o-Metalation of Benzyldimethylamine and Related Amines with *n*-Butyllithium. Condensations with Carbonyl Compounds to Form *ortho* Derivatives[1]

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o-Lithiobenzyldimethylamine (I′), prepared by metalation of benzyldimethylamine (I) with *n*-butyllithium in ether, was condensed with several aldehydes and ketones to form the corresponding aminocarbinols in good yields. I′ was condensed with benzonitrile, phenyl isocyanate, cyclohexene oxide, and methyl benzoate to give the corresponding amino ketone, amino amide, aminocarbinol, and diaminocarbinol, respectively. Similarly the *o*-lithioamines, prepared by metalation of dibenzylmethylamine and α,α-dimethylbenzyldimethylamine, were condensed with benzaldehyde and benzophenone, respectively. These reactions furnish a useful method for the synthesis of various *ortho* derivatives of the amines.

Recently benzyldimethylamine and dibenzylmethylamine were metalated with *n*-butyllithium in ether to form the *o*-lithioamines, which were deuterated with deuterium oxide to give the corresponding *o*-deuterioamines.[2]

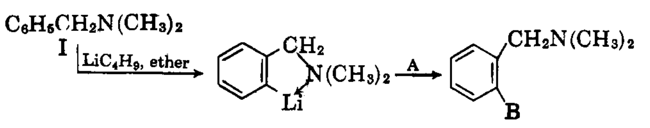
In the present investigation such *o*-lithioamines were condensed with aldehydes, ketones, and certain other compounds to form the corresponding *ortho* derivatives of the amines. Thus, *o*-lithioamine (I′), prepared by metalation of benzyldimethylamine (I), was condensed with various electrophilic compounds as illustrated in Schemes A and B. The corresponding *ortho* derivatives were obtained in 40–84% yields (Table I).

Originally the metalation of I to form I′ was effected with 100% excess[3] of *n*-butyllithium in ether at room temperature (25–30°) during 18–20 hours. Preliminary experiments had shown that the optimum time for metalation under these conditions was about 18 hours. Thus, the yields of aminocarbinol IIIb obtained on adding excess acetone to the metalation mixture after 6, 12, 18, and 24 hours were 27, 47, 56, and 57%, respectively, (determined by vapor phase chromatography).

Later, the metalation of I was effected equally well with only a 20% excess of *n*-butyllithium at room temperature during 30 hours. Moreover, the yields of certain condensation products were as good when the reactions were carried out in ether–hexane as in ether alone (see Table I). However, the yield of IIa was much lower when the metalation and condensation were effected in hexane alone under otherwise similar conditions (see footnote *h,* Table I).

In condensations of I′ with electrophilic compounds, the amount of the latter used was equivalent to the moles of *n*-butyllithium (plus 10% excess) since the electrophilic compound condensed with the excess *n*-

SCHEME A

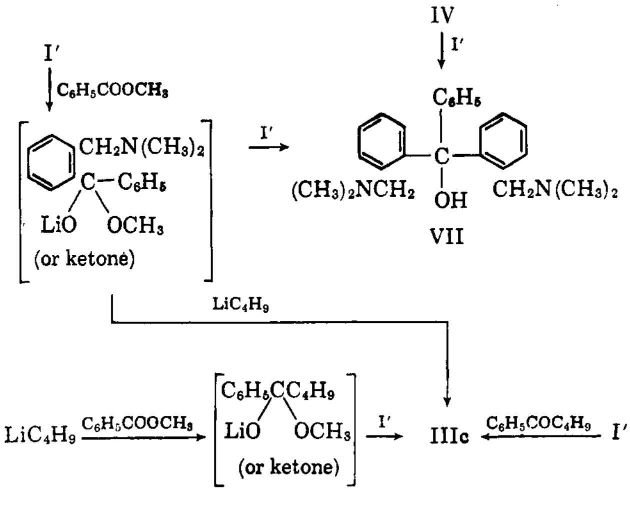


I′

A	B	Compound
RCHO	-CH(OH)R	IIa, R = C_6H_5
		IIb, R = 4-$CH_3OC_6H_4$
		IIc, R = 3,4,5-$(CH_3O)_3C_6H_2$
		IId, R = 2-ClC_6H_4
RCOR′	-C(OH)RR′	IIIa, R = R′ = C_6H_5
		IIIb, R = R′ = CH_3
		IIIc, R = C_6H_5; R′ = *n*-C_4H_9
C_6H_5CN	-COC_6H_5	IV
C_6H_5NCO	-$CONHC_6H_5$	V
Cyclohexene oxide	2-Hydroxycyclohexyl	VI
$C_6H_5COOCH_3$	-$COH(C_6H_5)[C_6H_4\text{-}2\text{-}CH_2N(CH_3)_2]$[a]	VII
$C_6H_5COOCH_3$	-$C(OH)(C_6H_5)n\text{-}C_4H_9$[b]	IIIc

[a] Metalation was effected with 20% excess LiC_4H_9. [b] Metalation was effected with 100% excess LiC_4H_9.

SCHEME B



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[1] (a) Supported by Army Research Office (Durham) and National Institutes of Health; (b) for a communication see F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 701 (1962).

[2] F. N. Jones, M. F. Zinn, and C. R. Hauser, *ibid.*, **28**, 663 (1963).

[3] This large excess of *n*-butyllithium was chosen not only because this reagent is known to decompose slowly in ether but also to facilitate the metalation.

TABLE I

CONDENSATIONS OF BENZYLDIMETHYLAMINE (I) WITH ELECTROPHILIC COMPOUNDS THROUGH *o*-LITHIOAMINE (I′) PREPARED BY METALATION WITH *n*-BUTYLLITHIUM

Moles of I	Moles of LiC_4H_9	Electrophilic compound[a]	Condensation product	M.p. or b.p. (mm.), °C.	Yield,[b] %
0.10	0.20[c]	Benzaldehyde	2-(Dimethylaminomethyl)benzhydrol (IIa)	72.5–73[d]	76,[e] 78[f]
0.10	0.12[g]	Benzaldehyde	2-(Dimethylaminomethyl)benzhydrol (IIa)	70–72[d]	78[f,h]
0.20	0.40[c]	4-Methoxybenzaldehyde	2-(Dimethylaminomethyl)-4′-methoxybenzhydrol (IIb)	88.5–90[i]	78[e]
0.20	0.40[c]	3,4,5-Trimethoxybenzaldehyde	2-(Dimethylaminomethyl)-3′,4′,5′-trimethoxybenzhydrol (IIc)	98.5–99.5[i]	56[e]
0.20	0.40[c]	2-Chlorobenzaldehyde	2-(Dimethylaminomethyl)-2′-chlorobenzhydrol (IId)	Noncrystalline[j]	80[e]
0.05	0.10[c]	Benzophenone	2-(Dimethylaminomethyl)triphenylcarbinol (IIIa)	152–154[k]	82[e], 84[f]
0.10	0.12[g]	Benzophenone	2-(Dimethylaminomethyl)triphenylcarbinol (IIIa)	153–155[k]	77[f]
0.10	0.20[c]	Acetone	2-(Dimethylaminomethyl)phenyldimethylcarbinol (IIIb)	63.5–65 (0.15)	40–46[e]
0.10	0.12[g]	*n*-Valerophenone	2-(Dimethylaminomethyl)diphenyl-*n*-butylcarbinol (IIIc)	91–92[k]	Good[f]
0.14	0.28[c]	Benzonitrile	2-(Dimethylaminomethyl)benzophenone (IV)	45–46[d]	63[f]
0.10	0.12[g]	Phenyl isocyanate	2-(Dimethylaminomethyl)-N-phenylbenzamide (V)	69–70.5[l]	65[f]
0.08	0.16[c]	Cyclohexene oxide	2-(2-Hydroxycyclohexyl)benzyldimethylamine (VI)	67–68[k]	36[f]
0.10	0.12[g]	Methyl benzoate	2,2′-Bisdimethylaminomethyltriphenylcarbinol (VII)	122–124[d]	59[f]

[a] A 10% excess of this component over the moles of *n*-butyllithium was used except in the reactions of benzonitrile and phenyl isocyanate (see Experimental). [b] The yield is based on the starting amine. [c] The metalation time was 18–20 hr. at 25–30°. [d] Recrystallized from hexane. [e] The metalation and condensation were effected in ether. [f] The metalation and condensation were effected in ether–hexane. [g] The metalation time was 30 hr. at 25–30°, magnetic stirring. [h] When the metalation and condensation were effected in hexane (metalation time, 30 hr.), the yield was 40%. [i] Recrystallized from hexane–absolute ethanol. [j] Purified through its hydrobromide (see Experimental). [k] Recrystallized from 95% ethanol. [l] Recrystallized from hexane or absolute ethanol (see Experimental).

TABLE II

ANALYSES AND INFRARED DATA OF CONDENSATION PRODUCTS OF I WITH ELECTROPHILIC COMPOUNDS

		Elemental analysis						Infrared data		
		Calcd., %			Found, %			Frequencies of strong peaks, cm.$^{-1}$ [a–c]		
Product	Empirical formula	C	H	N	C	H	N	853–837[d]	800–710[e]	710–690[e]
IIb	$C_{17}H_{21}NO_2$	75.24	7.80	5.16	75.38	7.82	5.24	843	783, 775, 759	None
IIc	$C_{19}H_{25}NO_4$	68.86	7.60	4.23	68.96	7.51	4.33	841	798, 780, 775, 761, 740, 723	None
IId	$C_{16}H_{18}ClNO$	69.70	6.58	5.08	69.55	6.38	5.11	842	762, 750	None
IIIb	$C_{12}H_{19}NO$	74.57	9.91	7.25	74.70	10.03	7.17	841	768, 747	None
IIIc	$C_{20}H_{27}NO$	80.76	9.15	4.71	81.08	8.84	4.99	842	775, 759, 744, 737	708
IV	$C_{16}H_{17}NO$	80.30	7.16	5.85	80.30	7.23	5.64	852	765, 738	703
V	$C_{16}H_{18}N_2O$	75.56	7.13	11.02	75.79	7.23	10.94	847	755, 745	690
VI	$C_{15}H_{23}NO$	77.20	9.94	6.00	76.91	9.70	5.91	840	753, 743	None
VII	$C_{25}H_{30}N_2O$	80.17	8.07	7.48	79.91	7.89	7.66	840	763, 752	704

[a] For spectra of the starting materials, see ref. 2. [b] Spectra of solids were determined by the potassium bromide pellet method· Spectra of liquids are of the neat liquid between sodium chloride plates. [c] Additional strong peaks: IV, 1668 cm.$^{-1}$ (carbonyl vibration for diaryl ketone), see ref. 5, p. 132; V, 1650, 1550, 1270 cm.$^{-1}$ (carbonyl absorption, secondary amide); peaks in 1700–1200-cm.$^{-1}$ region: 1625, 1575, and 1320 cm.$^{-1}$, see ref. 5, p. 205. [d] See ref. 4. [e] See ref. 5.

butyllithium. The latter reaction afforded neutral material, from which the desired amino product was usually separated readily by extraction with hydrochloric acid. However, amino amide V (see Scheme A) afforded an oily water-insoluble hydrochloride salt which was difficult to separate from the relatively large amount of neutral material produced when 100% excess of *n*-butyllithium was used. Amino amide V was obtained satisfactorily by employing only a 20% excess of *n*-butyllithium, with which the acid extraction was unnecessary (see Experimental).

Interestingly, the condensation of I′ with methyl benzoate afforded diaminocarbinol VII in good (59%) yield when a 20% excess of *n*-butyllithium was employed but not when a 100% excess of this reagent was used (see Scheme B). Under the latter condition, VII was isolated in only 17% yield, monoaminocarbinol IIIc being obtained in 33% yield. Evidently methyl benzoate reacted more rapidly with *n*-butyllithium than with lithioamine I′. Only the experiment with 20% excess of *n*-butyllithium is recorded in Table I, since IIIc is prepared more satisfactorily by condensation of I′ with *n*-valerophenone (see Scheme A).

The structures of the condensation products were supported by analyses and infrared spectra (Table II), and by formation of derivatives (Table III). The spectrum of each of the compounds showed a strong peak in the region 850–837 cm.$^{-1}$, which can be attributed to the unaltered dimethylaminomethyl group.[4] A peak in the 770–730-cm.$^{-1}$ region appeared in the spectra of IIb–IId, IIIb, and VI and is consistent with the products having four adjacent aromatic hydrogens (see Table II).[5] Condensation products IIa, IIIa, IIIc, IV, V, and VII showed peaks in the 770–730-cm.$^{-1}$ and 710–690-cm.$^{-1}$ regions indicating four and five adjacent aromatic hydrogens.[5] The spectra of the aminocarbinols exhibited strong hydroxyl peaks but these are not listed because they may have been due partly to moisture. The spectrum of product IV from benzonitrile showed the expected carbonyl peak and that from phenyl isocyanate several peaks consistent with its being a secondary amide (Table II, footnote *d*).

The structures of amino alcohols IIa and IIIa were established by independent syntheses from 2-bromobenzyldimethylamine (VIII) employing two different

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

[5] See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 76-78.

TABLE III

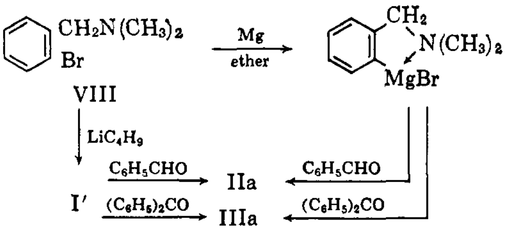
MELTING POINTS AND ANALYSES OF DERIVATIVES OF CONDENSATION PRODUCTS OF I WITH ELECTROPHILIC COMPOUNDS

Product	Derivative	M.p., °C.	Empirical formula	Elemental analysis Calcd., % C	H	N	Found, % C	H	N
IIb	Methiodide[a,b]	163–164	$C_{18}H_{24}INO_2$	52.30	5.85	3.39	52.34	5.94	3.42
IId	Hydrobromide[c]	192.5–193	$C_{16}H_{19}BrClNO$	54.02	5.38	3.94	54.12	5.36	4.06
IIIb	Methiodide	172–173	$C_{13}H_{22}INO$	46.58	6.61	4.18	46.54	6.66	4.34
IIIb	Methpicrate[d]	196.5–198	$C_{19}H_{24}N_4O_8$	52.29	5.54	12.84	52.23	5.44	12.95
IV	Methiodide[e]	175 dec	$C_{17}H_{20}INO$	53.55	5.29	3.67	53.55	5.16	3.58
V	Picrate[f,g]	174–175	$C_{22}H_{21}N_5O_8$	54.66	4.38	14.49	54.83	4.55	14.23
VI	Methiodide[h]	190–191.5	$C_{16}H_{26}INO$	51.20	6.89	3.73	51.19	7.13	3.48

[a] Prepared with excess methyl iodide in acetonitrile (refluxed several hours); the salt was precipitated by slow addition of anhydrous ether to the cold solution. [b] Recrystallized from absolute ethanol or acetonitrile–ether. [c] Recrystallized from absolute ethanol–ether. [d] Prepared from methiodide of IIIb. [e] Recrystallized from absolute ethanol. [f] Prepared with warm ethanolic picric acid. [g] Recrystallized from 95% ethanol. [h] Recrystallized from acetonitrile.

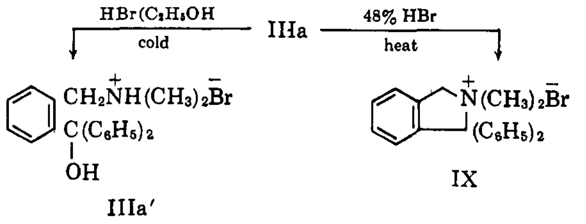
procedures in each case. One procedure involved intermediate formation of the Grignard reagent[1b,6] and the other intermediate formation of I′ by halogen–metal interchange of VIII with n-butyllithium[1b,6] (Scheme C).

SCHEME C



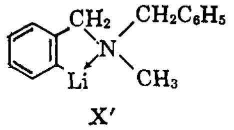
Aminocarbinol IIIa was cyclized by hot 48% hydrobromic acid to form evidently quaternary ammonium bromide IX in 85% yield. Cold ethanolic hydrogen bromide merely converted IIIa to the corresponding hydrobromide IIIa′ (Scheme D).

SCHEME D

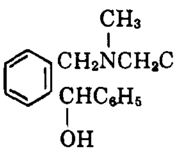


The structure of diaminocarbinol VII from methyl benzoate (see Scheme B) was established by independent synthesis from I′ and amino ketone IV; the latter compound was obtained from I′ and benzonitrile (see Scheme A). It is noteworthy that the yield of VII from I′ and IV was good (73%) even though the metalation of I was effected with only a molecular equivalent of n-butyllithium (see Experimental).

Similarly, dibenzylmethylamine (X) was metalated (48 hours), and the resulting o-lithio derivative X′ was condensed with benzaldehyde to form amino alcohol XI in 56% yield. A lower yield of VI was obtained when the aldehyde was added after 24 hours of metalation.



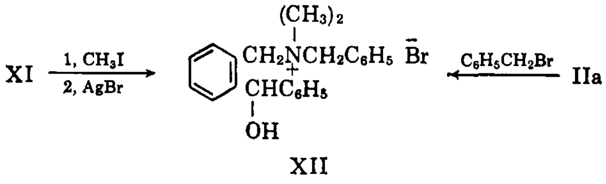
X′



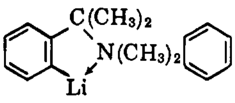
XI

The structure of XI was indicated by its infrared spectrum (see Experimental) and confirmed by conversion to the methbromide XII, which was independently prepared from amino alcohol IIa (Scheme E).

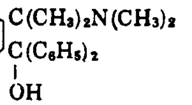
SCHEME E



Likewise, α,α-dimethylbenzyldimethylamine (XIII) was metalated (18 hours), and the resulting lithio intermediate XIII′ was condensed with benzophenone to form amino alcohol XIV in 57% yield.



XIII′



XIV

The structure of XIV was supported by its infrared spectrum (see Experimental) and by its nuclear magnetic resonance spectrum, which indicated the presence of the two identical N-methyl groups, the two identical C-methyl groups, the hydrogen bonded hydroxyl group, and the aromatic hydrogens.

Discussion

The preceding results not only substantiate the earlier conclusion[2] that metalations of benzyldimethylamine and related amines with n-butyllithium afford the o-lithioamines, but they also illustrate a useful new method for the synthesis of a variety of *ortho* derivatives of the amines. This method is more convenient than that illustrated by Scheme C in which the Grignard[1b,6,7]

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(6) F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 4389 (1962).

(7) See N. B. Mehta and J. Z. Strelitz, *ibid.*, **27**, 4412 (1962).

or lithium[1b,6] reagent of 2-bromobenzyldimethylamine (VIII) is the reactive intermediate, since benzyldimethylamine is more readily available than VIII.

The possibility that metalations of benzyldimethylamine and dibenzylmethylamine with *n*-butyllithium involve intermediate formation of the α-lithioamines which isomerize to the *o*-lithioamines seems unlikely. Thus, α-lithiobenzyldimethylamine recently has been shown[8] not to undergo such an isomerization to form the *o*-lithioamine under conditions similar to those employed in the preparation of *o*-lithiobenzyldimethylamine from benzyldimethylamine and *n*-butyllithium. The α-lithioamine was prepared from α-sodiobenzyldimethylamine and lithium bromide.[8] At least α,α-dimethylbenzyldimethylamine (XIII), which has no α-hydrogen, must undergo direct *o*-metalation with *n*-butyllithium. Moreover, this metalation appears to occur about as readily as that of benzyldimethylamine.

Experimental[9]

Metalation of Benzyldimethylamine (I) with *n*-Butyllithium to Form *o*-Lithiobenzyldimethylamine (I′).—In the early part of this work *n*-butyllithium was prepared and analysed in ether,[10] but in the latter part it was obtained commercially[11] and diluted with ether. The commercial butyllithium in hexane was analysed as described recently.[12]

To 0.05–0.20 mole of benzyldimethylamine in a 250- or 500-ml. erlenmeyer flask was added 0.10–0.40 mole of *n*-butyllithium (see Table I). The flask was filled completely with anhydrous ether, tightly stoppered, and allowed to stand at room temperature (25–30°) for 18–20 or 30 hr., depending on the ratio of reactants (see Table I). If precipitation of the resulting *o*-lithiobenzyldimethylamine (I′) occurred, the mixture was stirred with a magnetic stirrer.

Condensations of I′ with Electrophilic Compounds (Tables I–III). A. With Aldehydes and Ketones.—To a boiling solution of the appropriate aldehyde or ketone (10% over the *n*-butyllithium) in 200–300 ml. of anhydrous ether contained in a 1-l. erlenmeyer flask[13] was added slowly the solution or suspension of I′ (see Table I). The resulting mixture was allowed to stand at room temperature for 4–8 hr., then hydrolyzed by cautious addition of water. When all species had dissolved,[14] the two layers were separated. The ether layer was extracted twice with 2 *N* hydrochloric acid. The acid extracts were combined and made basic with excess 3 *M* sodium hydroxide. The resulting mixture was extracted three times with ether and the ethereal solution was dried over anhydrous magnesium sulfate. The solvent was removed, and the residue distilled or recrystallized from appropriate solvents (see footnotes to Table I). Following distillation, amino alcohol IIIb was further purified by preparative scale gas phase chromatography. Noncrystalline IId was purified by conversion to its hydrobromide, recrystallization of the hydrobromide from ether–absolute ethanol, and regeneration of IId with aqueous sodium hydroxide.

Amino carbinols IIa and IIIa were identified by comparison of melting points and infrared spectra with authentic samples (see Scheme C).

Cyclization of 5 g. (0.015 mole) of aminocarbinol IIIa in 50 ml. of 48% hydrobromic acid was effected by refluxing the solution for 1.5 hr. The resulting precipitate was collected on a funnel, dried, and digested in boiling absolute ethanol (very slightly soluble) to give 5.1 g. (85%) of presumed 1,1-diphenyl-2,2-dimethyldihydroisoindolinium bromide (IX), m.p. 252–254°. A sample melted at 253.5–254.5° after two recrystallizations from absolute ethanol. The infrared spectrum had peaks at 755, 742, and 731 cm.$^{-1}$ in the 800–690-cm.$^{-1}$ region.

Anal. Calcd. for $C_{22}H_{22}BrN$: C, 69.47; H, 5.83; N, 3.68. Found: C, 69.44; H, 5.72; N, 3.80.

When a sample of amino alcohol IIIa was dissolved in excess ethanolic hydrogen bromide and anhydrous ether was added, the hydrobromide salt IIIa′ precipitated. After two recrystallizations from absolute ethanol by slow addition of anhydrous ether, salt IIIa′ melted at 209–210°.

Anal. Calcd. for $C_{22}H_{24}BrNO$: C, 66.33; H, 6.07; N, 3.52. Found: C, 66.35; H, 6.04; N, 3.64.

The other aminocarbinols, IIb–IId and IIIb–IIIc were analysed (Table II) and derivatives prepared (Table III).

B. With Benzonitrile.—To a stirred solution of I′ in a three-necked flask (which had been flushed with dry nitrogen) was added dropwise 41.2 g. (0.4 mole) of benzonitrile (see Table I). After refluxing under nitrogen for 6 hr., the red mixture was cooled and 51 ml. of water was added, followed by 17.7 ml. (0.31 mole) of glacial acetic acid. The layers were separated. The ether layer was combined with two ether extracts of the aqueous layer and the solution dried over anhydrous magnesium sulfate. The solvent was removed, and the residue (brown oil) was stirred and refluxed with 500 ml. of 6 *M* hydrochloric acid for 72 hr. After distilling about 200 ml. of the liquid, the mixture was cooled and made basic with sodium hydroxide pellets. The liberated amino ketone was taken up in ether and the ether solution dried over anhydrous magnesium sulfate. The solvent was removed and the oily residue was crystallized from hexane to give amino ketone IV (see Tables I and II). A sample of IV afforded the methiodide in 98% yield (see Table III).

C. With Phenyl Isocyanate.—To a stirred solution of 14.3 g. (0.12 mole)[15] of freshly distilled (under nitrogen) phenyl isocyanate in 250 ml. of anhydrous ether was added dropwise under nitrogen a suspension of I′ (see Table I). After the exothermic reaction had subsided, the reaction mixture was refluxed for 4 hr., then cooled, and decomposed with saturated ammonium chloride solution. The layers were separated. The ether layer was combined with an ether extract of the aqueous layer, and the ether solution was dried over anhydrous magnesium sulfate. The solvent was removed, and the residue (orange oil) was distilled to give, after a small forerun of diphenylurea, the amino amide V, b.p. 190–200° (1 mm.), which on cooling became a glass. Crystalline V was obtained by dissolving the glass in warm hexane and slowly cooling the solution with scratching (see Tables I and II). The analytical sample of V was obtained by recrystallization from absolute ethanol (dissolved at room temperature and chilled in Dry Ice). A sample of V was converted to its picrate (Table III).

D. With Cyclohexene Oxide.—To a stirred solution of I′ was added, over 1 hr., 25 g. (0.25 mole) of cyclohexene oxide in 100 ml. ether under nitrogen essentially as described previously for the condensations with benzonitrile (see Table I). After stirring several hours at room temperature, the mixture was worked up as described for the condensations with aldehydes and ketones to give the product VI, b.p. 117–121° (0.3 mm.), m.p. 59–63°. More of VI was collected from the inside of the condenser. Recrystallization from hexane afforded VI, m.p. 67–68° in 36% yield (see Tables I and II). In another experiment the product was recrystallized from hexane without prior distillation to give slightly impure VI, m.p. 65–67°, in 31% yield. In this experiment, VI was difficult to separate from polymeric material. A sample of VI was converted to its methiodide in 97% yield (see Table III).

E. With Methyl Benzoate.—To a boiling solution of 9.5 g. (0.07 mole) of methyl benzoate in 200 ml. of anhydrous ether was added a suspension of I′ (prepared by metalation of amine I with 1.2 molecular equivalents of *n*-butyllithium) essentially as described previously for the condensations of I′ with aldehydes and ketones (see Table I). After standing overnight at room temperature, the reaction mixture was worked up to give an oil

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(8) See W. H. Puterbaugh and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 2467 (1963).

(9) Melting points and boiling points are uncorrected. Elemental analyses were performed by Ing. Schoeller, Kronach, West Germany, Micro-Tech Laboratories, Chicago, Ill., and Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded using a Perkin-Elmer Model 21 spectrophotometer, a Perkin-Elmer Model 237 Infracord, and a Perkin-Elmer Model 137 Infracord.

(10) R. G. Jones and H. Gilman, *Org. Reactions*, **6**, 339 (1951).

(11) Foote Mineral Company, New Johnsonville, Tenn.

(12) C. W. Kamienski and D. L. Esmay, *J. Org. Chem.*, **25**, 115 (1960).

(13) Since the ether vapors completely filled the flask above the solution, nitrogen was not considered necessary in this procedure as in the deuteration of I′ described previously; see ref. 2.

(14) At this point some of condensation product IIIa precipitated from solution and was collected by filtration.

(15) No excess of phenyl isocyanate over the *n*-butyllithium was used to minimize subsequent formation of diphenylurea during the working up process, since this amide was difficult to separate from the desired amino amide V.

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. Drefahl 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.