that soon crystallized. Recrystallization from hexane gave diaminocarbinol VII, m.p. 122–124°, in 59% yield. After two more recrystallizations, VII started to melt at 126–127°, then partially solidified and remelted at 133–134°, an indication of two crystalline forms. After another recrystallization, VII melted at 133–134°.

Independent synthesis of diaminocarbinol VII from I′ and amino ketone IV (prepared from I and benzonitrile) was accomplished as follows. To I′, prepared from 0.1 mole each of amine I and *n*-butyllithium in ether–hexane (metalation time, 35 hr.), was added, under nitrogen, 21.2 g. (0.09 mole) of IV in 200 ml. of ether. After stirring and refluxing for 3 hr., the reaction mixture was worked up as described for condensations with aldehydes and ketones to give an oil that soon crystallized. Recrystallization from hexane gave VII, m.p. 132–133° (final), in 73% yield based on IV. Samples of VII prepared from IV and from methyl benzoate were shown to be identical by comparison of infrared spectra and by the mixture melting point method.

Metalation of Dibenzylmethylamine (X) and Condensation with Benzaldehyde.—This amine[2] (10.6 g., 0.05 mole) was metalated during 48 hr. with 0.15 mole of ethereal *n*-butyllithium to form X′, which was condensed with benzaldehyde essentially as described for the condensation of I′. After work-up, there was obtained 17 g. of crude oil, which was crystallized from a mixture of 50 ml. of hexane and 10 ml. of absolute ethanol to give 8.9 g. (56%) of 2-(benzylmethylaminomethyl)benzhydrol (XI), m.p. 94–96°. After four recrystallizations, a sample melted at 97.5–98.5°. Its infrared spectrum showed bands at 760, 749, 736, 729, and 697 cm.$^{-1}$ in the 800–690-cm.$^{-1}$ region.

Anal. Calcd. for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 83.18; H, 7.21; N, 4.57

The methiodide, recrystallized from acetonitrile–ether, appeared to melt at 116–117°.

Anal. Calcd. for $C_{23}H_{26}INO$: C, 60.13; H, 5.71; N, 3.05. Found: C, 60.10; H, 5.76; N, 3.18.

A 1.1-g. sample of the methiodide of XI was stirred for 0.5 hr. with excess silver bromide suspended in 50% ethanol. Filtration of the mixture and evaporation of the filtrate left 0.79 g. (81%) of the methbromide XII, m.p. 172–172.5°, after five recrystallizations from absolute ethanol.

Anal. Calcd. for $C_{23}H_{26}BrNO$: C, 66.99; H, 6.36; N, 3.40. Found: C, 66.95; H, 6.22; N, 3.42.

Independent synthesis of XII was effected from 5 g. of amino alcohol IIa and 4 g. of benzyl bromide in 50 ml. of acetonitrile (refluxed 2 hr.). The product XII, recrystallized twice from absolute ethanol, melted at 171.5–172.5° which was not depressed on admixture with a sample of XII prepared from amine X. The infrared spectra of the two samples were identical.

Metalation of α,α-Dimethylbenzyldimethylamine (XIII) and Condensation with Benzophenone.—This amine[16] (3.30 g., 0.020 mole) was metalated during 18 hr. with 0.05 mole of ethereal *n*-butyllithium to form XIII′, which was condensed with benzophenone essentially as described for the condensation of I′. There was obtained after work-up 5.6 g. of oil, which was crystallized from heptane to give 3.93 g. (57%) of 2-(N,N-α,α-tetramethylaminomethyl)benzhydrol (XIV), m.p. 126.5–127.5°. After recrystallization from heptane, a sample melted at 127–128°. Its infrared spectrum showed bands at 795, 767, 753, and 703 cm.$^{-1}$ in the 800–690-cm.$^{-1}$ region.

Anal. Calcd. for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.05. Found: C, 83.45; H, 7.66; N, 3.98.

The picrate, recrystallized three times from 95% ethanol, melted at 212.5–213°.

Anal. Calcd. for $C_{30}H_{30}N_4O_8$: C, 62.71; H, 5.26; N, 9.75. Found: C, 63.05; H, 5.23; N, 9.88.

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[16] H. M. Taylor and C. R. Hauser, *J. Am. Chem. Soc.*, **82**, 1960 (1960)

Synthesis of Functional α-Derivatives of Benzyldimethylamine through Metalation with Phenylsodium and Condensations with Carbonyl Compounds[1a]

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Benzyldimethylamine was metalated at the α-position with phenylsodium to form the α-sodioamine, which was condensed with typical carbonyl compounds and benzonitrile. The α-sodioamine was converted by lithium bromide to the α-lithioamine, which was condensed with ketones having α-hydrogen. These methods are useful for the synthesis of α-substituted benzyldimethylamines having a functional group in the α-substituent.

In connection with a recent study[2] of ring *vs.* side-chain metalation of benzyldimethylamine (I) with organosodium compounds, exclusive side-chain metalation was observed with phenylsodium. This was established by condensation of the resulting α-sodioamine I′ with benzophenone to form amino alcohol II. Although the α-sodioamine I′ effected mainly ionization of the α-hydrogen of cyclohexanone, the α-lithioamine I″, prepared from I′ and lithium bromide, underwent mainly condensation with this ketone to give amino alcohol VI.

These methods have now been found quite general, and have been employed to synthesize not only other amino alcohols, but also an amino amide and an amino ketone (Schemes A and B).

The condensation of I′ with benzaldehyde (Scheme A) evidently afforded a mixture of the *erythro* and *threo* isomers of amino alcohol III, since the product and its methiodide melted over a wide range somewhat below the melting points reported recently[3] for each of these isomers and for their methiodides. The condensation product, which gave a satisfactory analysis, was indicated by vapor phase chromatography to consist of about equal amounts of the two isomers (see Experimental).

The structures of amino alcohols II and VI were established previously.[2] The structures of the other products shown in Schemes A and B were supported by analysis[4] by the formation and analysis of appropriate derivatives (Table I), and by infrared spectra. The spectra of amino alcohols II, III, VI, VII, and VIII showed broad hydroxyl bands in the 3320–3480-cm.$^{-1}$ region.[5] The spectrum of amino ketone V showed carbonyl absorption[6] at 1675 cm.$^{-1}$, and that of amino amide IV exhibited a sharp peak at 3280 cm.$^{-1}$ for a secondary

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[1] (a) Supported in part by a National Institutes of Health grant; (b) National Science Foundation Science Faculty Fellow, on leave from Thiel College.

[2] W. H. Puterbaugh and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 2467 (1963).

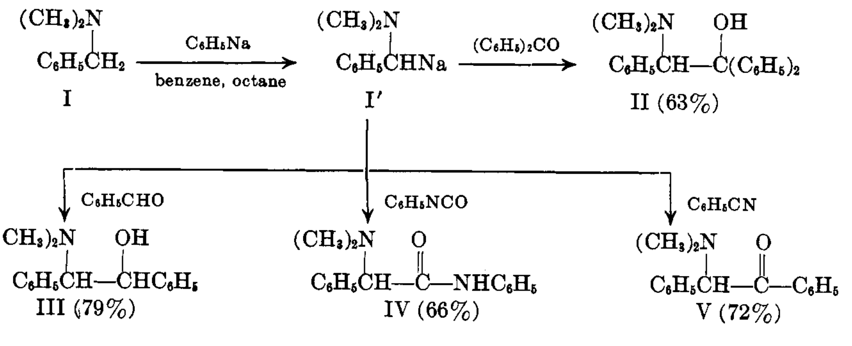
[3] G. Drefohl and H. H. Horbald, *Ber.*, **94**, 1657 (1961).

[4] Although the analysis on amino alcohol VIII was 0.9% low for carbon, the values for hydrogen and nitrogen were satisfactory. Moreover, a vapor phase chromatogram of this compound showed a single peak, and the methiodide, which was obtained almost quantitatively, gave a satisfactory analysis (see Table I).

[5] See L. H. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 95–105.

[6] See ref. 5, p. 207.

SCHEME A



SCHEME B

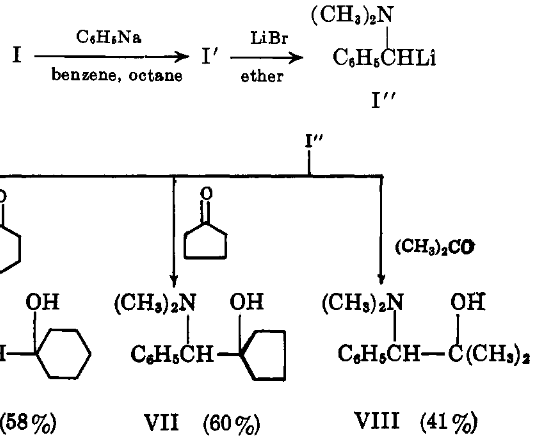


TABLE I

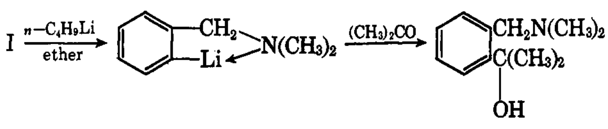
METHIODIDES OF CONDENSATION PRODUCTS

Methiodide	Recrystallizing solvent	M.p., °C.	Empirical formula	Analyses: Calcd., %: C	H	N	Found, %: C	H	N
II[a]	Methanol	181.5–183	$C_{23}H_{26}INO$	60.13	5.71	3.05	60.22	5.85	3.18
III		158–190[b]	$C_{17}H_{22}INO$						
IV	Ethanol	190–191.5	$C_{17}H_{21}IN_2O$	51.52	5.34	7.07	51.34	5.36	6.96
V	Benzene–ethanol	162–163.5[c]	$C_{17}H_{20}INO$	53.55	5.29	3.67	53.40	5.34	4.02
VII	Ethanol–ether	164.5–166.5	$C_{15}H_{24}INO$	49.87	6.70	3.88	50.01	6.75	3.67
VIII	Ethanol–ether	156–157	$C_{13}H_{22}INO$	46.57	6.62	4.18	46.45	6.71	4.18

[a] Amino alcohol II was prepared earlier,[2] but its methiodide was not then reported. [b] Not analyzed. Lit.[3] m.p. 189–190° (*erythro*), 221–222° (*threo*). [c] Lit.[13] m.p. 153°.

amide[6] and at 1660 cm.$^{-1}$ for an amide carbonyl group.[7] Rather surprisingly, the spectra of compounds II, V, and VI showed moderately strong peaks at 842, 837, and 845 cm.$^{-1}$, respectively. Absorption in the 837–853-cm.$^{-1}$ region has been considered characteristic of benzyldimethylamines, but not of α-substituted benzyldimethylamines.[8] This band was weak or absent in the spectra of compounds III, IV, VII, and VIII. Like the spectra of starting amine I, the spectra of all the compounds in Schemes A and B exhibited two peaks near 750 and 700 cm.$^{-1}$, which are characteristic of monosubstituted aromatic rings.[9] However, these peaks offer definite evidence of side-chain rather than ring substitution only for compounds VI, VII, and VIII, since the other compounds have one or two additional aromatic rings.

As indicated in Schemes A and B, the yields of the α-derivatives of benzyldimethylamine (I) were good to excellent (41–79%). Interestingly, these condensation products are isomeric with certain of those obtained recently through the *o*-metalation of amine I with *n*-butyllithium followed by condensation with the appropriate compound.[10] For example, VIII is isomeric with IX obtained according to equation 1.



IX

(1)

In contrast to infrared spectrum of VIII, that of IX showed only one peak in the 690–770-cm.$^{-1}$ region indicative of an *ortho* disubstituted aromatic ring,[4] and also a peak in the 837–853-cm.$^{-1}$ region for the dimethylaminomethyl group.[8]

Of the compounds shown in Schemes A and B, only three appear to have been prepared by other methods. The *erythro* isomer of amino alcohol III has been syn-

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(7) See ref. 5, p. 209.

(8) W. Q. Beard, Jr., and C. R. Hauser, *J. Org. Chem.*, **25**, 334 (1960).

(9) See ref. 5, p. 77.

(10) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *J. Org. Chem.*, **28**, 3461 (1963).

thesized in four steps from benzaldehyde[3]; the *threo* isomer also has been made.[3] Amino ketone V has been prepared from desoxybenzoin through its α-bromo derivative and dimethylamine,[11,12] and through its α-sodio derivative and chlorodimethylamine.[13] Amino ketone V obtained by the former method has been converted to amino alcohol II by reaction with phenylmagnesium bromide.[12]

With the possible exception of the earlier method for amino ketone V,[11,12] the present methods (Schemes A and B) seem more direct and convenient. Moreover, our methods should be applicable to the synthesis of various α-substituted benzyldialkylamines having a functional group in the α-substituent.

Experimental[14]

Metalation of Amine I with Phenylsodium. Condensations of α-Sodioamine I′.—The metalation of 13.5 g. (0.10 mole) of benzyldimethylamine (I) was effected by the previous procedure[2] with phenylsodium prepared from 6.58 g. (0.286 mole) of dispersed sodium and 14.62 g. (0.13 mole) of chlorobenzene in 55 ml. of benzene and 25 ml. of octane. After refluxing for 2 hr., the resulting red suspension of α-sodioamine I′ was cooled to 25° and employed in the condensations described in subsequent sections.

A. With Benzaldehyde.—To the stirred suspension of I′ was added, during 8 min., a solution of 18.0 g. (0.17 mole) of benzaldehyde in 70 ml. of ether while the temperature was maintained below 40°. After stirring at room temperature for 2 hr. and decomposing the excess sodium with 30 ml. of methanol, the reaction mixture was poured into 150 ml. of cold water. The organic layer was combined with an ether washing of the aqueous layer and extracted with 2 *M* hydrochloric acid. The acidic extracts were washed with ether and made basic (cooled and stirred) with sodium hydroxide solution. The resulting mixture was extracted with ether, and the combined ether extracts were washed with saturated sodium chloride and dried over sodium sulfate. The solvent was removed, and the liquid residue (22.6 g.) was distilled to recover 2.6 g. (18%) of amine I, b.p. 65–66° (12 mm.). A portion of the remaining viscous liquid residue was scratched under pentane to form crystals; these were used to seed the bulk of the product which crystallized to give 18.6 g. (79%) of a mixture of *erythro* and *threo* forms of 2-dimethylamino-1,2-diphenylethanol (III), m.p. 50–84°. Recrystallization of an aliquot from pentane gave an 82% recovery of III, m.p. 63–89°; lit.[3] m.p. for *erythro* isomer 88–89°, and for *threo* isomer 97–98°. A 33% solution of the product in acetone was subjected to v.p.c. starting at 125° and programming at 15°/min. to 200°. This showed two closely split peaks of nearly equal area with retention times of 7.6 and 8.0 min., respectively.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.81. Found: C, 79.69; H, 8.04; N, 5.84.

B. With Phenyl Isocyanate.—A solution of 18.6 ml. (20.3 g., 0.17 mole) of freshly distilled phenyl isocyanate in 70 ml. of ether was added to the stirred suspension of I′. After stirring at room temperature for 5 hr., the reaction mixture was worked up essentially as described under A. Evaporation of the dried ethereal solution of the product left tan material (22.2 g.) which was recrystallized from ethanol–hexane to give 16.7 g. (66%) of 2-dimethylamino-2-phenylacetanilide (IV), m.p. 112–115°. Two more recrystallizations from ethanol–hexane raised the melting point to 116–118°.

Anal. Calcd. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.25; H, 7.10; N, 10.91.

Some (1.4 g., 10%) of amine I, b.p. 72–73° at 19 mm., was recovered by distillation of the filtrate from the first recrystallization of the product, leaving 2.3 g. of tacky residue.

C. With Benzonitrile.—A solution of 17.5 g. (0.17 mole) of benzonitrile in 50 ml. of benzene was added to the stirred suspension of I′, and the mixture was stirred for 3 hr. at room temperature. After decomposing with methanol, the reaction mixture was poured into a solution of 75 ml. of concentrated hydrochloric acid in 125 ml. of ice–water. The aqueous layer was combined with an acidic extract (75 ml. of 3 *M* hydrochloric acid) of the organic layer and, after washing with ether, was refluxed for 1 hr. to hydrolyze the intermediate imine.[15] The resulting solution was cooled, made basic, and the mixture extracted with ether. The solvent was removed from the dried ethereal solution, and the residue (20.3 g.) was distilled to give 17.2 g. (72%) of α-benzoylbenzyldimethylamine (V), b.p. 134–138° (0.3 mm.); lit.[13] b.p. 193° (15 mm.). After standing several weeks in a desiccator, the viscous yellow liquid product solidified and was recrystallized twice from pentane to give m.p. 58–59.5°; lit.[11] m.p. 55°.

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.65; H, 7.44; N, 6.05.

Preparation and Condensations of α-Lithioamine I″.—Following the earlier procedure,[2] 19.9 g. (0.147 mole) of amine I was metalated with phenylsodium prepared from 9.67 g. (0.42 mole) of sodium and 21.6 g. (0.192 mole) of chlorobenzene in 125 ml. of benzene and 55 ml. of octane. The resulting suspension of α-sodioamine I′ was cooled to 20°, and 250 ml. of (0.25 mole) of a 1 *M* solution of lithium bromide in ether was added. After stirring for 2.5 hr. at room temperature the orange-brown suspension of I″ was used in the condensations described in following procedures.

A. With Cyclopentanone.—To the stirred suspension of I″ maintained at 20–30° (water bath) was added 25.3 g. (0.30 mole) of cyclopentanone. After stirring for 4 hr. at room temperature and standing overnight, the reaction mixture was worked up as described previously for the condensation of I′ with benzaldehyde except that three ether washings were made of the combined aqueous layers. The solvent was removed from the dried ethereal solution, and the residue (28.3 g.) was distilled to give 5.3 g. (27%) of recovered amine I, b.p. 60–64° (9 mm.), and 19.2 g. (60%) of 1-(α-dimethylaminobenzyl)cyclopentanol (VII), b.p. 107–111° (0.7 mm.). Redistillation of VII gave an analytical sample, b.p. 92° (0.2 mm.).

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.87; H, 9.86; N, 6.40.

B. With Acetone.—This experiment was carried out as in method A, employing 14.5 g. (0.25 mole) of acetone. The solvent was removed from the dried ethereal solution, and the residue (25.0 g.) was distilled to give 6.6 g. (33%) of recovered amine I, b.p. 58–60° (8 mm.), an intermediate fraction (1.6 g.), b.p. 68–71° (0.5 mm.), and 11.6 g. (41%) of α,α-dimethyl-β-dimethylaminophenethyl alcohol (VIII), b.p. 82–86° (0.4 mm.). Redistillation of VIII afforded an analytical sample, b.p. 82° (0.5 mm.).

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 73.68; H, 9.95; N, 7.40.

A vapor phase chromatogram at 150° on the intermediate fraction showed it to contain an additional 0.6 g. (3%) of amine I and 1.0 g. (3%) of amino alcohol VIII. A vapor phase chromatogram at 150° on the analytical sample of VIII gave only one peak, with a retention time of a 2.4 min.

Methiodides of Condensation Products.—To 50–100 ml. of an approximately 1 *M* solution of condensation product in acetonitrile was added 100% excess of methyl iodide. After standing 5 hr., the solution was refluxed for 1 hr. and allowed to stand overnight. The methiodide was precipitated by adding two volumes of dry ether with stirring and was recrystallized from an appropriate solvent (Table I). The yields were 88–96%.

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[11] J. Matti and P. Reynaud, *Bull. soc. chim. France*, [5] **21**, 603 (1954).

[12] A. Lespagnol, F. Mercier, J. Bertrand, and J. Mercier, *Ann. Pharm. Franc.*, **8**, 241 (1950).

[13] P. Rabe, *Ber.*, **45**, 2168 (1912). This worker reported a melting point for the methiodide of V which was 10° below that observed by us (see Table I).

[14] Melting points were taken on a Fisher-Johns melting point stage which had been calibrated with standard samples. Analyses were by Dr. Ing. Schoeller, Kronach, West Germany, and Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were taken on a Perkin-Elmer Model 237 Infracord using the potassium bromide pellet method for solids, and the neat liquid between sodium chloride plates for liquids. Vapor phase chromatography was carried out on an F & M Model 500 gas chromatograph using a 2-ft. silicone gum rubber column and 40 lb./in.^{2} helium pressure.

[15] In another experiment in which the reaction mixture was worked up as described under A without the acidic hydrolysis, the yield of V subsequently isolated was only 45%.