since I was stable in aqueous solution,[2] the "geminal alkyl effect" was established in this series of bromo amines.

(7) J. J. Ritter and J. Kalish, THIS JOURNAL, **70**, 4048 (1948).
(8) F. R. Duke, *Ind. Eng. Chem., Anal. Ed.*, **17**, 196 (1945).
(9) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

Experimental[10]

4-Bromobutylamine Hydrobromide (I).—A solution of 49.5 g. of 4-phenoxybutylamine, b.p. 148–151° (22 mm.), lit. b.p. 146–148° (17 mm.),[11] in 330 ml. of concentrated hydrobromic acid was distilled over a period of about four hours from an oil-bath at 145°, giving 250 ml. of distilled hydrobromic acid. The solution was evaporated to dryness at the aspirator and the remaining traces of solvent were removed by codistillation with ethylene chloride on the steam-bath. The residue was taken up in acetone and decolorized. After concentration, the addition of ethyl acetate gave 50.9 g. (73%) of product, m.p. 156–158°. The material was recrystallized from a mixture of 10 ml./g. of ethyl acetate and 1 ml./g. of acetonitrile with 90% recovery, m.p. 157–158°. The pure material was hygroscopic, but much less so than was the crude material.

Anal. Calcd. for $C_4H_{11}Br_2N$: C, 20.60; H, 4.76. Found: C, 20.82; H, 4.76.

An attempt to prepare the picrate of the bromo amine by prolonged boiling of a *t*-butyl alcohol solution of I and picric acid was partially successful, as the yellow color deepened, but the trace of picrate could not be separated from the hydrobromide, which was less soluble in all solvents. The addition of one equivalent of silver picrate to I gave very impure picrate, which, after many recrystallizations from ethylene chloride, had m.p. 110–112°. Melting points of 105 and 127° have been reported for the picrate.[3,4] Hinsberg treatment of I gave N-benzenesulfonylpyrrolidine, m.p. 51.5–52.0° from carbon tetrachloride, identical with material from authentic du Pont pyrrolidine.

Methyl 3-Cyanopropionate.—A solution of 172.2 g. of methyl acrylate, 120 g. of glacial acetic acid and 2 l. of 95% ethanol was warmed to 35°, and a solution of 260 g. of potassium cyanide in 750 ml. of water was added over a quarter-hour period with stirring. Stirring was continued for four hours, and then the solution was allowed to stand for eight hours. Benzene and a saturated solution of sodium chloride were added and the layers separated. The aqueous layer was extracted twice with benzene and the combined organic layers were washed twice with a saturated solution of sodium chloride solution. The benzene solution was distilled at atmospheric pressure to remove the bulk of the benzene and then subjected to vacuum distillation to give 152 g. (67%) of oil, b.p. 72–90° (1 mm.).

4-Hydroxybutylamine.—A solution of 57 g. of methyl 3-cyanopropionate in 600 ml. of absolute ether was added dropwise with stirring to a mixture of 26.5 g. of lithium aluminum hydride and 750 ml. of absolute ether. During the addition, a gummy white precipitate was formed. After the addition was completed, the mixture was stirred for two hours on a warm water-bath, after which time the gummy mass had disintegrated into a white powder. Sufficient water[12] was added dropwise to destroy excess lithium aluminum hydride, and 325 ml. of concentrated hydrochloric acid was added. All material was brought into solution by warming. The acid solution was extracted with ether to remove non-amine impurities and then added dropwise to 400 g. of sodium hydroxide as a 33% solution. Not all alumina formed went back into solution, and it was found necessary to heat the mixture to boiling. The solution, after allowing to cool, was filtered and extracted five times with chloroform. Distillation gave 9 g. (20% yield) of oil, b.p. 201–205°, lit. b.p. 206°.[13] 4-Hydroxybutylamine was converted to I by the procedure that was used with 4-phenoxybutylamine.

(10) All m.p.'s and b.p.'s are uncorrected. Analyses by Mr. W. J. Schenck of this department.
(11) C. S. Marvel and A. L. Tannenbaum, THIS JOURNAL, **44**, 2645 (1922).
(12) See 4-hydroxy-1,1-dimethylbutylamine for a superior method of decomposition of a reduction, the product of which is an amino alcohol.
(13) L. Henry, *Ber.*, **33**, 3169 (1900).

Hexamethylenetetramine Adduct of Tetramethylene Dibromide.—A mixture of 44 g. of tetramethylene dibromide, 84 g. of hexamethylenetetramine and 500 ml. of chloroform was heated on the steam-bath for 5 minutes to bring most of the material into solution. The mixture was allowed to stand for one week, during which time the hexamethylenetetramine slowly dissolved as the reaction proceeded. The adduct was filtered off, washed with chloroform and dried, weight 71.4 g. (100%). The melting point of the adduct varied from 140 to 160° (with decomposition 10° below the m.p.) depending upon the batch and was not a good characteristic constant for the compound.

One gram of adduct was warmed with 2 ml. of concentrated hydrobromic acid for an hour on the steam-bath. The hydrobromic acid was removed *in vacuo* and the solid was extracted with chloroform. The solution was evaporated to dryness and the residue crystallized from ethyl acetate. Recrystallization from ethylene chloride afforded a small quantity of colorless hygroscopic needles, m.p. 151–154°. When the above procedure was applied to 172 g. of adduct, intractable dark-colored tars resulted. Similar treatment of 71.4 g. gave a dark tar, which was further treated with hydrogen bromide in acetic acid, which also was ineffective. A slight odor of formaldehyde was still noted above warm acidic solutions of the tar, even after all of the foregoing treatment.

Methyl 4-Methyl-4-nitropentanoate.—The directions given by Bruson were followed.[14] Forty-three grams of freshly distilled methyl acrylate was added dropwise, with stirring, over a one-hour period, to a solution of 44.5 g. of commercial 2-nitropropane, 25 ml. of *t*-butyl alcohol and 6 g. of benzyltrimethylammonium hydroxide (35% in methanol). The temperature was maintained between 35 and 40° during the addition. The mixture was then stirred for five hours at 25–30°, made acid to litmus with dilute hydrochloric acid and extracted with ethylene dichloride. The organic layer was washed with water and distilled at the water-pump to remove solvent. The residual oil was vacuum distilled, giving 75 g. (86%) of blue liquid, b.p. 95–105° (5 mm.).

4-Hydroxy-1,1-dimethylbutylamine.—A solution of 44 g. of methyl 4-methyl-4-nitropentanoate in 125 ml. of ether was added dropwise to a stirred refluxing slurry of 23.7 g. of lithium aluminum hydride in 700 ml. of ether. The rate of addition was governed by the capacity of the condenser. Heating was continued for 30 minutes. The mixture was decomposed by slowly adding 192 ml. of 2-propanol with cooling. Next, 156 ml. of saturated sodium chloride solution was added and stirring was continued for 15 minutes to break up the lumps of inorganic material. The mixture was filtered and the filter cake was washed with a mixture of two parts of 2-propanol and three parts of ether. The solvents were removed from the amino alcohol solution *in vacuo* leaving a blue oil, which was distilled to give 21.5 g. (74%) of blue product, b.p. 100–120° (13 mm.). Partial crystallization occurred upon standing.

The blue color probably arose from an impurity in the original nitro ester, which was blue when freshly prepared. Purification of the amino alcohol was attempted through the formation of a suitable salt. The picrate, *p*-chlorobenzoate, trichloroacetate, citrate, maleate and *p*-toluenesulfonate were all found to be liquids as initially prepared, although the last salt crystallized at the end of a week. The oxalate was a solid.

A solution of 8.9 g. of oxalic acid dihydrate in 100% ethanol was added to a solution of 16.2 g. of the crude amino alcohol in 100% ethanol. The salt (13.8 g., 63 %) was collected and recrystallized several times from ethanol containing a small amount of methanol. During this process the m.p. decreased from 206.7° dec. to 199° dec.

Anal. Calcd. for $C_{14}H_{32}N_2O_6$: C, 51.83; H, 9.94. Found: C, 52.05; H, 9.70.

The oxalate, although not very hygroscopic, did absorb moisture from the air. The oxalate may alternatively be prepared in acetone or in ether, which are good solvents for hydrated oxalic acid, but the product so obtained was usually oily. Since the oxalate is slightly soluble in ethanol, especially in the crude state, 2-propanol was a more satisfactory solvent for the preparation. The low yield of oxalate was due to the fact that the amount of oxalic acid which was used was calculated on the assumption that the amino alcohol was 100% pure. Since this was not the actual case, the oxalic acid was in excess and excess oxalic acid dissolves the precipitated diamine oxalate with the formation of the very soluble amine hydrogen oxalate.

The pure amino alcohol was liberated from the oxalate by treating a solution of 9.0 g. of the salt in 150 ml. of absolute methanol with a solution of 1.6 g. of magnesium in 100 ml. of absolute methanol. The supernatant liquid gave no test for magnesium with oxalic acid. The precipitate was digested, centrifuged and washed twice with methanol. The methanol was removed from the clear solution by distillation and the residual oil was distilled to give 5.8 g. (90%) of colorless hygroscopic product, b.p. 108° (15 mm.). The product completely solidified upon standing, f.p. 42.5°.

Treatment of the oxalate with either one or two equivalents of benzenesulfonyl chloride and aqueous potassium hydroxide gave two products in the same ratio, but in varying total yield. The major product, N-phenylsulfonyl-2,2-dimethylpyrrolidine, was insoluble in base. It was crystallized from methanol; m.p. 62–63°.

Anal. Calcd. for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16. Found: C, 60.43; H, 7.28.

The minor product, N-(4-hydroxy-1,1-dimethylbutyl)-benzenesulfonamide, was soluble in base. It was crystallized from petroleum hexane and recrystallized from aqueous methanol, m.p. 93–94°.

Anal. Calcd. for $C_{12}H_{19}NO_3S$: C, 56.00; H, 7.44. Found: C, 56.22; H, 7.19.

4-Bromo-1,1-dimethylbutylamine Hydrobromide (II).—A mixture of 3.24 g. of the oxalate and 20 ml. of concentrated hydrobromic acid was distilled from an oil-bath at 150° until 15 ml. of distillate had been collected. The remainder of the hydrobromic acid was removed *in vacuo*. The solid was dissolved in chloroform and the last traces of hydrobromic acid were codistilled. After concentration, ethyl acetate was added, precipitating 4.52 g. (87%) of amine salt, m.p. 179–180° (oxalic acid remained in solution). The salt was recrystallized several times from ethylene chloride with little loss and no change in m.p. The material may also be crystallized from acetonitrile (5 ml./g.).

Anal. Calcd. for $C_6H_{16}Br_2N$: C, 27.61; H, 5.79. Found: C, 27.51; H, 5.63.

The use of the oxalate salt gave a practically colorless product directly. The crude blue amino alcohol gave a lower yield (30%) of black product upon hydrobromic acid treatment.

The Hinsberg product was N-phenylsulfonyl-2,2-dimethylpyrrolidine (m.p. and mixed m.p. with material from the amino alcohol). The *p*H of a 0.02 *M* solution of II varied with time as follows: initial, 4.60; 35 min., 4.00; 85 min., 3.80; 1030 min., 3.30; 2440 min., 3.04. 2,2-Dimethylpyrrolidine was prepared from II by treatment with aqueous sodium hydroxide. The amine layer was separated and dried first with potassium hydroxide and then with calcium hydride. Distillation afforded 61% of product, b.p. 106°, lit. b.p. 105–106°.[15] The 2,4-dinitrophenylurea derivative (m.p. 129–130°) and the picrate (m.p. 186–187°) were prepared according to the directions of Buckley and Elliott, who report melting points of 131° and 190–191°, respectively.[15] In an attempt to prepare N-butyl-2,2-dimethylpyrrolidine hydrobromide, 1 g. of II was treated with aqueous sodium hydroxide and the upper layer of 2,2-dimethylpyrrolidine was taken up in ether and dried with magnesium sulfate. Butyl bromide (5 ml.) was added and after standing for 2 weeks, the hygroscopic crystals of product were collected and recrystallized from ethylene chloride, m.p. 173–174°. Since this was not the m.p. of the N-butyl compound, a sample of 2,2-dimethylpyrrolidine hydrobromide was prepared from the free base (liberated by alkaline treatment of II) by neutralization with hydrobromic acid. The hygroscopic salt was found to have m.p. 172–174°. The mixed m.p. was undepressed.

N-Butyl-2,2-dimethylpyrrolidine Hydrobromide.—To 2,2-dimethylpyrrolidine prepared from 1 g. of II, butyl bromide (3 ml.) and 2 drops of phenolphthalein were added. The solution was allowed to stand one week, during which time small amounts of aqueous sodium hydroxide were added periodically to maintain slight alkalinity, and to prevent the

(14) H. A. Bruson, U. S. Patent 2,390,918 [*C. A.*, **40**, 2456 (1946)].

(15) G. D. Buckley and T. J. Elliott, *J. Chem. Soc.*, 1508 (1947).

separation of the poorly soluble 2,2-dimethylpyrrolidine hydrobromide. The solution was treated with hydrochloric acid and evaporated to dryness. The solid was taken up in base and the amine layer was separated. The amine was heated with acetic anhydride in benzene to destroy unreacted pyrrolidine. The benzene solution was extracted with dilute hydrobromic acid. Evaporation of the acid solution *in vacuo* left a brown solid which was recrystallized several times from an ethylene chloride and carbon tetrachloride mixture, once from ethyl acetate, twice from dioxane and once more from ethyl acetate with a few drops of acetone to give 0.3 g. of white crystals. With recrystallization, the salt became less hygroscopic and the m.p. was raised from 144–145.5° to 146–147°, lit. m.p. 148–149.5°.[16]

Anal. Calcd. for $C_{10}H_{22}BrN$: N, 5.93. Found: N, 6.06.

1,1-Dimethylbutylamine.—To a mixture of 126 ml. of 2-methyl-2-pentanol,[17] 125 ml. of acetic acid and 51.8 g. of 95% sodium cyanide, was added to a solution of 136 ml. of concd. sulfuric acid and 125 ml. of acetic acid over a period of 30 minutes with stirring, under a hood. A cold water-bath was used to maintain the temperature between 50 and 60°. The mixture was stirred for 0.25 hour after the addition and allowed to stand overnight. A condenser was attached and a solution of 500 g. of sodium hydroxide in 1750 ml. of water was added through the top. After heating under reflux for 7 hours, the amine was steam distilled into 100 ml. of concd. hydrochloric acid. The acidic solution was extracted with benzene, decolorized and made basic with 33% sodium hydroxide. The amine was separated and the basic solution was extracted with ether. The amine and extract were combined, dried with potassium hydroxide and distilled to give 75 g., b.p. 99–104°, lit. b.p. 101–103°.[18] The amine was found to be highly volatile and therefore the ether forerun and the residue were acidified with hydrochloric acid and evaporated to dryness. The residue was crystallized from chloroform–ethyl acetate and recrystallized from 2-propanol and ethyl acetate to give 8.5 g. of the amine hydrochloride m.p. 207–208°, lit.[19] m.p. 190–198°.

N-(1,1-Dimethylbutyl)-benzenesulfonamide.—A mixture of 10.1 g. of amine, 15.4 ml. of benzenesulfonyl chloride, 12 g. of sodium hydroxide and 90 ml. of water was shaken for several minutes. The crystalline product was filtered off and crystallized from petroleum hexane to give 22.7 g. (95%) of product, m.p. 89–90°. The analytical sample was recrystallized several times from petroleum hexane and finally from methanol, lowering the m.p. to 88–89°.

Anal. Calcd. for $C_{12}H_{19}NO_2S$: N, 5.80. Found: N, 5.88.

The sulfonamide was degraded by hydrolysis in order to verify its structure. A mixture of 13 g. of the sulfonamide and 70 ml. of concd. hydrobromic acid was distilled at a bath temperature of 150°. The oil was decanted from the distillate, washed with water and dried. Two distillations afforded a low-boiling unsaturated fraction, b.p. 40–70°, which instantaneously added bromine, and a liquid of b.p. 131° dec. which instantaneously reacted with silver nitrate; Favorskii[20] reported for 2-bromo-2-methylpentane, b.p. 77–78° (145 mm.). The corresponding boiling point at 760 mm. was estimated to be 132°. Timmermans[21] listed 2-methylpentene-2, b.p. 67.3°.

A methanolic solution of the sulfonamide with sodium acetate as a base instantaneously decolorized bromine. The solution was placed in the sun for 2 days. A negative starch–iodide test was obtained and addition of water precipitated unchanged starting material as the sole product. Behavior with sodium hydroxide was similar. The sulfonamide was dissolved in a solution of potassium *t*-butoxide in absolute *t*-butyl alcohol. The solution instantly decolorized bromine and, after 2 days in the sun, the starch–iodide test was found to be negative. In working up the mixture, the product was accidentally evaporated to dryness. The sole isolable product was benzenesulfonamide.

3-Ethoxypropanol was prepared in 45% yield from ethyl bromide and the monosodium salt of trimethylene glycol, using an excess of the glycol as the solvent according to the procedure of Smith and Sprung.[22] Because of the unworkable viscosity of the alkoxide solution two further runs were made, using 1,2-dimethoxyethane as a diluent in one case and toluene in the other. The yields were 44 and 36%, respectively.

3-Ethoxypropyl bromide was prepared in a 34% yield from the alcohol using phosphorus tribromide, according to the method of Anderson.[23] When their procedure was modified by using pyridine to neutralize free hydrogen bromide, which might cleave the ether, a yield of 71% was realized.

A solution of 247 g. of 3-ethoxypropanol and 47.5 ml. of pyridine was added slowly (2 hours) with stirring to 90 ml. of phosphorus tribromide in an ice-bath. The mixture was then heated to 75° for one hour. After cooling, the liquid phase was decanted from the pyridine salts, which were washed with benzene. The combined solution was washed successively with water and saturated sodium bicarbonate solution, dried, and distilled. The fraction, b.p. 135–155°, was collected and found to be slightly acidic. It was again washed with saturated sodium bicarbonate, dried and distilled. The product, b.p. 145–155°, weighed 281 g. (71%).

5-Ethoxy-2-methyl-2-pentanol was prepared by adding a solution of 161 g. of 3-ethoxypropyl bromide in 300 ml. of ether to 26.6 g. of magnesium in 300 ml. of ether with stirring, the reaction being started with 1 ml. of methyl iodide. After the addition, which required 1.25 hours, the mixture was boiled for one hour. After cooling in ice, 85 ml. (1.2 mole) of acetone in 85 ml. of ether was added over a period of 0.5 hour. Toward the end of the addition, the mixture became almost solid with precipitated salts, necessitating the addition of 100 ml. of ether to increase the fluidity. The mixture was heated under reflux for 0.5 hour, and then decomposed with 165 ml. of saturated ammonium chloride. The ether solution was decanted and distilled, giving 105.2 g. (75%) of product, b.p. 175–188°.

4-Ethoxy-1,1-dimethylbutylamine by the Ritter and Kalish Method.[7]—In a 250-ml. erlenmeyer flask was placed a mixture of 36.5 g. of 5-ethoxy-2-methyl-2-pentanol, 13 g. of 95% sodium cyanide and 31 ml. of acetic acid. A solution of 34 ml. of concd. sulfuric acid in 31 ml. of acetic acid was added portionwise over an 0.5-hour period with shaking. The temperature did not exceed 55° during this operation. The flask was stoppered and allowed to stand overnight. After the addition of 150 g. of sodium hydroxide in 310 ml. of water, the mixture was heated under reflux for five hours and then steam distilled. Concentrated hydrochloric acid (21 ml.) was added to the first 400-ml. portion of distillate, which contained all of the amine. After ether extraction to remove insoluble oil, 40 g. of sodium hydroxide in 50 ml. of water was added to liberate the amine which was extracted with ether. The extract was dried and distilled, giving 20.1 g. of amine (55% yield), b.p. 170–180°, which was characterized as the picrate, m.p. 118–120° from chloroform.

Anal. Calcd. for $C_{14}H_{22}N_4O_8$: C, 44.92; H, 5.92; N, 14.97. Found: C, 44.86; H, 5.99; N, 14.71.

Concentrated hydrochloric acid was added to 0.37 g. of the picrate in a minimum quantity of water. The picric acid was filtered off and the solution was basified and steam distilled, catching the distillate in 2 ml. of concentrated hydriodic acid. The distillate was evaporated to dryness *in vacuo* and 2 ml. of acetic acid and 2.5 ml. of concentrated hydriodic acid were added. After heating under reflux for 1 hour, the solvent was removed *in vacuo*, water was added and an oily impurity was removed by extraction with carbon tetrachloride. Basification and treatment with 0.3 ml. of benzenesulfonyl chloride gave N-benzenesulfonyl-2,2-dimethylpyrrolidine, m.p. 62–63° from petroleum hexane. The mixed m.p. with authentic material (m.p. 63.5–64°) was 63–63.5°.

2-Chloro-5-ethoxy-2-methylpentane.—A mixture of 105 g. of 5-ethoxy-2-methyl-2-pentanol and 360 ml. of concentrated hydrochloric acid (4.32 moles) was shaken for 10 minutes in a separatory funnel. The layers were separated, and the lower acid layer was extracted with petroleum hex-

(16) R. C. Elderfield and H. A. Hageman, *J. Org. Chem.*, **14**, 605 (1949).

(17) L. Henry, *Rec. trav. chim.*, **26**, 89 (1907).

(18) M. Montagne, *Ann. chim.*, [10] **13**, 118 (1930).

(19) I. Bewad, *J. prakt. Chem.*, **63**, 233 (1901).

(20) A. E. Favorskii and N. Sakara, *J. Russ. Phys. Chem. Soc.*, **50**, 43 (1918).

(21) J. Timmermans, *Bull. soc. chim. Belg.*, **31**, 390 (1922).

(22) L. I. Smith and J. A. Sprung, THIS JOURNAL, **65**, 1276 (1943).

(23) E. P. Anderson, J. V. Crawford and M. L. Sherrill, *ibid.*, **68**, 1294 (1946).

ane. The combined organic layers were washed with water and saturated sodium bicarbonate solution, dried with calcium chloride and distilled. Copious evolution of hydrogen chloride occurred during the distillation, and it was necessary to treat the distillate with potassium carbonate. After drying over phosphorus pentoxide, the material was distilled (more decomposition) to give 44 g. (37%) of product, b.p. 164–176°.[24]

(24) P. Bruylants and A. Dewael, *Bull. classe sci., Acad. roy. Belg.*, **14**, 150 (1928), report that the compound is stable.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

The Preparation of Geminally Substituted 4-Bromobutylamines. II. 4-Bromo-2,2-dialkyl- and diarylbutylamines[1]

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The preparation and properties of the hydrobromides of 4-bromo-2,2-dimethyl-, diethyl-, diisopropyl-, diphenyl- and di-*p*-tolylbutylamines are described. Alternate synthetic routes were explored. Some of the analogous hydroxy, methoxy and phenoxy amines were made, and the cyclization products of all the compounds were prepared. The best sequence started with the alkylation of the properly substituted acetonitrile with phenoxy- or methoxyethyl bromide using lithium diethylamide as the catalyst. The resulting nitrile was converted to the desired product by reduction followed by cleavage of the ether group with hydrobromic acid.

As part of a study on the effect of *gem*-substituents on the rate of ring closure of 4-bromobutylamines to pyrrolidines, the effect of size and character of substituents required the preparation of the hydrobromides of 4-bromo-2,2-dimethylbutylamine (I), and the analogous 2,2-diethyl (II), diisopropyl (III), diphenyl (IV) and di-*p*-tolyl (V) compounds. I is a member of another series designed to test the effect of position on the rate of ring closure.[2] We wish to report here the synthetic work on the 2,2-series. Later papers will describe compounds not already reported and discuss the rate studies.

The excellent method of Ziegler[3] for using lithium diethylamide in the alkylation of nitriles served as the key step for the preparation of members of the 2,2-series. Using phenoxy- or methoxyethyl bromide for the alkylation of the properly substituted acetonitrile, followed by reduction, we obtained good yields of the properly substituted alkoxy- or aryloxybutylamine ready for cleavage with hydrobromic acid.

Diphenylacetonitrile was a commercial product, but the other disubstituted acetonitriles were prepared from the corresponding acids *via* the amides. These transformations were carried out by a technique which was developed for the large-scale conversion of an acid to the corresponding nitrile in yields of approximately 90% with a minimum of manipulation. Isobutyric and diethylacetic acids were commercial products, but di-*p*-tolylacetic acid was prepared by the unusual route of condensing toluene with chloral, and hydrolyzing the trichloroethane to the product. Diisopropylacetonitrile was prepared by a substantial improvement of Marshall's method[4] whereby cyanoacetic ester was alkylated with isopropyl iodide and the product was hydrolyzed and decarboxylated to give the nitrile. Use of easily prepared sodium isopropoxide as the alkylation base gave diisopropylcyanoacetic ester in easily reproducible yields of 93%. Marshall, using the weaker base sodium ethoxide, was able to obtain a yield of only 58% in this step. The use of bases stronger than sodium ethoxide has been advocated several times in the past.[5]

The yields for alkylation of the disubstituted acetonitriles with phenoxyethyl bromide in the presence of lithium diethylamide where R may be methyl, ethyl, isopropyl, phenyl or *p*-tolyl, were 88, 75, 25, 87 and more than 88%, respectively. Sodamide may also be used in the alkylation step but it gave distinctly lower yields.

In the second step of the sequence, reduction was carried out with lithium aluminum hydride where R was methyl, ethyl, phenyl and *p*-tolyl, and afforded yields of greater than 80% in each instance. The use of sodium with 2-butanol as a reducing agent also was tried in the cases where R was methyl and phenyl. When R was methyl, the yield was only 62% and when R was phenyl, the reaction took another course, giving phenyl 3,3-diphenylpropyl ether. This type of cleavage is common with nitriles having aryl groups in the α-position.[6] The reduction of 2,2-diisopropyl-4-phenoxybutyronitrile with lithium aluminum hydride in ether proceeded very slowly and incompletely, in comparison to the vigorous reductions of the other nitriles. Furthermore, the amine isolated was not the expected product, 2,2-diisopropyl-4-phenoxybutylamine, although the anion of this amine must have been the proximate product, since 3,3-diisopropylpyrrolidine was isolated in 9% yield. In boiling tetrahydrofuran, the reduction afforded 26% of 3,3-diisopropylpyrrolidine. The instability of the anion or ion pair and elimination of phenoxide demonstrates the profound effect which geminal isopropyl groups must exert upon ring closure since no difficulty was experienced with the other reductions. Sodium and alcohol also were utilized in the hope of effecting the reduction, since the anion or ion pair might

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(2) R. F. Brown and N. M. van Gulick, THIS JOURNAL, **77**, 1079 (1955).

(3) K. Ziegler and H. Ohlinger, *Ann.*, **495**, 84 (1932).

(4) F. C. B. Marshall, *J. Chem. Soc.*, 2754 (1930).

(5) See refs. 3, 13, 14, 15, 20, 21, 22, 28 of W. J. Humphlett, *Org. Chem. Bull.*, **25**, No. 4 (1953).

(6) M. Freund and P. Immerwahr, *Ber.*, **23**, 2845 (1890).