pimelamide which melted at 205°. Upon recrystallization from water the melting point was raised to 209.5°.

2-Benzyl-2-(2-cyanoethyl)cyanoacetamide (Method A). A mixture of 3.48 g. (0.02 mole) of 2-benzylcyanoacetamide and 1.06 g. (0.02 mole) of acrylonitrile in a glass pressure vessel was treated with 30 cc. of liquid ammonia for 2 hr. at room temperature. Then the ammonia was evaporated, and the residual crystalline product was washed with water; yield 4.5 g. (quantitative). The melting point was 133–135° after recrystallization from ethanol.

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YOKOSUKA, JAPAN

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

The Synthesis of Some Substituted 5-Bromopentylamine Hydrobromides

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The preparation of the hydrobromides of 5-bromopentylamine and of 5-bromo-1,1-, 2,2-, 3,3-, and 4,4-dimethylpentylamines is described.

For a continuation of our study of the effects of *gem*-dialkyl substitution on the rates of cyclization of ω-bromoalkylamines,[2] it became necessary to prepare a series of 5-bromopentylamine hydrobromides. This paper reports the synthesis of the hydrobromides of 5-bromopentylamine, 5-bromo-1,1-dimethylpentylamine, 5-bromo-2,2-dimethylpentylamine, 5-bromo-3,3-dimethylpentylamine, and 5-bromo-4,4-dimethylpentylamine.

Of the five compounds listed only the unsubstituted 5-bromopentylamine hydrobromide has been prepared previously. Although Freundlich[3] studied the rates of cyclization of a series of bromoalkylamines, he did not describe in detail the method of preparation nor the physical properties of the 5-bromopentylamine hydrobromide used. Blank[4] seems to have been the first to report this compound in the literature but neither he nor von Braun and Steindorff[5] gave any physical constants. Keimatsu and Takamoto[6] reported the preparation of the amine by the action of phosphorus tribromide in chloroform upon 5-hydroxypentylamine. Our product was synthesized from 1,4-dibromobutane by conversion to 1-bromo-4-phenoxybutane followed by replacement of the remaining bromine by cyanide ion and reduction with lithium aluminum hydride to give 5-phenoxypentylamine. Cleavage of the ether with hydrobromic acid[7] then gave the product in excellent yield. Our salt, upon treatment with alkali, gave piperidine which was characterized in several ways. However, we are at a loss to explain the discrepancy between the properties of our product and those reported by Keimatso and Takamoto. Since they report a b.p. 78–79° (749 mm.) and we found the cyclization to proceed with rapidity at room temperature, it seems strange that the amine would exist long enough to allow distillation to occur as the unchanged amine.

The second compound in our list, 5-bromo-1,1-dimethylpentylamine hydrobromide was obtained by the action of the Grignard reagent from 1-bromo-4-ethoxybutane on acetone followed by the Ritter and Kalisch[8] conversion of the resulting tertiary alcohol to the corresponding amine, 5-ethoxy-1,1-dimethylpentylamine, which underwent ether cleavage smoothly with hydrobromic acid to give the product. On our first attempt to use the Ritter and Kalisch reaction the phenoxy group was present rather than the ethoxy and only a 10% yield was obtained. Since this reaction probably proceeds *via* the carbonium ion from the tertiary alcohol, it seemed likely that the ion was attacking other phenoxy groups in the reaction mixture as well as the hydrogen cyanide which is the normal course for this reaction.[9] This explanation was substantiated by the isolation of a high-boiling viscous oil as the major product, and by an increase in the yield of the amine to 66% when ethoxy was used in place of the phenoxy group in the tertiary alcohol. The final product, 5-bromo-1,1-dimethylpentylamine hydrobromide, gave 2,2-dimethylpiperidine upon cyclization by treatment with alkali.

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(1) This work was supported by a grant from the National Science Foundation. It is based on a dissertation submitted by G. H. Schmid to the Graduate School of the University of Southern California in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) R. F. Brown and N. M. van Gulick, *J. Am. Chem. Soc.*, **77**, 1079, 1083, 1089 (1955), and *J. Org. Chem.*, **21**, 1046 (1956).

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

(4) P. Blank, *Ber.*, **25**, 3047 (1892).

(5) J. von Braun and A. Steindorff, *Ber.*, **38**, 172 (1905).

(6) S. Keimatsu and R. Takamoto, *J. Pharm. Soc. Japan*, 75 (1927)

(7) G. Salomon, *Trans. Faraday Soc.*, **34**, 1311 (1938), reported that this reaction did not go.

(8) J. J. Ritter and J. Kalisch, *J. Am. Chem. Soc.*, **70**, 4048 (1948).

(9) This explanation was offered by Professor E. W. Warnhoff.

Although 2,2-dimethylpiperidine has been reported,[10] no mention was made of the method of preparation nor of the physical properties. Thus the structure of our product cannot be established by characterization. However, it has been shown previously[2] that a reaction sequence similar to the one used here may be used to prepare 4-bromo-1,1-dimethylbutylamine hydrobromide, which was also prepared by an independent route and which cyclized to give 2,2-dimethylpyrrolidine which could be characterized and shown to be identical with those properties reported in the literature. By analogy, it seems reasonable to assume that our product was indeed 5-bromo-1,1-dimethylpentylamine hydrobromide.

The 5-bromo-2,2-dimethylpentylamine hydrobromide was prepared by the hydrobromic acid treatment of 5-ethoxy-2,2-dimethylpentylamine, which was easily obtained by the lithium aluminum hydride reduction of 5-ethoxy-2,2-dimethylpentanenitrile. The nitrile was prepared in 80% yield by the alkylation with 1-bromo-3-ethoxypropane of isobutyronitrile in the presence of lithium diethylamide.[11] An attempt to use sodamide proved to be unsuccessful, the major product being isobutyramide. Although the addition of sodamide to nitriles is well known, it is usually considered to be a side reaction in the alkylation of nitriles.[12] Cyclization of the product gave 3,3-dimethylpiperidine which was identified as the hydrochloride salt.

The anhydride of 3,3-dimethylglutaric acid[2] served as the starting point for the preparation of 5-bromo-3,3-dimethylpentylamine hydrobromide. From the anhydride, the half ester was easily prepared by reaction with the calculated amount of sodium methoxide. The remaining carboxylic acid group in the half ester was converted to the acid chloride by treatment with thionyl chloride, but subsequent reaction with ammonium hydroxide to form the carboxamide failed to give a pure product until the conversion was effected in excellent yield by treatment of the acid chloride with gaseous ammonia. The amido ester, it was found, was difficult to purify because of a great tendency to cyclize to 3,3-dimethylglutarimide. Consequently, the amido ester was reduced directly with lithium aluminum hydride to give 3,3-dimethyl-5-hydroxypentylamine which upon treatment with hydrobromic acid gave the bromoamine salt. The salt, when treated with alkali, underwent cyclization to 4,4-dimethylpiperidine which was isolated as the hydrobromide. That the structure was correct was shown by lithium aluminum hydride reduction of 3,3-dimethylglutarimide to 4,4-dimethylpiperidine, half of which was converted to the known hydrochloride and the remainder was converted to the hydrobromide for comparison with the cyclized material by means of melting point.

The preparation of 5-bromo-4,4-dimethylpentylamine hydrobromide depended upon the hindrance of neopentyl type halides to displacement reactions as was employed in the synthesis of 4-bromo-3,3-dimethylbutylamine hydrobromide.[2] Thus, 1,5-dibromo-2,2-dimethylpentane reacted with potassium phthalimide to give 1-bromo-2,2-dimethyl-5-phthalimidopentane which yielded the product upon treatment with a mixture of acetic acid and concentrated hydrobromic acid. The dibromoalkane was prepared from 2,2-dimethyl-5-ethoxypentanenitrile by hydrolysis to the acid which was reduced with lithium aluminum hydride to give 2,2-dimethyl-5-ethoxy-1-pentanol. The alcohol was treated with phosphorus tribromide in quinoline[13] to give 1,5-dibromo-2,2-dimethylpentane which was not isolated as such but which reacted with potassium phthalimide to give a product in 25% yield based upon the alcohol. The structure of 5-bromo-4,4-dimethylpentylamine hydrobromide was confirmed by cyclization in the presence of alkali to form 3,3-dimethylpiperidine the hydrobromide of which proved to be identical with that obtained from 5-bromo-2,2-dimethylpentylamine hydrobromide.

An attempt to synthesize 1,5-dibromo-2,2-dimethylpentane starting from 2,2-dimethylglutaric acid was also successful but in much lower yield. Direct lithium aluminum hydride reduction of the acid gave only a 50% yield of the corresponding glycol,[14] but the over-all yield for conversion to the ester and and reduction of the ester was 75%. The conversion of the glycol to the dibromoalkane, however, was less successful than with the ethoxy alcohol described above, probably because of the greater reactivity of the 5-hydroxy group than of the 5-ethoxy. We experienced difficulty in finding a good method for the synthesis of 2,2-dimethylglutaric acid. We found the procedure of Bruson[15] superior to that of Hoch and Karrer[16] for the addition of isobutyraldehyde to acrylonitrile and we were unable to duplicate the simultaneous oxidation and hydrolysis of 4-cyano-2,2-dimethylbutanal.[16] Separate oxidation and hydrolysis steps on the cyanoaldehyde gave only very low yields of 2,2-dimethylglutaric acid. The alkylation of isobutyronitrile in the presence of lithium diethylamide

(10) C. R. Scott, A. L. Ayers, and J. E. Mahan, U. S. Patent **2,771,737**; *Chem. Abstr.*, **51**, 3969e (1957).

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

(12) A. C. Cope, H. L. Holmes, and H. O. House, *Org. Reactions*, **IX**, 107 (1957).

(13) L. H. Sommers, H. D. Blankman, and P. C. Miller, *J. Am. Chem. Soc.*, **76**, 803 (1954).

(14) Reductions of acids, especially dibasic and polybasic acids, are known to proceed in low yields because of the formation of insoluble salts. See N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, 1956, p. 322.

(15) H. A. Bruson and T. W. Reiner, *J. Am. Chem. Soc.*, 66, 56 (1944).

(16) D. Hoch and P. Karrer, *Helv. Chim. Acta*, **37**, 397 (1954).

with 1-bromo-2-chloroethane gave good yields of 4-chloro-2,2-dimethylbutanenitrile, but the use of 1,2-dibromoethane in this reaction led as expected to the formation of considerable dialkylated product which unfortunately sublimed readily near the boiling point of 4-bromo-2,2-dimethylbutanenitrile so that good separation became impossible. Again, as expected, the replacement of the chlorine in the chloronitrile proved to be difficult and required drastic conditions. However, although the yield of 2,2-dimethylglutaronitrile was low, the principal by-product was 2,2-dimethylglutaric acid. The hydrolysis of 2,2-dimethylglutaronitrile to form 2,2-dimethylglutaric acid was carried out in excellent yield and purity by the use of concentrated hydrochloric acid rather than sulfuric acid which is usually used,[17] and which in this instance gave a lower yield of a very impure product.

The results of the rate studies on the cyclization of the 5-bromopentylamines will be reported in the near future.

EXPERIMENTAL[18]

1,4-Dibromobutane was prepared by the addition over a period of 0.5 hr., of 221 ml. (4.5 moles) of concd. sulfuric acid to a mixture of 100 g. (1.39 moles) of tetrahydrofuran and 318 g. (3.1 moles) of sodium bromide in 100 ml. of water. After the addition, the mixture was heated under reflux until two layers became visible (approximately 3 hr.). After cooling, the mixture was extracted with ether. The ether layer was washed with water, then 10% sodium bicarbonate solution, and water. The ether layer was dried and distilled to give 252.2 g. of product, b.p. 194.5–196.5°, 84% yield. Marvel[19] reported b.p. 81–85°/18 mm.

4-Phenoxybutyl bromide was prepared by the addition of a solution of 44 g. (1.1 moles) of sodium hydroxide in 100 ml. of water to a stirred, refluxing solution of 324 g. (1.5 moles) of 1,4-dibromobutane and 113 g. (1.20 moles) of phenol in 400 ml. of water. After the addition, the mixture was heated under reflux for 4.5 hr., then cooled, and the upper water layer was separated and discarded. After the addition of 100 ml. of benzene, the lower layer was washed successively with dilute sodium hydroxide and water, and dried. Distillation gave 97.5 g. of forerun, b.p. 88–95°/16 mm.; 18.5 g. of material, b.p. 95–151°/16 mm.; and 155 g. of product, b.p. 151–155°/16 mm., 71% yield. Upon standing, the material soon crystallized to give 4-phenoxybutylbromide as a low-melting solid. Marvel[19] reported b.p. 153–156°/18 mm.

5-Phenoxypentanenitrile was prepared by the addition of a solution of 38.3 g. (0.58 mole) of potassium cyanide in 150 ml. of water to a solution of 110.2 g. (0.48 mole) of 4-phenoxybutylbromide in 450 ml. of absolute ethanol. After the mixture was heated under reflux for 28 hr., 400 ml. of solvent was removed under reduced pressure. The two layers that resulted were separated and the aqueous layer was extracted with two 50-ml. portions of benzene. The combined organic layer was successively washed with dilute sodium hydroxide and water, dried, and distilled to give 71.0 g. of oil, b.p. 130–135°/1 mm., 82.5% yield. Gabriel[20] reported b.p. 299–304°.

5-Phenoxypentylamine was prepared by the slow addition of a solution of 20.0 g. (0.114 mole) of 5-phenoxypentanenitrile in 50 ml. of sodium-dried ether to a stirred refluxing slurry of 5.3 g. (0.14 mole) of lithium aluminum hydride in 200 ml. of sodium-dried ether. The mixture was heated under reflux for 3.25 hr. after the addition. The mixture was cooled in ice and decomposed by the slow addition of 47 ml. of saturated sodium chloride solution. The mixture was stirred for an additional 15 min. and filtered. The filter cake was thoroughly washed with ether. The filtrate was distilled giving 14.3 g. of amine, b.p. 167–170°/28 mm., 70% yield. Gabriel[20] reported b.p. 274–275°.

To a small sample of the amine in benzene was added an excess of hydrogen bromide gas. The benzene solution was warmed until the evolution of hydrogen bromide ceased. Cooling gave 5-phenoxypentylamine hydrobromide, m.p. 149–150°.

Anal. Calcd. for $C_{11}H_{18}NOBr$: C, 50.77; H, 6.97; N, 5.34; Br, 30.71. Found: C, 50.63; H, 6.91; N, 5.40; Br, 30.86.

5-Bromopentylamine hydrobromide.[18] A solution of 65.0 g. (0.25 mole) of 5-phenoxypentylamine hydrobromide in 250 ml. of concd. hydrobromic acid was distilled over a period of 5 hr. from an oil bath at 160° giving 200 ml. of distilled hydrobromic acid. The solution was evaporated to dryness under reduced pressure, and the remaining traces of hydrobromic acid were removed by codistillation with chloroform. After all the hydrobromic acid was removed, the last traces of chloroform were removed under reduced pressure. The residue was dissolved in acetone and decolorized. After concentration, ethyl acetate was added and the solution was cooled to give 53.0 g. of product, m.p. 136–138°, 72% yield. A small sample was recrystallized from benzene for analysis, m.p. 141–142°.

Anal. Calcd. for $C_5H_{13}NBr_2$: C, 24.32; H, 5.26; N, 5.67; Br, 64.73. Found: C, 24.41; H, 5.27; N, 5.60; Br, 64.68.

A small sample on treatment with alcoholic sodium hydroxide gave piperidine which was identified as the benzenesulfonamide.

4-Ethoxy-1-butanol. Sodium (92.0 g., 4.0 g.-atoms) was added over a period of 2.5 hr. to a hot (115–120°) and vigorously stirred solution of 901 g. (10.0 moles) of 1,4-butanediol and 400 ml. of xylene. Heating was stopped while the sodium was added but after the addition heat was necessary to maintain the reaction temperature at between 110–120° for 1 hr. Over a period of 4 hr., 400 g. (3.66 moles) of ethyl bromide was added dropwise to the hot solution. After the addition, the reaction mixture was heated under reflux with stirring for 16 hr., then cooled in an ice bath to 5°. The cold mixture was filtered to remove the precipitated salts. The lower layer was carefully separated and distilled. After a forerun of xylene, 34.8 g. of an intermediate fraction was collected, b.p. 152–178°, followed by 258.5 g. of the product, b.p. 178–184°. Redistillation gave 233.0 g. of 4-ethoxybutanol, b.p. 181–183°, 54% yield. Wall[21] reported b.p. 181°.

1-Bromo-4-ethoxybutane was prepared by the addition of a mixture of 226 g. (1.92 moles) of 4-ethoxybutanol and 37.1 g. (0.46 moles) of pyridine over a period of 2 hr. with stirring to 200 g. (0.74 mole) of phosphorus tribromide cooled in an ice bath. The mixture was then heated to between 70° and 80° for 1.5 hr. After cooling, the liquid phase was decanted from the pyridine salts which were washed with benzene. The combined organic layers were washed successively with water, saturated sodium bicarbonate solution, and water. After drying, the organic layer was distilled to give 261.5 g. of 1-bromo-4-ethoxybutane, b.p. 168–172°, 76% yield, Kon[22] reported b.p. 169°.

(17) A. A. Larsen, A. W. Ruddy, B. Elpern, and M. MacMullin, *J. Am. Chem. Soc.*, **71**, 532 (1949).

(18) All boiling and melting points are uncorrected. Analyses were performed by Elek Micro Analytical Laboratories, Los Angeles, Calif., and by Alicino Analytical Laboratories, Metuchen, N. J. The infrared spectra of all compounds noted with a superscript 18 are reproduced in Appendix II of the dissertation.[1]

(19) C. S. Marvel and A. L. Tanenbaum, *J. Am. Chem. Soc.*, **44**, 2645 (1922).

(20) S. Gabriel, *Ber.*, **25**, 419 (1892).

(21) F. T. Wall and W. F. Claussen, *J. Am. Chem. Soc.*, **61**, 2680 (1939).

(22) G. A. R. Kon, R. P. Linstead, and C. Simons, *J. Chem. Soc.*, 816 (1937).

6-Ethoxy-2-methyl-2-hexanol[18] was prepared by adding, with stirring, a solution of 136 g. (0.75 mole) of 4-ethoxybutyl bromide in 500 ml. of dry ether to 18.2 g. (0.75 g.-atom) of magnesium in 1.0 l. of dry ether, the reaction being started with 1 ml. of methyl iodide. After the addition, which required 2 hr., the mixture was heated under reflux for 1 hr. After cooling in ice, a solution of 43.5 g. (0.75 mole) of acetone in 200 ml. of ether was added over a period of 45 min. After the addition, the ice bath was removed and the reaction mixture was heated under reflux for 3 hr., cooled, and then decomposed by the addition of 87 ml. of saturated sodium chloride solution. Stirring was continued for 15 min. after the addition of the salt solution. The ether was decanted and the salts were thoroughly washed with ether. The combined ether layer was dried and distilled to give 88.0 g. of alcohol, b.p. 101–105°/18 mm., 72% yield. A small sample was redistilled for analysis, b.p. 109–109.5°/25 mm.

Anal. Calcd. for $C_9H_{20}O_2$: C, 67.46; H, 12.58. Found: C, 67.23; H, 12.60.

1,1-Dimethyl-5-ethoxypentylamine.[18] In a 250-ml. Erlenmeyer flask equipped with a magnetic bar stirrer was placed a mixture of 32.0 g., (0.20 mole) of 6-ethoxy-2-methyl-2-hexanol, 10.4 g. (0.20 mole) of 95% sodium cyanide, and 25 ml. of glacial acetic acid. A solution of 50 g. of concd. sulfuric acid in 25 ml. of glacial acetic acid was added dropwise over a period of 1 hr. with stirring. The temperature did not exceed 70° during this operation. The flask was stoppered and allowed to stand overnight with stirring. After the addition of 120 g. of sodium hydroxide in 250 ml. of water, the solution was heated under reflux for 5 hr. and then steam distilled. Twenty milliliters of concd. hydrochloric acid (0.25 mole) was added to the first 400 ml. of distillate, which contained all of the amine. After ether extraction to remove an insoluble oil, 40 g. of sodium hydroxide in 50 ml. of water was added to liberate the amine. The amine was separated and the aqueous layer extracted with ether. The ether layer was combined with the amine and the mixture was dried and distilled, giving 21.0 g. of product, b.p. 85–88°/20 mm., 66% yield. A sample was redistilled for analysis, b.p. 83.5–84.5°/16 mm.

Anal. Calcd. for $C_9H_{21}ON$: C, 67.87; H, 13.30; N, 8.79. Found: C, 67.97; H, 13.43; N, 8.80.

5-Bromo-1,1-dimethylpentylamine hydrobromide.[18] A solution of 15.9 g. (0.10 mole) of 1,1-dimethyl-5-ethoxypentylamine in 105 ml. of concd. hydrobromic acid was distilled from an oil bath at 150° until the head temperature reached 123°. At this point the oil bath was removed and the reaction mixture was cooled. The majority of the hydrobromic acid was removed under reduced pressure, the last traces being removed by codistillation with ethylene chloride. After removal of the ethylene chloride under reduced pressure, the viscous oil crystallized upon scratching. Recrystallization from cyclohexane gave 15.0 g., m.p. 100–103°, 54% yield. A sample was recrystallized from cyclohexane for analysis, m.p. 103–104°.

Anal. Calcd. for $C_7H_{17}NBr_2$: C, 30.56; H, 6.23; N, 5.09; Br, 58.11. Found: C, 30.76; H, 6.24; N, 5.01; Br, 57.94.

2,2-Dimethylpiperidine hydrobromide.[18] A mixture of 0.80 g. (0.0029 mole) of 1,1-dimethyl-5-bromopentylamine hydrobromide, 10 ml. of water, and 2.9 ml. of a 1 *N* sodium hydroxide solution was allowed to stand overnight. After the addition of an additional 2.9 ml. of 1 *N* sodium hydroxide solution, the reaction mixture was extracted with ten 10-ml. portions of chloroform. The chloroform solution was dried and concentrated. Benzene was added and the solution was warmed until all chloroform was removed. The benzene solution was cooled and saturated with hydrogen bromide gas. The benzene solution was warmed to remove water and excess hydrogen bromide. The solution was concentrated and the addition of petroleum hexane gave 0.41 g. of product, m.p. 188–190°. Concentration of the mother liquor gave an additional 0.11 g., m.p. 187–190°, 93% yield. A small sample was recrystallized for analysis from a mixture of chloroform and cyclohexane, m.p. 190–191°.

Anal. Calcd. for $C_7H_{10}NBr$: C, 43.31; H, 8.31; N, 7.21; Br, 41.17. Found: C, 43.22; H, 8.39; N, 7.25; Br, 41.02.

3-Ethoxy-1-propanol was prepared 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,[23] giving 400 g. of product, b.p. 157–163°, 59% yield. Smith and Sprung[23] reported b.p. 157–163°.

1-Bromo-3-ethoxypropane. A solution of 200 g. (0.92 mole) of 3-ethoxypropanol and 37.1 g. (0.46 mole) of pyridine was added over a period of 2 hr. with stirring to 200 g. (0.74 mole) of phosphorus tribromide cooled in an ice bath. After the addition, the reaction mixture was heated to 75° for 1 hr. After cooling, the liquid was decanted from the pyridine salts, which were washed with benzene. The combined solution was washed successively with water, saturated sodium bicarbonate solution, and water. After drying, distillation gave 221 g., b.p. 145–149°, 69% yield. Smith and Sprung[23] reported b.p. 147–150°.

2,2-Dimethyl-5-ethoxypentanenitrile.[18] Phenyllithium in ether was prepared in 1.1 molar quantity according to the directions of Gilman.[24] To the solution of phenyllithium was added with stirring 80.6 g., (1.1 moles) of calcium hydride–dried diethylamine in 125 ml. of ether over a period of 30 min. followed by 76.0 g. (1.1 moles) of isobutyronitrile in 125 ml. of ether over a period of 30 min. After the addition, the reaction mixture was heated under reflux and a solution of 167.0 g. (1.0 mole) of 3-ethoxypropyl bromide in 200 ml. of ether was added over a period of 2 hr. After the addition, heating under reflux was continued for an additional 3 hr., and then the reaction mixture was cooled. Water (750 ml.) was cautiously added, and the layers separated. The organic layer was washed successively with seven 100-ml. portions of 10% hydrochloric acid and two 250-ml. portions of water. After drying, distillation gave a forerun of 10 g. of 2-ethoxypropyl bromide, b.p. 61–70°/29 mm., followed by 116.5 g. of product, b.p. 105–111°/25 mm., 80% yield. A sample was redistilled for analysis, b.p. 96–98°/15 mm.

Anal. Calcd. for $C_9H_{17}ON$: C, 69.68; H, 11.05; N, 9.03. Found: C, 69.56; H, 10.89; N, 9.12.

The residue in the flask solidified after cooling. The solid was recrystallized from petroleum hexane to give 1.75 g. of material, m.p. 112–114°. A mixture of this solid with authentic $\alpha,\alpha,\alpha',\alpha'$-tetramethylpimelonitrile, kindly supplied by Mr. Dennis Karle, gave m.p. 112–113°.

2,2-Dimethyl-5-ethoxypentylamine[18] was prepared by the addition of a solution of 31.0 g. (0.20 mole) of 1,1-dimethyl-5-ethoxypentanenitrile in 100 ml. of sodium-dried ether to a stirred, refluxing slurry of 9.1 g. (0.24 mole) of lithium aluminum hydride in 500 ml. of sodium-dried ether. After the addition, the reaction mixture was heated under reflux overnight with stirring, and then cooled. The cold reaction mixture was decomposed by the addition of 50 ml. of saturated sodium chloride solution. After the addition, stirring was continued for an additional 45 min. The ether solution was decanted and the salts were thoroughly washed with ether. The combined ether solution was dried and the solvent removed at the steam bath. The distillation of the product was stopped because of excessive foaming. The residue was dissolved in benzene. The benzene solution was boiled to remove any water, cooled, and saturated with hydrogen bromide gas. The solution was again heated to remove excess hydrogen bromide and water. The addition of petroleum hexane gave 41.0 g. of the amine hydrobromide, m.p. 97–102°, 85.5% yield. The material was recrystallized from carbon tetrachloride for analysis, m.p. 98–99°.

Anal. Calcd. for $C_9H_{22}ONBr$: C, 45.00; H, 9.23; N, 5.83; Br, 33.27. Found: C, 45.11; H, 9.33; N, 5.85; Br, 33.19.

5-Bromo-2,2-dimethylpentylamine hydrobromide[18] was pre-

(23) L. Smith and J. Sprung, *J. Am. Chem. Soc.*, **65**, 1279 (1943).

(24) H. Gilman, *Org. Reactions* VI, 353 (1951).

pared by the distillation from an oil bath held at 150–160° of a solution of 40.0 g. (0.166 mole) of 2,2-dimethyl-5-ethoxypentylamine in 160 ml. of concd. hydrobromic acid over a period of 6 hr., giving 110 ml. of distilled hydrobromic acid. The solution was cooled and most of the hydrobromic acid was removed under reduced pressure. The last traces of acid were removed by codistillation with chloroform. After all the hydrobromic acid was removed, the chloroform was removed under reduced pressure. The remaining solid was dissolved in acetone, treated with decolorizing carbon, filtered, and concentrated. The addition of ethyl acetate gave 38.0 g. of colorless crystals, m.p. 135–137°, 85.5% yield. The material was recrystallized from a mixture of nitromethane and carbon tetrachloride for analysis, m.p. 137–139°.

Anal. Calcd. for $C_7H_{17}NBr$: C, 30.56; H, 6.23; N, 5.09; Br, 58.11. Found: C, 30.28; H, 6.19; N, 5.22; Br, 58.82.

3,3-Dimethylpiperidine hydrobromide.[18] A mixture of 2.75 g. (0.01 mole) of 5-bromo-2,2-dimethylpentylamine hydrobromide or of 5-bromo-4,4-dimethylpentylamine hydrobromide and 10 ml. of 1 *N* sodium hydroxide solution was allowed to stand overnight. After the addition of an additional 10 ml. of 1 *N* sodium hydroxide solution, the reaction mixture was extracted with ten 10-ml. portions of chloroform. The chloroform solution was dried and concentrated. Benzene was added and the solution was warmed until all chloroform was removed. The benzene solution was cooled and saturated with hydrogen bromide gas. The solution was warmed to remove water and excess hydrogen bromide. The solution was concentrated and petroleum hexane added to give 1.70 g. of colorless crystals, m.p. 179–181°. Concentration of the mother liquor gave an additional 0.14 g. of material, m.p. 177–180°, 95% yield. A small sample was recrystallized for analysis from a mixture of chloroform and cyclohexane, m.p. 181–182°.

Anal. Calcd. for $C_7H_{16}NBr$: C, 43.31; H, 8.31; N, 7.21; Br, 41.17. Found: C, 43.19; H, 8.42; N, 7.22; Br, 41.00.

3,3-Dimethylglutaric anhydride was prepared in 70% yield from acetone, ethyl cyanoacetate, and liquid ammonia by the method of Brown and van Gulick,[2] m.p. 123–124°. Brown and van Gulick[2] reported m.p. 123–124°.

Monomethyl 3,3-dimethylglutarate. A solution of 27.0 g. (0.50 mole) of sodium methoxide in 100 ml. of methanol was added to a solution of 71 g. (0.50 mole) of 3,3-dimethylglutaric anhydride in 250 ml. of methanol. After the addition, the solution was allowed to cool to room temperature before removing the methanol by distillation. After approximately 350 ml. of methanol had been removed, excess benzene was added to the solution and distillation continued to remove all of the methanol as the benzene–methanol azeotrope. The solution was cooled and concentrated hydrochloric acid was added until the aqueous layer remained acid to Congo Red indicator paper. The layers were separated and the aqueous layer was extracted with benzene. The combined benzene layers were dried, and distilled to give 81.6 g. of product, b.p. 168–172°/30 mm., 93% yield. Cason[25] reported b.p. 126–127°/4.5 mm. A small sample was redistilled for analysis, b.p. 128–128.5°/6 mm.

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.15; H, 8.10. Found: C, 55.18; H, 8.08.

4-Carbomethoxy-3,3-dimethylbutanoyl chloride. A solution of 15 ml. (0.21 mole) of thionyl chloride and 2 drops of pyridine was added to a solution of 33.0 g. (0.19 mole) of monomethyl 3,3-dimethylglutarate in 100 ml. of benzene. After the addition, the mixture was heated under reflux for 1 hr., cooled, and the benzene and excess thionyl chloride removed by distillation. The residue was distilled to give 28.5 g. of the acid chloride, b.p. 96–98°/7 mm., 78% yield. Cason[25] reported b.p. 75–76°/3 mm.

Anal. Calcd. for $C_8H_{13}O_3Cl$: C, 49.87; H, 6.80; Cl, 18.40. Found: C, 49.59; H, 6.52; Cl, 18.65.

A derivative was prepared by the addition of a solution of 1.3 g. (0.007 mole) of the acid chloride in 50 ml. of benzene to a solution of 2.0 g. (0.0145 mole) of *p*-nitroaniline in 100 ml. of benzene. After the addition, the mixture was heated on the steam bath for 10 min., cooled, and filtered. The solid was washed with benzene, and the benzene filtrate was washed successively with water, 10% hydrochloric acid solution, and water. After drying, addition of petroleum pentane gave 1.8 g. of material, m.p. 63.5–70°, 80% yield. The solid was recrystallized by dissolving in a minimum amount of methanol and adding water to the point of cloudiness. Standing overnight gave crystals, m.p. 73–74°.

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.09; H, 6.23; N, 9.43.

3,3-Dimethyl-5-hydroxypentylamine was prepared from a mixture of 52.2 g. (0.30 mole) of monomethyl 3,3-dimethylglutarate, 26.0 g. (0.36 mole) of thionyl chloride, 100 ml. of benzene, and 5 drops of pyridine by heating under reflux for 2 hr. After cooling in an ice bath, 25.5 g. (1.50 moles) of liquid ammonia was allowed to vaporize and the gas, after passing through Ascarite, was bubbled into the reaction mixture. After the addition, the reaction mixture was filtered to remove solids. The solid was thoroughly washed with benzene. The combined benzene filtrate was washed with water, dried, and immediately added to 34.1 g. (0.90 mole) of lithium aluminum hydride in 1 l. of sodium-dried ether. After the addition, the reaction mixture was heated under reflux for 3 days, cooled, and decomposed by the slow addition of 250 ml. of saturated sodium chloride solution. After the addition of the salt solution, stirring was continued for 1 hr. The reaction mixture was filtered and the filter cake thoroughly washed with ether. After removal of the solvent, distillation gave 27.5 g. of product, b.p. 100–104°/2 mm., 70% yield from monomethyl 3,3-dimethylglutarate.

A solution of 0.94 g. (0.0075 mole) of oxalic acid dihydrate in 10 ml. of 2-propanol was added to a solution of 2.00 g. (0.015 mole) of 3,3-dimethyl-5-hydroxypentylamine in 10 ml. of 2-propanol. A precipitate formed immediately. The solid was collected to give 2.0 g. of material,[18] m.p. 102–120°, 69% yield. Recrystallization several times from *t*-butyl alcohol raised the melting point to 136–138°.

Anal. Calcd. for $C_{16}H_{40}N_2O_8$: C, 49.46; H, 10.37. Found: C, 49.71; H, 10.09.

5-Bromo-3,3-dimethylpentylamine hydrobromide.[18] A solution of 27.5 g. (0.209 mole) of 3,3-dimethyl-5-hydroxypentylamine and 217 ml. (2.00 moles) of concd. hydrobromic acid was distilled from an oil bath at 155–165° over a period of 4 hr. giving 170 ml. of distilled hydrobromic acid. The remainder of the acid was removed under reduced pressure. The last traces of hydrobromic acid were removed by codistillation with chloroform. The remaining solid was taken up in acetone, treated with decolorizing carbon, filtered, and concentrated. Ethyl acetate was added to precipitate 29.6 g. of white crystals, m.p. 211–212°, 52.5% yield. A sample was recrystallized from ethylene chloride for analysis, m.p. 211–212°.

Anal. Calcd. for $C_7H_{17}NBr_2$: C, 30.56; H, 6.23; N, 5.09; Br, 58.11. Found: C, 30.39; H, 6.31; N, 5.14; Br, 58.41.

4,4-Dimethylpiperidine hydrobromide.[18] A mixture of 0.137 g. (0.0005 mole) of 5-bromo-3,3-dimethylpentylamine hydrobromide, 2.0 g. (0.05 mole) of sodium hydroxide, and 10 ml. of water was heated on the steam bath for 0.5 hr. The reaction mixture was cooled and extracted with ether. The ether layer was dried and saturated with hydrogen bromide gas. The ether solution was heated to remove excess hydrogen bromide. Chloroform was added and the solution was heated until all water and ether were removed. The chloroform solution was concentrated and petroleum hexane was added to give 0.087 g. of colorless crystals, m.p. 181–183°, 91% yield. The material was recrystallized from chloroform–cyclohexane, m.p. 184–185°.

Anal. Calcd. for $C_7H_{16}NBr$: C, 43.31; H, 8.31; N, 7.21; Br, 41.17. Found: C, 43.22; H, 8.31; N, 7.14; Br, 41.05.

A solution of 7.9 g. (0.05 mole) of 3,3-dimethylglutarimide

(25) J. Cason, G. Sumrell, and R. S. Mitchell, *J. Org. Chem.*, **15**, 850 (1950).

in 150 ml. of ether was slowly added to 5.0 g. (0.132 mole) of lithium aluminum hydride in 500 ml. of ether. The reaction mixture was heated under reflux for 20 hr., cooled, and decomposed by the careful addition of 40 ml. of saturated sodium chloride solution. After the addition of the salt solution, stirring was continued for 30 min. The ether solution was filtered and the salts thoroughly washed with ether. Distillation gave 2.0 g. of material, b.p. 134–137°, 35.8% yield. Hoch[16] reported b.p. 30–32°/12 mm.

Approximately half of the 4,4-dimethylpiperidine was dissolved in benzene and the benzene solution saturated with hydrogen bromide gas. The benzene solution was warmed to remove excess hydrogen bromide and water. Cooling gave crystals of the 4,4-dimethylpiperidine hydrobromide, m.p. 184–188°; of a mixture with the product from the cyclization of 5-bromo-3,3-dimethylpentylamine hydrobromide, m.p. 184–186°.

The remainder of the 4,4-dimethylpiperidine was treated with hydrogen chloride gas in benzene to give the hydrochloride, m.p. 226–228°. Hoch[16] reported m.p. 227–228°.

2,2-Dimethyl-5-ethoxypentanoic acid. A mixture of 77.5 g. (0.50 mole) of 2,2-dimethyl-5-ethoxypentanenitrile, 80.0 g. (2.0 moles) of sodium hydroxide in 200 ml. of water, and enough ethanol to make the mixture homogeneous, was heated under reflux for 5 days in a copper flask. The solvent was removed by distillation. Dilute hydrochloric acid was added to the reaction mixture until the aqueous layer was acid to Congo Red indicator paper. The layers were separated and the water layer was extracted with benzene. The combined organic layer was dried and distilled. After a forerun of starting material, 8.0 g., b.p. 55–70°/2 mm.. 64.5 g. of product was collected, b.p. 114–116.5°/2 mm., 82.5% yield. A sample was redistilled for analysis, b.p. 114–116.5°/2 mm.

Anal. Calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.96; H, 10.44.

2,2-Dimethyl-5-ethoxypentanol.[18] A solution of 60.0 g. (0.34 mole) of 2,2-dimethyl-5-ethoxypentanoic acid in 100 ml. of benzene was added slowly to a refluxing slurry of 12.9 g. (0.34 mole) of lithium aluminum hydride in 1200 ml. of anhydrous ether. The reaction mixture was heated under reflux for 20 hr., then allowed to stand at room temperature for an additional 30 hr. The reaction was decomposed by the slow addition of 75 ml. of saturated sodium chloride solution. After the addition, stirring was continued for 45 min. The liquid was decanted from the salts and the salts were thoroughly washed with ether. After drying, distillation gave 40.0 g. of product, b.p. 81–85°/3 mm., 73.8% yield. A sample was redistilled for analysis, b.p. 54.4–55.0°/0.5 mm.

Anal. Calcd. for $C_9H_{20}O_2$: C, 67.45; H, 12.58. Found: C, 67.36; H, 12.70.

1-Bromo-2,2-dimethyl-5-phthalimidopentane.[18] A mixture of 5.0 g. (0.30 mole) of 2,2-dimethyl-5-ethoxypentanol, 15.5 g. (0.120 mole) of synthetic quinoline, and 100 ml. of bromobenzene was cooled in an ice bath. To the cold mixture was added 16.2 g. (0.060 mole) of phosphorus tribromide. After the addition, the ice bath was removed and the mixture was heated under gentle reflux for twenty hours. After cooling to room temperature, the reaction mixture was poured onto ice. The layers were separated and the water layer was extracted with chloroform. The combined organic layer was washed successively with 1% sodium hydroxide solution, concd. sulfuric acid, and water. After drying, distillation under reduced pressure in order to remove the solvents was continued until 65 ml. of bromobenzene, b.p. 50–52°, was collected. To the residue was added a solution of 5.5 g. (0.03 mole) of potassium phthalimide in 60 ml. of dimethylformamide. The reaction mixture was heated on the steam bath for 45 min. After cooling, the reaction mixture was poured into water. The layers were separated and the water layer was extracted with chloroform. The combined organic layer was washed with 5% sodium hydroxide solution, followed by water. After drying, the solvent was removed in an air stream. Addition of cyclohexane to the residue caused crystallization. Recrystallization from cyclohexane gave 2.40 g. of material, m.p. 71–73°. Concentration of the mother liquor gave an additional 0.12 g. of material, 26% total yield. A small sample was recrystallized from cyclohexane for analysis, m.p. 70.0–70.5°.

Anal. Calcd. for $C_{15}H_{18}NBrO_2$: C, 55.57; H, 5.59; N, 4.32; Br, 24.65. Found: C, 55.39; H, 5.55; N, 4.35; Br, 24.77.

5-Bromo-4,4-dimethylpentylamine hydrobromide.[18] A mixture of 3.24 g. (0.010 mole) of 2,2-dimethyl-1-bromo-5-phthalimidopentane in 11 ml. (0.200 mole) of concd. hydrobromic acid and 11 ml. of glacial acetic acid was heated under reflux for 2 hr. The reaction mixture was chilled and the phthalic acid collected and washed with a minimum quantity of acetic acid. The solid residue was extracted with chloroform to recover 1.53 g. of starting material. The filtrate was evaporated to dryness under reduced pressure, and the residual traces of solvent were removed in a desiccator over potassium hydroxide. The product was recrystallized from carbon tetrachloride to give 0.200 g., m.p. 172–173°, 14% yield.

Anal. Calcd. for $C_7H_{17}NBr_2$: C, 30.56; H, 6.23; N, 5.09; Br, 58.11. Found: C, 30.60; H, 6.19; N, 5.06; Br, 58.06.

Dimethyl 2,2-dimethylglutarate was prepared according to the method developed by Clinton[26] for preparing esters in one molar and larger quantities. A mixture of 160.2 g. (1.00 mole) of 2,2-dimethylglutaric acid, 192 g. (6.0 moles) of commercial methanol, 600 ml. of ethylene dichloride, and 6 ml. of concd. sulfuric acid was heated under reflux for 18 hr., then cooled to room temperature. A small upper layer was separated and discarded. The lower layer was washed with water, saturated sodium bicarbonate solution, and water. After removal of the ethylene dichloride by distillation at atmospheric pressure, distillation under reduced pressure gave 158.0 g. of product, b.p. 108–110°/17 mm., 84% yield. Blaise[27] reported b.p. 215–216°.

2,2-Dimethylpentane-1,5-diol. A solution of 158.0 g. (0.84 mole) of dimethyl 2,2-dimethylglutarate in 2 l. of anhydrous ether was slowly added to a refluxing slurry of 37.9 g. (1.00 mole) of lithium aluminum hydride in 1 l. of anhydrous ether. The reaction mixture was heated under reflux for 18 hr., cooled, and decomposed by the slow addition of 280 ml. of saturated sodium chloride solution. After the addition, stirring was continued for 1 hr. The ether was decanted and the salts thoroughly washed with ether. After drying, distillation gave 100 g. of product, b.p. 140–142°/16 mm., 90.5% yield. Chabley[28] reported b.p. 133°/15 mm. The infrared spectrum showed no 5.7 μ absorption peak indicating the absence of a carbonyl group.

4-Cyano-2,2-dimethylbutanal. Over a period of 2 hr., 6.0 g. of a 50% aqueous potassium hydroxide solution was slowly added to a mixture of 116.6 g. (2.2 moles) of acrylonitrile and 144.2 g. (2.0 moles) of isobutyraldehyde. During the addition, the temperature was maintained between 55° and 60° by heating with a water bath or cooling with an ice bath as necessary. After the addition, the mixture was cooled, and dilute hydrochloric acid was added until the water layer was acid to Congo Red indicator paper. The layers were separated and after drying, the organic layer was distilled to give 136.8 g. of product, b.p. 112–123°/16 mm., 54.7% yield. Hoch[16] reported b.p. 106–108°/aspirator.

2,2-Dimethylglutaric acid was prepared by the addition of a solution of 9.8 g. (0.10 mole) of concd. sulfuric acid in 5.0 g. of water dropwise over a period of 20 min. to a mixture of 6.3 g. (0.05 mole) of 4-cyano-2,2-dimethylbutanal, 5.8 g. (0.02 mole) of potassium dichromate, and 5.0 g. of water heated on the steam bath. The reaction mixture was cooled and an additional 20 ml. of 50% sulfuric acid solution was

(26) R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).

(27) E. E. Blaise, *Bull. soc. chim. France*, [3], **21**, 626 (1896).

(28) E. Chabley, *Compt. rend.*, **156**, 1022 (1913).

added. The reaction mixture was extracted with ether. The ether layer was dried and all the ether was removed under reduced pressure. To the residue was added a solution of 2.4 g. (0.06 mole) of sodium hydroxide in 25 ml. of water. The reaction mixture was heated under reflux for approximately 20 hr., cooled, and made acid to Congo Red indicator paper by the addition of dilute hydrochloric acid. The acidic solution was extracted with benzene. The benzene layer was dried, concentrated, and petroleum hexane added to precipitate an oil that crystallized upon scratching, 1.42 g., m.p. 83.5–85°, 17.7% yield. Hoch[16] reported, m.p. 83–84°.

4-Chloro-2,2-dimethylbutanenitrile.[18] Phenyllithium was prepared in 2.3 molar quantity according to the directions of Gilman.[24] A solution of 168 g. (2.3 moles) of calcium hydride–dried diethylamine in 200 ml. of anhydrous ether was added to the solution of phenyllithium. After the reaction mixture cooled to room temperature, a solution of 159 g. (2.3 moles) of isobutyronitrile in 200 ml. of anhydrous ether was added. After cooling, the reaction mixture was added dropwise, over a period of 7.5 hr., under nitrogen, to a refluxing solution of 286.8 g. (2.0 moles) of 1-chloro-2-bromoethane in 1 l. of anhydrous ether. After the addition, the reaction mixture was heated under reflux overnight, then cooled to 5° in an ice bath, and 1 l. of water was added. The layers were separated and the ether layer was washed with water, 10% hydrochloric acid, and water. After drying, distillation gave 97.5 g. of product, b.p. 86–88°/18 mm., 37% yield. A sample was redistilled by Mr. D. W. Karle for analysis, b.p. 83.0–83.5°/16 mm.

Anal. Calcd. for $C_6H_{10}NCl$: C, 54.76; H, 7.66; N, 10.64. Found: C, 54.51; H, 7.75; N, 10.44.

2,2-Dimethylglutaronitrile.[18] A solution of 78.2 g. (1.50 moles) of 95% sodium cyanide in 150 ml. of water was added to 175.5 g. (1.33 moles) of 4-chloro-2,2-dimethylbutanenitrile in 500 ml. of 95% ethanol. More 95% ethanol was added until a homogeneous solution resulted. A few crystals of potassium iodide were added as a catalyst. The reaction mixture was heated under reflux for 5.5 days. The ethanol was removed by distillation which resulted in the formation of two layers. After cooling, the layers were separated. The water layer was extracted several times with ether. The combined organic layer was dried and distilled. After a forerun of starting material, 27.0 g., b.p. 80–85°/16 mm., and a middle fraction, 19.5 g., b.p. 85–130°/16 mm., the product was collected, 72.5 g., b.p. 130–137°/16 mm., 52.6% yield.

Anal. Calcd. for $C_7H_{10}N_2$: C, 68.76; H, 8.24. Found: C, 68.62; H, 8.31.

The water layer was made acidic by the addition of hydrochloric acid and heated under the hood to remove all hydrogen cyanide, and then evaporated to dryness under reduced pressure. The solid was extracted with chloroform. After drying and concentrating, addition of petroleum hexane caused crystallization of 10.0 g. of 2,2-dimethylglutaric acid, which upon mixing with authentic 2,2-dimethylglutaric acid, gave m.p. 71–73°. Hoch[16] reported m.p. 83–84° for 2,2-dimethylglutaric acid.

2,2-Dimethylglutaric acid. A mixture of 97.5 g. (0.80 mole) of 2,2-dimethylglutaronitrile, 400 g. (4.05 moles) of concd. hydrochloric acid, and 100 ml. of water was heated under reflux for 21 hr. The mixture was cooled and allowed to stand until the mixture solidified. The solid was collected and most of the hydrochloric acid was removed by suction. The still moist crystals were dissolved in chloroform. The chloroform layer was separated from the aqueous layer, dried, and concentrated. Addition of petroleum hexane caused crystallization. The solid was collected and dried in the air to give 119.0 g. of acid, m.p. 82–84°, 93% yield. Hoch[16] reported m.p. 83–84°.

Anal. Calcd.: Neut. equiv., 80.1. Found: Neut. equiv., 82.1.

LOS ANGELES 7, CALIF.

[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

The Selective Alkylation of Polyphenols. II. Methylation of 7-, 4′-, and 3′-Hydroxyl Groups in Flavonols

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The methylation, benzylation, or allylation of quercetin pentacetate in anhydrous acetone results in the replacement of acetyl groups by alkyl in the 7- and, to a lesser extent, 4′- positions only. Methylation of a fully acetylated flavonol in acetone containing methanol, however, preferentially methylates hydroxyls in the 7-, 4′- and 3′- positions. A wide variety of partial methyl ethers have been prepared by these reactions.

The methylation of quercetin pentacetate in *anhydrous* acetone yields 7-*O*-methylquercetin. Under similar conditions benzylation and subsequent alkaline hydrolysis gives 7-*O*-benzylquercetin[1] and, in addition, smaller quantities of 4′,7-di-*O*-benzylquercetin. These benzyl ethers differ markedly in their solubilities in benzene. They are therefore separated easily and are useful intermediates in the conversion of quercetin into a variety of its partial methyl ethers. Partial allyl ethers of quercetin, however, do not appear to be useful for these purposes. Thus, quercetin pentacetate reacts particularly readily with excess of allyl bromide in dry acetone to form chiefly 4′,7-di-*O*-allylquercetin triacetate from which 4′,7-di-*O*-allylquercetin is readily obtained. Unexpectedly, however, the allyloxy linkages in this compound proved remarkably stable to acid hydrolysis, all attempts to de-allylate its and its trimethyl ether having so far been unsuccessful.

The alkylations in dry acetone discussed above result in the replacement of acetyl groups in the 7- and, to a lesser extent, 4′- positions only. All acetoxy groups are hydrolyzed, however, when fully acetylated flavonols are methylated in a mixture of

(1) L. Jurd, *J. Am. Chem. Soc.*, **80**, 5531 (1958).