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]

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

LOS ANGELES 7, CALIFORNIA

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

[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).

be expected to equilibrate with the alcoholic solvent before ring closure could occur. However, 76% of the starting material was recovered, 11% of a neutral solid was isolated, and only a trace of basic material could be obtained. Catalytic hydrogenation failed also.

The steric requirements of lithium aluminum hydride are known to be considerably less than those of surface active catalysts and less than those of the Ponndorf reagent in the reduction of sterically hindered carbonyl groups.[7] We reasoned that a 4-alkoxy-2,2-diisopropylbutylamine might be obtained if the less easily displaced methoxy group were substituted for the phenoxy group in the lithium aluminum hydride reduction and such was found to be the case. 2,2-Diisopropyl-4-methoxybutyronitrile gave 2,2-diisopropyl-4-methoxybutylamine in 92% yield.

The dimethyl- and diethylphenoxyamines were converted readily to I and II by the usual treatment with hydrobromic acid. The diisopropylmethoxyamine, however, gave rise to a 36% yield of the pyrrolidine beside a 47% yield of the expected product. The diphenyl- and ditolylphenoxyamines reacted only sluggishly and gave high yields of the cyclization products. These cyclizations in strongly acidic solutions are a surprising phenomenon for which no explanation has yet been devised. The diisopropylphenoxyamine gave rise only to small amounts of impure bromoamine hydrobromides. Repetition of all of these syntheses using the methoxy group rather than the phenoxy might enable the cleavage step with hydrobromic acid to be more successful, and this could be the reason why less difficulty was experienced with the diisopropylmethoxyamine.

All of the 2,2-dialkyl-4-bromobutylamine hydrobromides in the series gave negative nickel tests for primary amines and positive tests for secondary amines.[2] The Hinsberg reaction gave the 1-phenylsulfonyl-3,3-dialkylpyrrolidines by cyclization. These bromoamine salts cyclize readily in aqueous solution, similar to 4-bromo-1,1-dimethylbutylamine hydrobromide.[2]

It was necessary to prove the structures of the compounds of the 2,2-dialkyl-4-bromobutylamine hydrobromide series to check on the possibility of rearrangement in the ether cleavage step. The recorded melting point of 3,3-diphenylpyrrolidine hydrochloride, a known compound,[8] was the same as that of the same compound as prepared *via* the cyclization of 4-bromo-2,2-diphenylbutylamine hydrobromide. Furthermore, 1-phenylsulfonyl-3,3-dimethylpyrrolidine, the product of the Hinsberg reaction with I, was synthesized unequivocally by an independent method (discussed below). 3,3-Diisopropylpyrrolidine from the cyclization of the corresponding bromoamine salt was found to be identical with material from the reduction of 2,2-diisopropyl-4-phenoxybutyronitrile. Reduction of *asym*-dimethylsuccinimide afforded 3,3-dimethylpyrrolidine, the Hinsberg product of which was identical with that formed from I.

The basic skeleton of I could, in principle, be obtained in another way by Michael addition of the elements of hydrogen cyanide or nitromethane to ethyl 3-methyl-2-butenoate. These additions failed to take place, but if the double bond was doubly activated, as in isopropylidenecyanoacetic ester, addition of nitromethane occurred readily. Acidic and basic hydrolyses of the nitro ester were attempted, but it was not possible to isolate any of the desired 3,3-dimethyl-4-nitrobutanoic acid. The alkaline hydrolysis yielded tar, which can be explained by the fact that alkaline treatment of primary nitroalkanes is known to yield trimeric condensation products.[9] Acid hydrolysis and decarboxylation produced large quantities of ammonium carbonate and a small quantity of *asym*-dimethylsuccinic acid. Acid treatment of primary nitroalkanes is known to induce oxidation of the nitro-bearing carbon atom giving hydroxylamine or ammonia and an acid having the same number of carbon atoms.[10]

Experimental[11]

α-Alkylation of Nitriles.—Phenyllithium in ether was prepared in half-molar quantity according to the directions of Gilman.[12] After cooling, 0.5 mole of calcium hydride dried diethylamine was added over a period of 5 minutes, followed by the addition of 0.5 mole of disubstituted acetonitrile in 100 ml. of ether (or benzene for the aromatic nitriles) over a period of 5 minutes. The metalation was exothermic for the aromatic nitriles, but not for the aliphatic nitriles. Gilman's color test[13] was negative for the aromatic nitriles, but positive for the aliphatic nitriles. The solution was heated to the boiling point and 0.5 mole of phenoxyethyl bromide[14] was added dropwise at such a rate that the capacity of the condenser was not exceeded. The aliphatic nitriles react violently and the addition requires 0.5 hr., but with the aromatic nitriles the bromide may be added over a period of 5–10 minutes. The solution was heated under reflux for an additional 2 hours and then cooled. After extraction with water and dilute hydrochloric acid, the ether and benzene were removed on the steam-bath and the aliphatic nitriles were distilled. When R was phenyl, methanol was added to the residue and the crystals were collected. This procedure was not successful when R was *p*-tolyl because the crystals melted at room temperature. The crude tolyl compound was used directly in the subsequent step. Table I lists the substituted nitriles prepared by this method.

TABLE I

2,2-DISUBSTITUTED-4-PHENOXYBUTYRONITRILES, $C_6H_5OCH_2CH_2CR_2CN$

R	Yield	B.p., °C. (1 mm.)	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Methyl	88	91–95	37–39	76.15	7.99	76.00	7.67
Ethyl	75	110–113	.....	...	..	...	..
Isopropyl	25	124–128	.....	78.32	9.45	78.40	9.25
Phenyl	87	.....	86–87	84.31	6.11	84.13	5.80
p-Tolyl	..	.....	Room temp.	...	..	...	..

Methoxyethyl bromide was prepared in 26% yield by the procedure used for ethoxypropyl bromide (phosphorus tribromide and pyridine). Other workers have also had this trouble with this preparation.[15] Diisopropylacetonitrile

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[7] N. H. Cromwell and K. C. Tsou, *J. Org. Chem.*, **15**, 1219 (1950), and P. L. Julian, W. Cole, G. Diemer and J. G. Schafer, THIS JOURNAL, **71**, 2058 (1949).

[8] N. Sperber and R. Fricano, *ibid.*, **75**, 2986 (1953).

[9] S. B. Lippincott, *ibid.*, **62**, 2604 (1940).

[10] H. B. Hass and E. F. Riley, *Chem. Revs.*, **32**, 373, 396 (1943).

[11] All m.p.'s and b.p.'s are uncorrected. Analyses by Mr. W. J. Schenck of this department.

[12] H. Gilman in "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 353.

[13] H. Gilman and F. Schultz, THIS JOURNAL, **47**, 2002 (1925).

[14] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, pp. 435–436.

[15] R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, Jr., THIS JOURNAL, **67**, 290 (1945).

was alkylated with methoxyethyl bromide to give 31% of product, b.p. 129–132° (24 mm.).

Isobutyronitrile was alkylated also with sodamide prepared by adding 11.5 g. of sodium piecewise to a solution of 0.2 g. of ferric nitrate in 500 ml. of liquid ammonia. After complete conversion to the amide, 34.6 g. of isobutyronitrile was added. After 5 minutes, a solution of 100.6 g. of phenoxyethyl bromide in 200 ml. of ether was added over a 15-minute period. The ammonia was allowed to evaporate and stirring was continued for one hour. The solution was filtered and the salts were washed with ether. The ethereal solution was washed with dilute hydrochloric acid, then water and dried. After removal of the ether on the steam-bath, the nitrile was left as an oil, which crystallized on cooling. This was distilled at 2 mm. to give 56 g. (59%), b.p. 96–126°, which after three recrystallizations from petroleum pentane gave 38.5 g. (41%), plates, m.p. 37–39°.

Reduction of nitriles was carried out by adding one mole of nitrile in 400 ml. of ether (benzene when R was phenyl) over a period of 30 minutes to a stirred refluxing slurry of 1.25 moles of lithium aluminum hydride in 1800 ml. of ether. After the vigorous reaction during the addition, heating was continued for 30 minutes and the reaction mixture was decomposed cautiously with 5 moles of 2-propanol, followed by 310 ml. of saturated salt solution. The mixture was filtered and the filter cake was washed with ether. The aliphatic amines were obtained by distillation and the aryl substituted amines were isolated in the form of their difficultly-soluble hydrobromides by the addition of 125 ml. of concentrated hydrobromic acid to the ether solution. The purified aliphatic amines were converted to their hydrobromides and crystallized from ethylene chloride. The aromatic hydrobromides were crystallized from methanol. These compounds are listed in Table II.

TABLE II

2,2-DISUBSTITUTED-4-PHENOXYBUTYLAMINES AND HYDROBROMIDES, $C_6H_5OCH_2CH_2CR_2CH_2NH_2$

R	Yield, %	B.p., °C. (20 mm.)	HBr, m.p., °C.	Analyses, % Calcd. C	H	Found C	H
Methyl	81	158–162	121–122	52.56	7.35	52.76	7.33
Ethyl	80	183–187	140–141	55.63	8.00	55.90	8.22
Phenyl	90	.....	215–216	66.33	6.07	66.43	6.22
p-Tolyl	88	.....	246–247	67.60	6.62	67.71	6.82

When R was isopropyl, the starting material was recovered in 85% yield and 3,3-diisopropylpyrrolidine was isolated in 9% yield. The hydrobromide of the latter, m.p. 124–125° from carbon tetrachloride and ether, gave a poor analysis, undoubtedly because of a hygroscopic tendency.

Anal. Calcd. for $C_{10}H_{22}BrN$: C, 50.84; H, 9.39; N, 5.93. Found: C, 50.29; H, 9.49; N, 5.62.

1-Phenylsulfonyl-3,3-diisopropylpyrrolidine, m.p. 88–89° from petroleum hexane, gave a better analysis.

Anal. Calcd. for $C_{16}H_{25}NO_2S$: C, 65.04; H, 8.53. Found: C, 65.37; H, 8.62.

2,2-Diisopropyl-4-phenoxybutyronitrile was reduced also in refluxing tetrahydrofuran, using the same procedure as for ether. The pyrrolidine was isolated in 26% yield and the starting material was recovered in 49% yield. An attempt to reduce the isopropyl compound with Raney nickel and hydrogen at 100° and 100 atmospheres for a period of 4 hours was unsuccessful. The starting material was recovered quantitatively. The reduction of 2,2-diisopropyl-4-methoxybutryonitrile with lithium aluminum hydride was carried out in boiling ether for 16 hours to give 92% of 2,2-diisopropyl-4-methoxybutylamine, b.p. 132–136° (24 mm.).

The reductions also were tried with sodium and alcohol, where R in the nitrile was methyl, isopropyl and phenyl. In the case of methyl, the yield was 62%, but when R was isopropyl a Prussian blue test for cyanide ion was obtained, and after extraction of a 0.5% yield of the pyrrolidine, the reaction mixture was distilled giving a distillate of recovered nitrile (76%) and a crystalline neutral residue, m.p. 114–115° from carbon tetrachloride and petroleum hexane. An analysis indicated the empirical formula $C_{10.3}H_{22.2}NO_{2.3}$.

Anal. Found: C, 62.80; H, 11.37; N, 7.11.

The phenyl compound gave a very heavy cyanide test and the sole isolable product was 1-phenoxy-3,3-diphenylpropane, m.p. 85–86° from ethyl acetate, in 91% yield.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.10; H, 6.73.

Dimethyl- and Diethylacetonitriles.—One mole of the corresponding acid and 1.1 moles of thionyl chloride were allowed to stand overnight with a boiling chip to facilitate gas evolution. After heating on the steam-bath for 15 minutes to complete the reaction, 150 ml. of ether was added and the solution was dropped over a period of one-half hour into a stirred solution of 4 moles of liquid ammonia in 400 ml. of tetrahydrofuran cooled in Dry Ice and acetone. After adding 600 ml. of petroleum hexane, the red slurry was filtered while still cold, and the solid was washed with additional petroleum hexane to remove most of the color. After adding 600 ml. of ligroin, b.p. 115–135°, the filtrate was evaporated until the vapor temperature reached 100°; cooling gave more solid. The total solid so collected was allowed to dry and was suspended in 400 ml. of chloroform and 1.2 moles of thionyl chloride was added. The mixture was heated on the steam-bath until hydrogen chloride evolution completely ceased (4–8 hours). Excess thionyl chloride was destroyed by the cautious addition of enough water to dissolve all solids. The chloroform layer was separated and washed with 5% sodium hydroxide and water. Good fractionation gave isobutyronitrile, b.p. 102–104° (lit.[16] b.p. 103.8), in 89% yield and diethylacetonitrile, b.p. 141–143° (lit.[17] b.p. 142–146°), in 88% yield.

Di-*p*-tolylacetic Acid and Nitrile.—1,1-Di-*p*-tolyl-2,2,2-trichloroethane was prepared by the sulfuric acid condensation of toluene and chloral according to Fischer[18] in 54% yield, m.p. 86–87°. This was hydrolyzed by adding 0.5 mole portionwise to a still hot solution of 2.5 atoms of sodium in 1 l. of redistilled 2-(2-ethoxyethoxy)-ethanol and heating under reflux for 8 hours. After cooling and filtration to remove salt, the bulk of the solvent was removed by distillation *in vacuo*, leaving a thick sirup to which was added 250 ml. of concentrated hydrochloric acid. Water was added and the granular solid was collected, washed with water and crystallized from 100 ml. of 80% acetic acid, giving 68 g. (51%) of dense stubby needles, m.p. 143–144°, lit.[19] m.p. 144°. The acid chloride was prepared by heating 0.246 mole of the acid with 0.28 mole of thionyl chloride and 50 ml. of ethylene chloride overnight on the steam-bath (the reaction fails to go in refluxing chloroform). The solvent was removed *in vacuo* and 60 ml. of ether was added. The solution was added over a period of 0.5 hour to a solution of 85 ml. of concentrated ammonia and 120 ml. of 2-propanol in an ice and methanol bath, keeping the temperature below 15°. The crude amide (98%), m.p. 184–185°, lit.[20] m.p. 190°, was removed by filtration.

The amide was dehydrated by heating 0.246 mole with 0.295 mole of thionyl chloride and 50 ml. of ethylene chloride on the steam-bath for 6 hours (the reaction fails to go in chloroform). The solvent was removed *in vacuo*, and the residue was taken up in petroleum hexane and extracted with 10% sodium hydroxide. The nitrile was distilled to remove color, 51 g. (94%), b.p. 160° (3 mm.), lit.[21] b.p. 212° (18 mm.). Crystallization from 50 ml. of cold methanol gave 49 g., m.p. 46.5–47° (not previously reported). The over-all yield from the acid was 88%.

Diispropylacetonitrile.—Diisopropylcyanoacetic ester was prepared by adding 0.75 mole of cyanoacetic ester to a warm solution of 0.75 g.-atom of sodium in 500 ml. of absolute 2-propanol. The solution was heated under reflux for 2 hours after the addition of 0.75 mole of isopropyl iodide. A boiling solution of 0.75 g.-atom of sodium in 500 ml. of absolute 2-propanol was added rapidly (before it cools and solidifies), followed by another 0.75-mole portion of isopropyl iodide. After three hours of further boiling 850 ml. of solvent was removed by distillation and the residue was poured into water. The layers were separated and the product was washed with 10% sodium hydroxide to remove monoalkylated product. Upon distillation, 136 g. (93%), b.p. 120–125° (17 mm.), lit.[4] b.p. 238–241°, was obtained. The ester was distilled slowly from twice its weight of potassium hydroxide pellets in a copper flask. The distillate was re-

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[16] J. Timmermans and Y. Delcourt, *J. Chim. Phys.*, **31**, 85 (1934).

[17] E. Bowden, THIS JOURNAL, **60**, 131 (1938).

[18] O. Fischer, *Ber.*, **7**, 1191 (1874).

[19] P. Fritsch and F. Feldmann, *Ann.*, **306**, 72 (1899).

[20] A. W. Dox and A. Thomas, THIS JOURNAL, **45**, 1811 (1923).

[21] J. Hoch, *Compt. rend.*, **197**, 770 (1933).

distilled and the residue was distilled again from potassium hydroxide. The combined distillates were fractionated to give 83% yield of diisopropylacetonitrile, b.p. 169–170°, lit.[4] b.p. 170–171°.

4-Bromo-2,2-dialkylbutylamine hydrobromides were prepared by treatment of the corresponding amino ethers with concentrated hydrobromic acid. The methyl and ethyl compounds were prepared as previously described[2] and recrystallized from chloroform. Further recrystallization from acetonitrile removed a trace of color. The isopropyl compound was treated according to the same procedure, but after removal of the bulk of hydrobromic acid at the water-pump, the remainder was removed in a desiccator over potassium hydroxide. The residue was taken up in a small volume of methylene chloride. The addition of petroleum hexane to the point of cloudiness and chilling deposited 47% of fairly pure III, m.p. 180–181° dec. Addition of a large excess of petroleum hexane to the filtrate precipitated 3,3-diisopropylpyrrolidine hydrobromide (36%). The bromo amine salt was recrystallized twice with 85% recovery from a mixture of 18 ml./g. of warm (50°) carbon tetrachloride and 15 ml./g. of petroleum pentane.

2,2-Diphenyl-4-phenoxybutylamine hydrobromide was boiled with 2 ml./g. of propionic acid which was found to be the best solvent for this reaction and 2.7 ml./g. of concentrated hydrobromic acid for 48 hours. 2,2-Di-*p*-tolyl-4-phenoxybutylamine hydrobromide was boiled with 3 ml./g. of propionic acid and 2.7 ml./g. of concentrated hydrobromic acid for 15 hours, whereupon another 2.6 ml./g. of concentrated hydrobromic acid was added and the heating was continued for a total of 48 hours. The solutions were distilled at the water-pump to remove the bulk of the hydrobromic and propionic acids. Trituration of the gummy residues with ethyl acetate extracted dark tars leaving behind the 3,3-diarylpyrrolidine hydrobromides in colorless crystalline form. The *gem*-phenylpyrrolidine salt was obtained in 72% yield and the *gem*-*p*-tolylpyrrolidine salt was obtained in 59% yield. The ethyl acetate extracts were evaporated to dryness *in vacuo* at a temperature of 50°. The residues were further dried in a desiccator over potassium hydroxide and triturated with dry ether to extract tars. This procedure left the crude bromo amine salts as tan powders. These were taken up in methylene chloride and filtered to remove the insoluble pyrrolidine salts. Treatment with charcoal removed most of the color and the solutions were evaporated almost to dryness at 40° in a current of air. The addition of ethyl acetate precipitated the bromo amine salts which were recrystallized from a mixture of methylene chloride and ethyl acetate to give material which was still impure. The final yields in both cases were 3%.

All of the 4-bromo-2,2-disubstituted butylamine hydrobromides decompose at the melting point. After hydrogen bromide evolution is complete, the samples may be chilled, whereupon they solidify and remelt at the temperature of the corresponding pyrrolidine salt. All behave as secondary amines toward benzenesulfonyl chloride and the nickel reagents. Table III lists the 4-bromo-2,2-disubstituted butylamine salts and Table IV lists the corresponding pyrrolidines obtained by cyclization. The alkyl pyrrolidine salts were crystallized from ethyl acetate and the sulfonamides from petroleum hexane. The aryl pyrrolidine salts were crystallized from methanol and the sulfonamides from aqueous acetone.

TABLE III

4-BROMO-2,2-DI-R-BUTYLAMINE HYDROBROMIDES

		Methyl (I)	Ethyl (II)	Iso-propyl (III)	Phenyl (IV)	*p*-Tolyl (V)
Yield, %		93	63	40	3	3
M.p., °C., dec.		188–189	170–171	186–187	194–195	240–241
Analyses, %						
Calcd.:	C	27.61	33.24	37.87	49.89	52.32
	H	5.79	6.62	7.31	4.97	5.61
Found:	C	27.73	33.44	37.94	52.22	68.38
	H	5.84	6.62	7.35	5.85	6.86

TABLE IV

3,3-DISUBSTITUTED PYRROLIDINES AND DERIVATIVES

		Methyl	Ethyl	Iso-propyl	Phenyl	*p*-Tolyl
B.p., °C.		114–115	169–170	206–208	.....	.....
M.p., °C.		.....	.....	.....	Oil	41–42
Hydrobromide, m.p., °C.		103–105	61–62	124–125	251–252	230–231
Analyses, %						
Calcd:	C			50.84	63.16	65.06
	H			9.39	5.96	6.67
Found:	C			50.29	63.24	65.23
	H			9.49	5.95	6.45
Benzenesulfonamide, m.p., °C.		49–50	37–38	88–89	127–128	100–101
Analyses, %						
Calcd:	C	60.22	62.88	65.04	72.70	73.62
	H	7.16	7.92	8.53	5.82	6.44
Found:	C	60.26	62.70	65.37	72.98	73.76
	H	7.28	7.86	8.62	5.91	6.42

asym-**Dimethylsuccinic anhydride** was prepared from *asym*-dimethylsuccinic acid which in turn was prepared by a modified method of Smith and Horwitz.[22] A mixture of 58 g. of acetone, 113 g. of ethyl cyanoacetate, 79 g. of pyridine and 63 g. of acetic acid was heated under reflux for one hour. Next, 100 ml. of absolute ethanol was added, and the heat source was removed. Immediately, 65 g. of potassium cyanide was added all at once, whereupon a vigorous reaction ensued. External heating was resumed for one hour. After cooling, 400 ml. of 3 *N* hydrochloric acid was added and the mixture warmed to bring solids into solution. The layers were separated and the aqueous layer was extracted twice with ether. After removal of ether from the combined organic solution on the steam-bath, 600 ml. of concentrated hydrochloric acid was added and the mixture was heated under reflux for 24 hours, after which time, another 150 ml. of concentrated hydrochloric acid was added, the heating being continued for another 24 hours. The solution was chilled, the crystals collected and the mother liquor evaporated to dryness *in vacuo*. All solid material was treated three times with hot acetone (600 ml. total) to separate the acid from ammonium chloride. The major portion of acetone was removed from the solution by distillation at atmospheric pressure, and 150 ml. of acetic anhydride was added. The remainder of the acetone was then removed, as well as some acetic acid, by distilling until the vapor temperature reached 120°. The heating was continued for a total of 1.5 hours, and then the solution was distilled at the water-pump to give 86 g. of the anhydride (67% over-all yield), b.p. 110–118° (18 mm.), lit.[23] b.p. 117° (22 mm.).

asym-**Dimethylsuccinimide**.—A solution of 86 g. of the anhydride in 100 ml. of ether was run into a mixture of 300 ml. of ether and 46 g. of liquid ammonia maintained in a Dry Ice-bath. The ammonia was allowed to evaporate, and the ether was removed on the steam-bath. Xylene (500 ml.) was added, and the mixture was heated to the reflux temperature. Continuous slow distillation removed water formed by the cyclization of the succinamic acid (formed by dissociation of the ammonium salt). After 0.5 hour, all solids had gone into solution, and within another 5 minutes, the clear solution suddenly became opaque and deposited a negligible quantity of a solid. The hot solution was filtered and chilled. The crystals were washed with petroleum pentane and the mother liquor was evaporated and chilled again to give a small second crop, which was washed as before. The yield at this point was 80.4 g. (94%) of oily crystals. Three crystallizations from ethyl acetate lowered the yield to 62.2 g. (73%), m.p. 107–109°, lit.[24] m.p. 106°.

3,3-Dimethylpyrrolidine.—Lithium aluminum hydride (61 g.) was added to 1.5 l. of tetrahydrofuran. The mixture was refluxed with stirring for one hour to bring most of the hydride into solution. The solution was cooled in an ice-bath, and a solution of 57.2 g. of *asym*-dimethylsuccinimide in 175 ml. of tetrahydrofuran was added over a period of 20 minutes. The ice-bath was removed, and the mixture was slowly distilled over a period of one hour, 1 l. of tetrahydrofuran being removed. The mixture was decomposed in the usual way, and 34.5 g. (79%) of 3,3-dimethylpyrrolidine, b.p. 114–115° was isolated. The benzenesulfonamide was

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(22) P. A. S. Smith and J. P. Horwitz, THIS JOURNAL, **71**, 3418 (1949).

(23) K. Auwers, *Ann.*, **292**, 132, 185 (1896).

(24) S. Levy and P. Englander, *ibid.*, **242**, 189, 205 (1887).

prepared by the Hinsberg method and recrystallized from aqueous methanol. It melted at 49–50° and the melting point was undepressed by admixture with the same compound (m.p. 49–50°) prepared from I. Furthermore, either of the sulfonamides effectively seeded a solution of the other.

Although lithium aluminum hydride has been used for the reduction of N-phenylsuccinimide[25] and lactams[25,26] to the corresponding cyclic imines, the reduction of N-unsubstituted succinimides with this reagent has not been reported. It might have been expected that the highly acidic hydrogen of succinimides would interfere in the reduction.

Since lactams have been reduced with sodium and alcohol,[27] this method also was tried on *asym*-dimethylsuccinimide. The reduction was conducted by rapidly adding a solution of 70 g. of the imide in 505 ml. of 2-butanol and 350 ml. of 1,2-diethoxyethane to a stirred slurry of 126 g. of molten sodium in 250 ml. of 1,2-diethoxyethane. The mixture was heated under reflux for one hour. The excess sodium was destroyed with butanol, and then 500 ml. of water and 500 ml. of concentrated hydrochloric acid were added successively. Steam distillation removed the solvents, and a small amount of dark insoluble oil was removed by ether extraction. A solution of 100 g. of sodium hydroxide in 200 ml. of water was added, but ether extraction failed to separate more than a trace of the amine, so the basic solution was steam distilled in order to concentrate the amine. Sufficient sodium hydroxide was added to the distillate to make a 40% solution. A layer of amine failed to separate; therefore, the solution was extracted with *o*-toluidine (since ether was again unsuccessful). Distillation of the extract gave 5 g. of a product which, after two further distillations, had b.p. 78–81°. This liquid had a strong piperidine-like odor, but gave negative tests for primary and secondary amines with both benzenesulfonyl chloride and the nickel reagents. When treated with methyl iodide, a negligible quantity of crystalline material deposited. This was too soluble, even in petroleum hexane, for recrystallization.

The stepwise reduction of *asym*-dimethylsuccinimide was conducted by rapidly adding a solution of 49.1 g. of the imide in 156 ml. of dry 2-butanol to a stirred slurry of 39.2 g. of sodium in 80 ml. of toluene. The solution was heated for 0.5 hour after the addition, and excess sodium was destroyed with ethanol. The solution was chilled in ice, and 150 ml. of water was added, followed by 142 ml. of concentrated hydrochloric acid. The layers were separated, and the aqueous layer was extracted with ether. The solvents were removed from the combined organic layers *in vacuo*. The residue was distilled at 20 mm. until crystals started subliming (240°). The distillate (b.p. 120–240°), upon chilling, deposited crystals identical with those of the residue. Fractional crystallization of the distillate and the residue from carbon tetrachloride and methanol, respectively, gave 1 g. of recovered starting material and *ca.* 10 g. of crystals, m.p. 232–233° with the empirical formula $(C_6H_9NO)_2$.

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.61; mol. wt., 222. Found: C, 64.45; H, 8.30; N, 12.14; mol. wt., 240 (Rast).

3,3-Dimethylglutaric anhydride was prepared by a modified method due to Vogel.[28] A mixture of 800 ml. of absolute ethanol, 147 ml. of acetone and 450 ml. of ethyl cyanoacetate was cooled to −40°, and 150 g. of liquid ammonia was added. The solution was allowed to warm up to 5° and placed in a refrigerator, at that temperature, for 12 hours. The crystalline mass was broken up and the flask was returned to the refrigerator for a four-day period. The mixture was filtered and the crystals washed successively with ether and cold ethyl acetate. Upon evaporating the mother liquor to a small volume and adding ether, a second crop was obtained, which was washed as before. The ammonium salt of the Guareschi imide amounted to 369 g. (89%). The lumps were broken up and 367 g. was added slowly (45 min.) with mechanical stirring, to 880 ml. of cold concentrated sulfuric acid maintained in an ice-bath to keep the temperature from rising above 20°. After all material had dissolved, the bath was removed and the solution was allowed to warm spontaneously to 50°, whereupon it was cooled to 38°. It remained at that temperature for 3 hours before cooling to room temperature. The stirring was stopped, and the clear golden solution was then transferred to a 5-liter flask, and 795 ml. of water and 20 ml. of concentrated hydrochloric acid were added. The solution was heated to the reflux temperature with a very small flame. Soon, a white solid deposited, whereupon serious foaming ensued. (The frothing seemed to be a function of the amount of white solid present, which apparently decarboxylates and goes into solution.) After 48 hours, all solid had gone into solution. The solution was cooled to 0° and the crude dimethylglutaric acid was collected and sucked as dry as possible. The moist crystals were dissolved in chloroform and decanted from the lower layer of sulfuric acid. After clarification and filtration, 330 ml. of acetic anhydride was added and chloroform was removed by distillation until a vapor temperature of 120° was reached. After being heated under reflux for a total time of two hours, acetic acid and anhydride were removed at the water-pump, and the liquid residue, after being allowed to cool somewhat, was treated with a 50–50 mixture of petroleum hexane and carbon tetrachloride. The light tan crystals of 3,3-dimethylglutaric anhydride were collected and washed with more of the 50–50 solvent, 169 g. (60% over-all yield from acetone), m.p. 123–124°, lit.[28] m.p. 125°. If a purer, colorless product is desired, distillation in an apparatus designed for the distillation of solids is recommended, as the color is difficult to remove by recrystallization.

4,4-Dimethyl-2-pyrrolidone.—Liquid ammonia (30 g.) was added to 300 ml. of commercial 2-propanol cooled to −40°. To this solution was added 85.2 g. of glutaric anhydride in portions. The mixture was allowed to warm to room temperature and petroleum pentane was added to render the slush filterable. The crystals of ammonium 3,3-dimethylglutaramate weighed 103.4 g. (98% yield).

The ammonium salt was dissolved in 100 ml. of water, and 24.1 g. of sodium hydroxide was added as a 50% aqueous solution. Boiling expelled ammonia, leaving a solution of the sodium salt. A solution equivalent to 0.25 mole of chlorine was prepared by collecting, in 2,350 ml. of cold 10% sodium hydroxide, the chlorine generated from 37.9 g. of potassium permanganate and 415 ml. of concentrated hydrochloric acid. To this solution was added the glutaramate solution and the mixture was warmed to 40°. Thereupon, the temperature rose spontaneously to 50°. The beaker was wrapped to insulate it and allowed to stand. At the end of 2.5 hours, the temperature had fallen to 38°, and the solution was neutralized with 455 ml. of concentrated hydrochloric acid, and allowed to stand overnight. Even after being saturated with salt, it was not possible to extract any product from the solution with chloroform, and the solution was concentrated to a very small volume (the precipitated salts were washed with acetone and the distillate was strongly acidified and evaporated to dryness and the residue was neutralized, so that no product was lost by this operation), and extracted with 1-butanol. The butanol solution of the combined products was distilled at 18 mm., yielding *ca.* 5 g. of very oily, crude crystals (b.p. 150–155°) which were too soluble even in petroleum hexane for further purification.[29]

Isopropylidenecyanoacetic Ester.—The directions of Cope[30] using ammonium acetate as a catalyst were modified in the first two runs. In the first run, using acetic anhydride to remove water, the starting materials were recovered, no product being isolated. In the second run, using calcium carbide to remove water, a soft golden resin was the sole reaction product. A third run using a modification of the procedure of Birch and Kon[31] was successful. A mixture of 81 ml. of acetone, 106 ml. of ethyl cyanoacetate and 2.3 g. of ammonium acetate was allowed to stand for three days. The water layer was removed by distilling the mixture until the vapor reached 90°. Benzene was added and the mixture distilled until the vapor reached 100°. One gram of ammonium acetate and 30 ml. of acetone were added and the mixture allowed to stand for two days. The water was re-

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(25) Spitzmueller in "Organic Reactions," R. Adams, ed., Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 492.

(26) L. Ruzicka, M. Kobelt, O. Häfliger and V. Prelog, *Helv. Chim. Acta*, **32**, 544 (1949).

(27) C. F. Koelsch, This Journal, **65**, 2460 (1943).

(28) A. I. Vogel, *J. Chem. Soc.*, 1758 (1934).

(29) S. S. Guha-Sircar, *J. Indian Chem. Soc.*, **5**, 549 (1928), has reported a yield of 35% of 4,4-dimethyl-2-pyrrolidone from this reaction.

(30) A. C. Cope, This Journal, **59**, 2327 (1937).

(31) S. F. Birch and G. A. R. Kon, *J. Chem. Soc.*, 2440 (1923).

moved by the same procedure. This process was repeated twice. The mixture was distilled to give 120 g. of product (78%), b.p. 116–132° (20 mm.), lit.[30] b.p. 99–101° (9 mm.).

Ethyl 2-Cyano-3,3-dimethyl-4-nitrobutanoate.—A trial run using a catalytic amount of benzyltrimethylammonium hydroxide gave only a 44% yield of product. Since the anion of nitromethane is the reactive species, it was decided to follow the method of Kohler,[32] using the sodium salt of nitromethane. To a solution of 23.7 g. of commercial sodium methoxide in 250 ml. of absolute methanol was added 64 ml. of nitromethane. The mixture was shaken to break up lumps of the sodium salt and 61.2 g. of isopropylidenecyanoacetic ester was added. The mixture was shaken until all solid had gone into solution (2 min.). The solution was cooled and 30 ml. of glacial acetic acid was added. After standing for 40 hours, a solution of 10 ml. of concentrated ammonia in 200 ml. of water was added and the layers were separated. The aqueous layer was extracted three times with chloroform and the combined organic solutions were dried. The solvent was removed at the aspirator, and the remaining oil was distilled at 2 mm. Material distilling in the range 107–115° was collected, 63 g. (74%); Bahner reports b.p. 110–111° (1 mm.).[33]

Basic Hydrolysis of Ethyl 2-Cyano-3,3-dimethyl-4-nitrobutanoate.—In two runs, previous to the development of the synthesis of the nitroester as given above, the nitroester was prepared according to the method of Kohler,[32] and hydrolyzed without isolation. From 30.6 g. of isopropylidenecyanoacetic ester less than 1 g. of crude pale yellow acid, m.p. 105–108°, was isolated. It was not felt worthwhile to further characterize or analyze the product in view of the low yield obtained.

To a solution of 8.8 g. of sodium hydroxide in 50 ml. of water was added 21.4 g. of the nitroester. A clear yellow solution was obtained, which was heated under reflux for 19 hours (ammonia was still being evolved and crystals of ammonium carbonate had deposited in the condenser). Since the solution was quite brown by this time, it was felt that it would be best to work it up without completing the hydrolysis. Therefore, 13 ml. of glacial acetic acid was added and the solution was allowed to stand overnight to reach equilibrium. After adding 12 ml. each of sulfuric acid and water, a heavy brown sludge was removed by filtration and the solution extracted with ether. After drying and clarification of the extract, the ether was distilled and toluene and 5 ml. of piperidine were added to effect decarboxylation. After boiling for two hours, the mixture was extracted with sodium carbonate solution and the extract treated with charcoal. Acidification, further decolorization and chilling of the solution deposited only sodium chloride. None of the organic acid with m.p. 105–108° could be isolated.

Acid Hydrolysis of Ethyl 2-Cyano-3,3-dimethyl-4-nitrobutanoate.—A mixture of 21.3 g. of the nitroester, 25 ml. of hydrochloric acid and 25 ml. of methanol was refluxed for 19 hours. The mixture was diluted with water and extracted with ether. The ether solution was extracted with sodium carbonate solution (evaporation of the ether left 8.4 g. of neutral oil which may have been the unreacted ester). The carbonate solution was acidified and extracted with ether. After removal of the ether, the material was heated to 170° for 0.5 hour to effect decarboxylation. Toluene was added and the solution was extracted with sodium carbonate solution. The carbonate solution eventually yielded 3 g. of white crystals, m.p. 136–138°, identified as *asym*-dimethylsuccinic acid, m.p. 138–139°.[22] The toluene solution of the decarboxylation products after the carbonate extraction was heated under vacuum to remove the toluene, leaving 2 g. of neutral oil. This was presumably 2,2-dimethyl-4-nitrobutyronitrile, since hydrolysis with concentrated hydrochloric acid gave a product of m.p. 139–141° showing no depression when mixed with *asym*-dimethylsuccinic acid.

Another run, using concentrated hydrochloric acid, dioxane and 21.4 g. of the ester, after refluxing for 100 hours, yielded several grams of ammonium chloride and 0.8 g. of crude *asym*-dimethylsuccinic acid, m.p. 131–136°.

The Curtius Reaction of 3,3-Dimethylglutaric Anhydride.—A mixture of 7.2 g. of sodium azide, 14.2 g. of the anhydride and 100 ml. of dry *n*-butyl ether was stirred in a water-bath which was rapidly heated from 60 to 100°. No gas evolution was observed, so the mixture was cooled and 5.7 ml. (0.1 mole) of glacial acetic acid was added. The mixture was heated again. Vigorous gas evolution began at 85°. The mixture was maintained at 100° for 0.5 hour, and then was heated to the reflux temperature and held there for 0.5 hour. Water and 5 g. of sodium hydroxide were added and the butyl ether was steam distilled. The aqueous solution was neutralized, saturated with salt and extracted with ether. Evaporation of the ether left 1 g. of crude oily product, m.p. 50–55°. Because of the low yield, this product was not characterized further.

The Preparation and Hofmann Degradation of 3,3-Dimethylglutaramic Acid.—Fifty milliliters of 2-butanol was cooled to −40° and 5 g. of liquid ammonia was added, followed by 14.2 g. of 3,3-dimethylglutaric anhydride. The mass was allowed to come to room temperature. After one hour, the solid was collected and washed with petroleum pentane. The yield was 17.3 g. (98% yield) of ammonium salt. One-third of a solution of 20.4 g. of sodium in 450 ml. of absolute methanol was added to a solution of 52 g. of the ammonium salt in 300 ml. of absolute methanol, and the solution was boiled for 15 minutes to expel the ammonia. The solution was cooled and the remainder of the methoxide solution was added, immediately followed by 15.1 ml. of bromine. The solution was placed on the steam-bath for 15 minutes to complete the reaction. The bulk of the methanol was removed *in vacuo*, 100 ml. of water was added, and the mixture was extracted with benzene. Removal of the benzene left 55.8 g. (19%) of a pale yellow, highly viscous oil. Distillation at 2 mm. gave 49 g. of a distillate with b.p. 130–158° and 6.5 g. of residual tar. The distillate partially crystallized upon standing. The neutral fraction of 3,3-dimethylglutarimide, m.p. 144–145°, was removed by ether extraction from a slightly alkaline solution. Acidification of the basic solution followed by extraction and distillation yielded a colorless and extremely viscous oil, b.p. 140–145° (2 mm.), which did not crystallize; neutralization equivalent, 171. It was found impossible to prepare insoluble mercury, lead, silver or S-benzylthiuronium salts. The sodium salt prepared in absolute butanol separated as an oil after the alcohol was completely displaced with anhydrous toluene by distillation, and the solution cooled in Dry Ice. The oil eventually turned into an oily semi-solid mass, which could not be recrystallized because of its high solubility.

A derivative was prepared by hydrolysis of the urethan function. Thus, 5.7 g. was refluxed for 4 hours with 33 ml. of 30% sodium hydroxide. To the solution was added 50 ml. of water and 6 ml. of benzoyl chloride. The mixture was shaken until the reaction was over and then acidified. The oily precipitate was found to be only partially soluble in sodium bicarbonate, and therefore neutral material was removed by ether extraction from alkaline solution. After acidification, the solid was collected and recrystallized twice from aqueous methanol and once from a chloroform–hexane mixture. The acid melted at 117–120°; neutralization equivalent, 239 (calcd. for $C_6H_5CONHCH_2C(CH_3)_2CH_2CO_2H$, 235).

Preparation and Hofmann Degradation of Methyl 3,3-Dimethylglutaramate.—A solution of 80 g. of 3,3-dimethylglutaric anhydride in 50 ml. of absolute methanol was refluxed for 4 hours. Distillation gave 95 g. (98% yield) of the monomethyl ester, b.p. 146–156° (18 mm.). A mixture of 56.6 g. of the monomethyl ester and 38.5 ml. of thionyl chloride was allowed to stand overnight at room temperature. After heating on the steam-bath for 10 minutes, the bulk of the excess thionyl chloride was removed under reduced pressure. Dry benzene was added and distilled at reduced pressure to remove the last traces of thionyl chloride. The crude acid chloride was dropped slowly into 100 ml. of concentrated ammonia with stirring. The temperature was maintained below 20°, with a salt–ice-bath. Extraction and distillation gave 46.5 g. (83% over-all) of the amide, b.p. 110–115° (2 mm.). A solution of 12.4 g. of sodium in 390 ml. of absolute methanol was added to a solution of 46.5 g. of the amide in 240 ml. of absolute methanol. Immediately, 15.5 ml. of bromine was added and the solution was heated gently for 15 minutes. The solution was neutralized with acetic acid, the bulk of the methanol was removed *in vacuo*, and sufficient water was added to dissolve precipitated salts and induce crystallization of

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(32) E. P. Kohler and H. Engelbrecht, THIS JOURNAL, **41**, 764 (1919).

(33) C. J. Bahner, U. S. Patent 2,426,158 [*C. A.*, **41**, 7410 (1947)].

the water-insoluble product. Twenty grams of oily crystals was collected (fraction 1). A second component which remained in solution despite the addition of more water, was isolated in the form of oily crystals by saturating the solution with salt, and extracting the solution with chloroform. After displacing the chloroform with petroleum heptane and cooling, 13 g. of oily crystals was collected (crude 3,3-dimethylglutarimide). Fraction 1, after several recrystallizations from aqueous methanol and several subsequent recrystallizations from chloroform, was obtained in the form of asbestos-like fibers, m.p. 269°. This neutral compound contained bromine and gave the following results upon analysis.

Found: C, 28.2; H, 3.1; N, 4.3. Calcd. for $C_7H_9Br_2NO_2$: C, 28.1; H, 3.0; N, 4.7. Calcd. for $C_8H_{11}Br_2NO_4$: C, 27.8; H, 3.2; N, 4.1.

Since this compound failed to depress the melting point of camphor, a Rast molecular weight could not be determined. The identity of the compound was not established further.

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

The Preparation of Geminally-substituted 4-Bromobutylamines.
III. 4-Bromo-3,3-dimethylbutylamine[1]

BY RONALD F. BROWN AND NORMAN M. VAN GULICK

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The preparation and properties of 4-bromo-3,3-dimethylbutylamine hydrobromide are described. Several alternate synthetic routes were explored. The analogous hydroxy and methoxy amines were prepared also. The best sequence started with *asym*-dimethylsuccinic anhydride reduction to 2,2-dimethyl-1,4-butanediol and conversion to the dibromide, the more reactive bromine of which was replaced by an amino group by way of the Gabriel synthesis.

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 position of substituents required the preparation of the hydrobromides of 4-bromobutylamine,[2] 4-bromo-1,1-dimethylbutylamine,[2] 4-bromo-2,2-dimethylbutylamine[3] and 4-bromo-3,3-dimethylbutylamine (I). A later paper will describe the rate studies. I was prepared by a method which depended upon the unreactivity of a neopentyl halide to displacement by intermolecular attack. The glycol, 2,2-dimethyl-1,4-butanediol, was converted to the dibromide, and the more reactive bromine replaced by an amino group *via* the Gabriel synthesis. The only unsatisfactory step was the conversion to dibromide, which despite repeated attempts with phosphorus tribromide and pyridine under various conditions gave consistent yields of around 10%. Reaction of the dibromide with potassium phthalimide gave N-(4-bromo-3,3-dimethylbutyl)-phthalimide in a yield of 80%. The Gabriel synthesis was carried out in dimethylformamide, an excellent solvent which allows the reaction to proceed at a low temperature in high yield.[4]

Compound I gave a positive nickel test for a primary amine and a slowly developing secondary amine test.[2,3] Cyclization was instantaneous in aqueous sodium hydroxide and treatment with benzenesulfonyl chloride gave 1-phenylsulfonyl-3,3-dimethylpyrrolidine identical to that derived from 4-bromo-2,2-dimethylbutylamine hydrobromide.[3] Thus the structures of I and its precursors were established unequivocally. That cyclization should occur rapidly in base is due to the fact that, although the neopentyl-type bromide is hindered with respect to intermolecular displacement, the structure is such that intramolecular displacement may occur readily. This point is nicely shown by examination of molecular models.

Another route to I from hydroxypivalaldehyde by condensation with nitromethane, dehydration, reduction and replacement of the hydroxy group by bromine was attempted. The addition of nitromethane to hydroxypivalaldehyde using diethylamine or sodium methoxide as a catalyst under a variety of conditions gave unreproducible yields of the nitro glycol. An attempt to avoid the difficult purification of the nitro glycol by substituting acetoxypivalaldehyde was not practical, since the corresponding product, from which the catalyst can be removed easily by washing with water, was obtained in very low yield. The reduction was straightforward.

4-Hydroxy-3,3-dimethylbutylamine differed from the isomer 4-hydroxy-1,1-dimethylbutylamine[2] in that the Hinsberg reaction gave only a base-soluble oil, which, upon treatment with benzenesulfonyl chloride and triethylamine, formed 1-phenylsulfonyl-3,3-dimethylpyrrolidine, identical with authentic material.[3] When 4-hydroxy-3,3-dimethylbutylamine was treated with thionyl bromide, a small quantity of gummy material was obtained which gave a trace of 1-phenylsulfonyl-3,3-dimethylpyrrolidine under Hinsberg conditions. This is not conclusive proof that I was formed, since the sulfonamide, only a trace of which was isolated, may have arisen from the hydroxy amine.

Acetoxypivalaldehyde decomposed extensively by several paths upon distillation at atmospheric pressure. The identified products were formaldehyde, isobutyl acetate and a colorless high boiling residue which may be the known dimer.[5] Even upon vacuum distillation decomposition occurred, but to a lesser extent. The distilled material effervesced for days, evolving an odorless gas, which was presumably carbon monoxide. Distillation of acetoxypivalaldehyde in the presence of a trace of toluenesulfonic acid gave rise to still

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

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

[3] R. F. Brown and N. M. van Gulick, *ibid.*, **77**, 1083 (1955).

[4] J. C. Sheehan and W. A. Bolhofer, *ibid.*, **72**, 2786 (1950).

[5] E. Späth and I. von Szilagyl, *Ber.*, **76**, 949 (1943).