A total of 1.2 g (60%) of product, mp >400°, was obtained. The product appeared to be the betaine of sulfopyrido[2,1-*a*]isoindolium hydroxide: uv max (H_2O) 306 mμ (log ε 4.08), 252 (4.19), 244 (4.21); nmr (CF_3COOH) δ 6.10 (s, 2, CH_2), 7.87–9.05 (m, 6 Ar), 9.15 (d, 1, C-4 H).

Anal. Calcd for $C_{12}H_9NO_3S$: C, 58.29; H, 3.67; N, 5.66. Found: C, 58.20; H, 3.77; N, 5.56.

Dodecahydropyrido[2,1-*a*]isoindole Methiodide (14).—A solution of 1 g of **2a** in 100 ml of ethanol containing 2 ml of 48% hydrobromic acid was stirred with 0.5 g of platinum oxide for 4.5 hr under 1 atm of hydrogen. The calculated volume of hydrogen was absorbed. The filtered solution was concentrated, dilute sodium hydroxide added, and the amine extracted with ether. The dried ($MgSO_4$) ethereal solution was concentrated and the oily residue taken up in acetone containing 3 ml of methyl iodide. The mixture was refluxed for 18 hr and then concentrated and ether added, affording 0.85 g (66%) of colorless powder, mp 192–195° dec. It was recrystallized from methanol–ethyl acetate as microcrystals: mp 197–199° dec; nmr (D_2O) δ 2.22 (d, 14), 2.92–3.55 (m, 2), 3.67 (s, 3), 3.88–4.45 (m, 5).

Anal. Calcd for $C_{13}H_{24}IN$: C, 48.60; H, 7.53; N, 4.36. Found: C, 48.23; H, 7.36; N, 4.24.

Registry No.—**1c**, 28901-35-1; **2c**, 28901-36-2; **2d** perchlorate, 28901-37-3; **3c**, 28901-38-4; **3d**, 28901-39-5; **5**, 28901-47-5; **6a** bromide, 28901-48-6; **6a** perchlorate, 28841-17-0; **6b** bromide, 28901-49-7; **6b** perchlorate, 28901-50-0; **6c** perchlorate, 28901-51-1; **7a**, 28901-52-2; **7b**, 28901-53-3; **10a** bromide, 28901-54-4; **10a** perchlorate, 28901-55-5; **10b** perchlorate, 28901-56-6; **10c**, 28901-57-7; **11**, 28901-58-8; **12**, 28901-59-9; **13**, 28901-60-2; **14**, 28901-61-3; betaine of sulfopyrido[2,1-*a*]isoindolium hydroxide, 28883-86-5.

The Effect of Tetramethylethylenediamine on the Metalation of *N*-Methyl- and *N*-Phenylbenzylamine with *n*-Butyllithium. Deuteration and Electrophilic Condensations of Intermediate Lithioamines. Cyclodehydrations to Give N-Substituted Isoindolines[1]

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Received August 24, 1970

N-Methylbenzylamine underwent dimetalation with *n*-butyllithium–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine-(TMEDA) predominantly at the nitrogen and the *o*-benzyl positions as evidenced by deuteration studies. The intermediate dilithioamine (**2**) was condensed with benzophenone, benzaldehyde, cyclohexanone, acetophenone, and propiophenone. The resulting *o*-carbinolamines from the benzophenone and benzaldehyde condensations underwent acid-catalyzed cyclodehydration to form *N*-methylisoindoline derivatives, while the ortho condensation products from the latter three ketones underwent acid-catalyzed linear dehydration reactions, rather than cyclodehydration to form isoindolines. *N*-Phenylbenzylamine was similarly dimetalated at the nitrogen and *o*-benzyl positions with TMEDA-activated *n*-butyllithium. *o*-Carbonyl addition reactions of the dilithioamine intermediate with carbon dioxide, benzophenone, benzaldehyde, and 9-fluorenone resulted in an acid and *o*-carbinolamines, which were readily cyclodehydrated to *N*-phenylphthalimidine and *N*-phenylisoindoline derivatives.

Many aromatic compounds having a nitrogen attached either on or α to the aromatic nucleus have been shown to undergo selective ortho[3] or lateral[4] metalation with *n*-butyllithium. However, there are relatively few instances of successful ring metalation of secondary amines[5] with the exception of the dilithiation of phenothiazine[6] and its benzo derivatives[7] which proceeded in good to excellent yields. Thus, the discovery that certain tertiary amines greatly increase the activity of *n*-butyllithium offers a new approach in the investigation of the metalation of secondary amines.[8–10]

In the present investigation the metalation of *N*-methyl- and *N*-phenylbenzylamine was studied. First, the sites of dimetalation in the respective amines were determined by quenching the intermediate lithioamines with deuterium oxide. Secondly, the extent of dimetalation in these two amines using *n*-butyllithium *vs.* metalations using *n*-butyllithium–TMEDA was compared by condensing the dilithio intermediates with various electrophilic compounds. Finally, the transformations of the *o*-benzyl addition products to N-substituted isoindolines was investigated.

Metalation of N-Substituted Benzylamines. Deuteration with Deuterium Oxide.—The metalation of *N*-methylbenzylamine (**1**) and *N*-phenylbenzylamine (**3**) was attempted using *n*-butyllithium and/or *n*-butyllithium–TMEDA. Determination of the sites and qualitative estimation of the extent of dimetalation in amines **1** and **3** under the various metalating conditions were accomplished by observing the positions of deuterium incorporation on quenching with deuterium oxide and examining the ir and nmr spectra of the deuterated samples.

This method of analysis indicates that dimetalation of amine **1** must occur predominantly at the nitrogen and in the ring, ortho to the *N*-methylamino group, because each ir spectrum of deuterated amine **1**, which was shown by integration of the corresponding nmr spectrum to have 0.8–1.2 D in the aromatic ring, ex-

(1) (a) Supported by the Army Research Office (Durham) and by the National Institute of Health Grant No. CA 04455-11 from the National Cancer Institute. (b) This work represents part of the research of R. E. L., partially fulfilling the requirements for the degree of Doctor of Philosophy at Duke University.

(2) (a) Department of Chemistry, Virginia Military Institute, Lexington, Va. 24450; (b) Deceased, Jan 6, 1970.

(3) (a) F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963); (b) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *ibid.*, **28**, 3461 (1963); (c) A. R. Lepley, W. A. Khan, A. B. Guimanini, and A. G. Guimanini, *ibid.*, **31**, 2047 (1966).

(4) R. L. Vaulx, F. N. Jones, and C. R. Hauser, *ibid.*, **29**, 1387 (1964).

(5) (a) H. Gilman, G. E. Brown, F. J. Webb, and S. M. Spatz, *J. Amer. Chem. Soc.*, **62**, 977 (1950(; (b) H. Gilman and L. A. Woods, *ibid.*, **65**, 33 (1943); (c) R. T. Hawkins and D. B. Stroup, *J. Org. Chem.*, **34**, 1173 (1969).

(6) H. Gilman, D. A. Shirley, and P. R. VanEss, *J. Amer. Chem. Soc.*, **66**, 625 (1944).

(7) D. A. Shirley and J. C. Gilmer, *J. Org. Chem.*, **27**, 4421 (1962).

(8) (a) J. F. Eastham and C. G. Screttas, *J. Amer. Chem. Soc.*, **87**, 3276 (1965); (b) G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964).

(9) R. West and P. C. Jones, *J. Amer. Chem. Soc.*, **90**,2656 (1968).

(10) R. E. Ludt, G. P. Crowther, and C. R. Hauser, *J. Org. Chem.*, **35**, 1288 (1970).

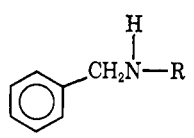
TABLE I

METALATION OF N-METHYLBENZYLAMINE (1) USING n-BUTYLLITHIUM AND n-BUTYLLITHIUM–TMEDA. DEUTERATION OF INTERMEDIATE LITHIOAMINES WITH DEUTERIUM OXIDE

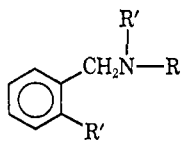
Expt no.	Ratio of n-C_4H_9Li/1	Solvent (metalation procedure)	Metalation time	—No. of D atoms incorporated— Lateral	Ortho
1	2.1:1	Hexane–TMEDA (direct)[d]	5 min	0.32–0.39	0.6–0.64
2[c]	2.1:1	Hexane–TMEDA (direct)	25 min	0.47	0.77–0.85
3[a,b]	2.1:1	Hexane–TMEDA (direct)	20 hr	0.08	0.99
4	1:1; 1.1:0	Hexane–TMEDA (two-step)[d]	30–60 min; 3 hr	0.12	0.88
5[a,b]	2.1:1	Ether–TMEDA	5 hr	0.13	1.2
6[a,b]	2.5:1	Hexane–TMEDA (indirect)[d]	1.5 hr	0.06–0.19	0.97
7[a,b]	2.5:1	Hexane–TMEDA (indirect)	25 min	0.16	1.01

[a] Observed 1,2-disubstituted absorption band in ir spectrum of deuterated sample. [b] Distinct absorption band near 2230 cm^{-1} in ir spectrum assigned to ring deuterium. [c] Small absorption band near 2230 cm^{-1} in ir spectrum assigned to ring deuterium. [d] See Experimental Section for definition of these terms.

hibited strong 1,2-disubstitution absorption bands in the 600–800-cm^{-1} region and a strong N–D absorption band.[11] However, the site and extent of metalation in amine **1** apparently depend upon two factors: (1) the method of mixing the lithium reagent and the secondary and tertiary amines, and (2) the period of metalation.



1, R = CH_3
3, R = C_6H_5

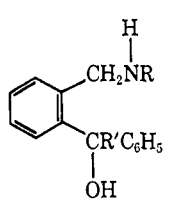


2, R = CH_3; R′ = Li
4, R = C_6H_5; R′ = Li
5, R = C_6H_5; R′ = D

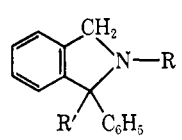
Unlike the results with amine **1**, this method of deuterium analysis cannot conclusively determine the sites of dimetalation in amine **3**, since the data obtained in this case cannot eliminate the possibility that ring metalation of **3** had occurred in the *N*-phenyl ring rather than in the *o*-benzyl position. The deuteration study of metalated **3** does indicate (1) that dimetalation of **3** occurs, presumably to form dilithioamine **4**, (2) that this dimetalation proceeds in much higher yield and in a shorter time using TMEDA-activated *n*-butyllithium than in the metalation using *n*-butyllithium alone, and (3) that the formation of **4** proceeds more satisfactorily using the indirect rather than the direct metalation procedure.

An unexpected finding was the apparent difference in the amount of ring deuterium incorporation which was observed when metalation of **3** was effected in ether and in hexane. Thus, in contrast to *N*-methylbenzylamine (**1**) where ortho metalation and subsequent condensation (see below) were found to proceed best in ether–hexane, deuteration of **4** suggests that the best conditions for effecting ortho metalation of *N*-phenylbenzylamine would be in hexane alone.

Metalation of *N*-Methylbenzylamine to Form Lithioamine 2. Condensation with Various Electrophilic Reagents.—The results of the deuteration study suggest that dilithioamine **2** could be prepared using TMEDA-activated *n*-butyllithium in either ether–hexane or hexane alone (*cf.* Table I; expt 5 and 6). In both of these instances, the ring (ortho) to α-deuterium incorporation ratio was nearly 10:1. To determine whether these two methods of metalation could be applied with equal success to synthetic problems, dilithioamine **2** was prepared under these conditions and then condensed with benzaldehyde and benzophenone. The results of these condensation reactions, summarized in Table II, show that the yields of benzophenone adduct (**6**) and benzaldehyde adduct (**7**) expected from the extent of deuterium incorporation in amine **1** were not realized. However, these results do show (1) that TMEDA–*n*-butyllithium is a more efficient metalating reagent of amine **1** than is *n*-butyllithium alone (*cf.* Table II; expt 1 and 4) and (2) that condensation reactions of dilithioamine **2** generally proceed more satisfactorily when **1** is metalated using TMEDA-activated *n*-butyllithium in ether–hexane rather than in hexane alone. This latter finding is of added interest since some workers have found that TMEDA-activated *n*-butyllithium metalations of benzene and toluene do not occur satisfactorily in ether.[8,9]



6, R = CH_3; R′ = C_6H_5
7, R = CH_3; R′ = H



8, R = CH_3; R′ = C_6H_5
9, R = CH_3; R′ = H
21, R = R′ = C_6H_5
22, R = C_6H_5; R′ = H

Chemical verification that ortho ring metalation of amine **1** was occurring was afforded by the acid-catalyzed cyclodehydration of **6** to form 1,2-diphenyl-2-methylisoindoline (**8**). This cyclization was effected by refluxing **6** in either 20% sulfuric acid or 48% hydrobromic acid for 2–4 hr. Attempts to cyclize **6** with either concentrated sulfuric acid at 0°,[12] or with 5%

(11) Deuterium atom is known to act as any substituted functional group in determining the absorption pattern of an aromatic compound in the 690–990-cm^{-1} region: G. V. D. Tiers, *J. Chem. Phys.*, **20**, 761 (1952).

(12) C. L. Mao, I. T. Barnish, and C. R. Hauser, *J. Heterocycl. Chem.*, **6**, 475 (1969).

TABLE II

METALATION OF N-METHYLBENZYLAMINE (1). CONDENSATION OF THE INTERMEDIATE LITHIOAMINE WITH BENZOPHENONE[a] AND BENZALDEHYDE[a] TO FORM CARBINOLAMINES 6 AND 7, RESPECTIVELY

Expt no.	Ratio of n-C_4H_9Li/1	Lithiating reagent	Solvent	Metalation time, hr	% yield of 6	% yield of 7[b]
1[c]	2.1:1	n-C_4H_9Li–TMEDA (4:1)	Ether–hexane	5	48–52	63[g]
2[d]	2.5:1	n-C_4H_9Li–TMEDA (4:1)	Hexane	1.5	35–42	64
3[e]	1.1:1; 1.1:0	n-C_4H_9Li; n-C_4H_9Li–TMEDA (1:0; 3:1)	Ether–hexane	1; 3	15–20	48–53
4	2.1:1	n-C_4H_9Li	Ether–hexane	48	46–48[f]	55[g]

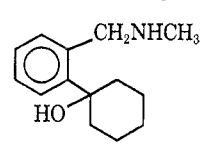
[a] The ratio of amine 1 to benzophenone was 1:2 in each condensation reaction; the ratio of 1 to benzaldehyde was 1:1.5 in each reaction. [b] Interestingly, the nmr spectrum of 7 contained an AB quartet which was assigned to the methylene protons. Nonequivalent as a result of the asymmetric carbon at the ortho position in 7: C. J. Nelson, M.A. Thesis, Duke University, 1965. Similar AB patterns have been observed in the nmr spectra of the ortho condensation products of dimethylbenzylamine: J. C. Randall, J. J. McLeskey, III, P. Smith, and M. E. Hobbs, *J. Amer. Chem. Soc.*, **86**, 3229 (1964); see also Nelson, this footnote. [c] The n-butyllithium was added to an ether solution of amine 1 and TMEDA. [d] The indirect metalation procedure was used. [e] A two-step metalation procedure was used. [f] Unpublished preliminary work in these laboratories on the metalation of secondary amines using n-butyllithium alone was done by R. L. Gay, R. L. Vaulx, and F. N. Jones. [g] In addition to recovered amine 1, up to 10% yield of diadduct 10 was isolated under these reaction conditions.

sulfuric acid in acetic acid at room temperature,[13] failed.

Benzaldehyde adduct 7 underwent a similar cyclodehydration reaction when refluxed for 2 hr in 48% hydrobromic acid. Attempted cyclization with refluxing 20% sulfuric acid gave only recovered carbinolamine 7.

Using TMEDA–n-butyllithium in ether–hexane as the metalating conditions, dilithioamine 2 was also successfully condensed with cyclohexanone, acetophenone, and propiophenone to give carbinolamines 12, 13, and 14, respectively. In each of these condensation reactions, better yields of the carbinols were realized at 0 or −80° than at room temperature.[14]

When carbinols 12, 13, and 14 were subjected to the same acid-catalyzed reaction conditions which converted 6 and 7 to isoindolines 8 and 9, there was no evidence that any cyclized products had been produced. Instead, these carbinolamines underwent linear dehydration, rather than cyclodehydration, to form olefin amines 15, 16, and 17, respectively; the linear dehydration of carbinol 14 afforded a mixture of geometrical isomers, as evidenced by the complex nmr spectrum of 17. It thus appears that isoindoline formation occurs only when linear dehydration cannot occur.



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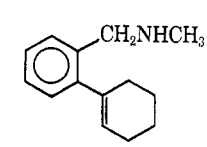

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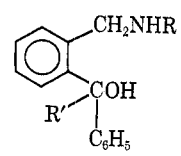
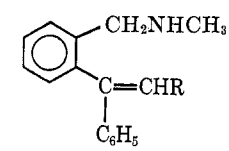
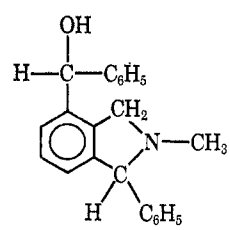


13, R = R′ = CH_3
14, R = CH_3; R′ = C_2H_5
18, R = R′ = C_6H_5
19, R = C_6H_5; R′ = H
24, R = C_6H_5; R = CH_3



16, R = H
17, R = CH_3 (*cis* and *trans*)

While the condensation reactions of 2 with benzophenone, acetophenone, propiophenone, and cyclohexanone proceeded in much better yield in ether–hexane than in hexane alone, there was no significant difference in yield of benzaldehyde adduct 7 using the different solvent systems (*cf.* Table II; expt 1 and 2). Of additional synthetic interest was the observation that, when amine 1 was metalated with a large excess of TMEDA-activated n-butyllithium (2.5–2.7 equiv), using the direct metalating procedure (in hexane), and then condensed with excess benzaldehyde, the 2,6 diadduct was isolated as the cyclized product 10, which showed strong absorption bands at 762 and 740 cm^{-1}, characteristic of 1,2,3 trisubstitution, and a clear two-proton benzylic methylene AB quartet (J_{obsd} = 14 Hz) centered at δ 4.5 in the nmr spectrum. Whether the cyclization of this adduct occurred under the reaction conditions or during work-up procedures has not been ascertained.



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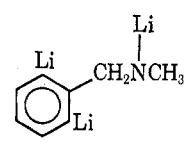
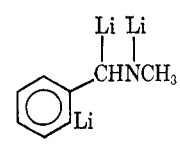


11a



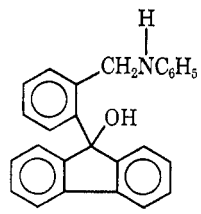
11b

It should be noted that, while 10 was the major isolated product using a large excess of the lithium reagent in hexane, this diadduct was also isolated in varying yields as a minor product when other metalation procedures were employed in the benzaldehyde condensation reaction (*cf.* Table II; footnote *g*).

The isolation of diadduct 10 in 55–57% yield has two significant implications. First, it apparently represents the first such 2,6-dicondensation adduct isolated in the metalation of a benzylamine, although a similar dicondensation was previously observed in the metalation of *N,N,N′,N′*-tetramethyl-*p*-xylenediamine using excess n-butyllithium in ether in which some 2,5-disubstituted benzophenone adduct was isolated, along with the mono-2-substituted derivative.[15] In the second place, the isolation of diadduct 10 suggests that a trilithioamine intermediate, conceivably either 11a or 11b, is formed in the metalation of amine 1 using excess TMEDA-activated n-butyllithium.

(13) A. Gandini and P. H. Plesh, *J. Chem. Soc.*, **3**, 6019 (1965).
(14) G. Wittig, W. Boll, and H. H. Kruch, *Chem., Ber.*, **95**, 2514 (1962).
(15) G. P. Crowther, Ph.D. Dissertation, Duke University, 1967.

Carbonation and Carbonyl Addition Reactions of Lithioamine 4. Cyclodehydration of the Resulting Ortho Derivatives.—Dilithioamine **4** was prepared using TMEDA-activated *n*-butyllithium in hexane and then condensed with benzophenone, benzaldehyde, and 9-fluorenone to form carbinolamines **18**, **19**,[16] and **20**, respectively, in good to excellent yields. The near-quantitative yield of **20** observed, even when only 1 equiv of ketone was employed, suggests that quantitative metalation of amine **3** must occur during the 1.5-hr metalation period, since related results in these laboratories have shown that excess *n*-butyllithium will react competitively with the lithioamine for the electrophilic compound.



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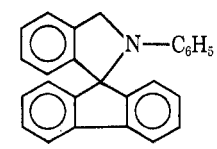
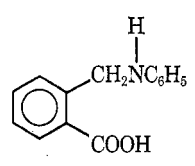


23

Chemical confirmation that metalation of amine **3** had occurred in the benzyl ring to form **4**, rather than in the *N*-phenyl ring, was obtained by the acid-catalyzed cyclodehydration of **18**, **19**, and **20** to form isoindolines **21**, **22**, and **23**, respectively.

While the condensations of **4** with benzophenone, benzaldehyde, and 9-fluorenone proceeded in excellent yields, attempted condensations of dilithioamine **4** with either cyclohexanone or acetophenone were unsuccessful; some carbonyl addition of **4** and acetophenone did occur, for a 10% yield of **24** was isolated in this condensation along with 65–75% of recovered amine **3**.

Carbonation of **4** afforded 61–65% of *o*-(*N*-phenylaminomethyl)benzoic acid (**25**) along with a 10% yield of phthalimidine (**26**). Amino acid **25** was thermally cyclized to give 2-phenylphthalimide (**26**) in 90% yield. The isolation of **26** from the thermal cyclization of carbonated amine further confirms that metalation of amine **3** occurs ortho to the *N*-phenylaminomethyl group.



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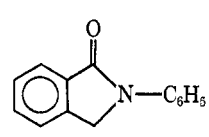

26

Discussion

The preceding results have shown that metalations of certain secondary benzylamines occur more efficiently using TMEDA-activated *n*-butyllithium than in metalations using *n*-butyllithium alone. Secondly, many of the *o*-carbonyl addition products were successfully converted to N-substituted isoindolines, thus providing a simple two-step procedure for converting N-substituted benzylamines to N-substituted isoindoles.

(16) Carbinolamine **19** was isolated as a viscous oil by distilling the reaction mixture under reduced pressure. A solid diacetyl derivative of **19** was obtained by refluxing the carbinolamine in acetic anhydride (see Experimental Section).

Each of the isolated products was identified by absorption spectra and/or by comparison of physical properties with those of known compounds. Of particular interest were the nmr spectra of isoindolines **9** and **22**, which afford good examples of long-range ABC spin coupled systems. (Similar long-range coupling has been observed previously in other isoindoline systems.[17]) The available evidence suggests that such long-range coupling over four bonds is observable only when nuclei lie in a favorable geometrical arrangement ("M" or "W" pattern), usually enforced by a rigid bicyclic carbon skeleton, or when an sp^2 hybridized atom intervenes between the remote protons.[18]

It was also noted that the signal for the benzylic methylene in the nmr spectra of isoindolines **22**, **23**, and **24** shifted downfield to δ 4.95. This downfield shift of the benzylic methylene from δ 2.0–4.0 in the nmr spectra of the respective carbinolamines to near δ 5.0 in the nmr spectra of the *N*-phenylisoindoline derivatives synthesized in this investigation is apparently characteristic.

Experimental Section

Melting points were taken in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. All boiling points are uncorrected. Elemental analyses were performed by M-H-W Laboratories in Garden City, Mich. Infrared spectra were determined with a Perkin-Elmer Model 137 Infracord using the potassium bromide pellet method for solids and sodium chloride plates for the liquids. The nmr spectra were obtained on both Varian A-60 and Varian T-60 spectrometers. All chemical shifts are reported in parts per million downfield from a tetramethylsilane (TMS) standard.

Unless otherwise stated, the metalation reactions were done in a 500-ml round-bottom flask fitted with a Claisen adapter. A dropping funnel was placed directly about the flask, and a condenser was placed in the other side of the Claisen adapter. The entire apparatus was predried and kept under a nitrogen atmosphere.

Both hexane and the ethyl ether were distilled over an appropriate drying reagent before being used as solvents in the metalation reactions.

Metalation of *N*-Methylbenzylamine Using *n*-Butyllithium–TMEDA in Ether.—A solution of 2.0 g (0.017 mol) of TMEDA and 4.0 g (0.033 mol) of *N*-methylbenzylamine in 200 ml of anhydrous ether was placed in a dry 500-ml round-bottomed flask. To this stirred solution was added 32 ml (0.071 mol) of approximately 2.25 *M* *n*-butyllithium in hexane.[19] The resulting cherry-red solution was stirred for 5–6 hr, and then treated with the appropriate electrophile.

Metalation of *N*-Methylbenzylamine Using *n*-Butyllithium and *n*-Butyllithium–TMEDA (Two-Step Procedure).—To a solution of 4.0 g (0.033 mol) of *N*-methylbenzylamine in 150 ml of dry hexane was added 16 ml (0.036 mol) of approximately 2.25 *M* *n*-butyllithium in hexane. The resulting mixture was stirred 30–60 min at room temperature when a premixed (10–15 min) solution of 1.8 g (0.016 mol) of TMEDA and 16 ml (0.036 mol) of *n*-butyllithium was added dropwise over a 5-min period. The resulting suspension was stirred from 30 min to 3 hr and then treated with the appropriate electrophile.

Metalation of *N*-Substituted Benzylamine Using *n*-Butyllithium–TMEDA in Hexane (Direct Method).—A solution of 4.0 g (0.033 mol) of *N*-methylbenzylamine or 5.0 g (0.0273 mol) of *N*-phenylbenzylamine in 150 ml of dry hexane was placed in a dry 500-ml round-bottomed flask. To this clear solution was added a premixed solution of 1.50–6.0 g (0.0174–0.07 mol) of TMEDA and 29–44 ml (0.066–0.099 mol) of approximately 2.25 *M* *n*-butyllithium in hexane. The resulting suspension was stirred from 1.5 to 4 hr and then treated with the appropriate electrophilic compound.

(17) (a) W. Metlesics, T. Anton, and L. H. Sternbach, *J. Org. Chem.*, **32**, 2185 (1967); (b) J. T. Gerig, *Tetrahedron Lett.*, 4625 (1967).

(18) S. Sternhell, *Quart. Rev. Chem. Soc.*, **23**, 236 (1969).

(19) Alpha Inorganic, Inc., Beverly, Mass.

Metalation of N-Substituted Benzylamine Using n-Butyllithium–TMEDA in Hexane (Indirect Method).—A solution of 1.35–3.0 g (0.0116–0.025 mol) of TMEDA in 150–200 ml of hexane was placed in a dry 500-ml round-bottomed flask. To this stirred solution was added 21–37 ml (0.046–0.82 mol) of approximately 2.25 *M* *n*-butyllithium in hexane. After addition of the lithium reagent, stirring was continued 10–15 min (during this period a white precipitate usually formed). To this white suspension was added 4.0 g (0.044 mol) of *N*-methylbenzylamine [or 5.0 g (0.0273 mol) of *N*-phenylbenzylamine] in 60 ml of hexane. The resulting suspension was stirred for 1.5–4 hr and then treated with the appropriate electrophile.

Deuteration of Intermediate Lithioamines with Deuterium Oxide.—To the magnetically stirred suspension of the respective lithioamine was added a 2–3 *M* excess of deuterium oxide (99.8% deuterium). Stirring was continued until a clear yellow solution resulted (5–120 min). The organic layer was filtered free of the solid which had separated, dried ($MgSO_4$), and then concentrated to give the respective deuterated amine. The recovery of undistilled deuterated amines ranged from 75 to 100%. The crude liquids were fractionated at reduced pressure through a 15-cm Vigreux column [65–70° (12–13 mm) for amine **1** and 114–120° (0.1 mm) for amine **3**], a midcut being collected for deuterium analysis (see Table I and below). The TMEDA employed in the metalations was distilled at atmospheric pressure (120–123°).

The nmr spectra of the deuterated amines were run either neat or in deuteriochloroform solutions. The integration data were obtained by comparing the integration areas of the signals in the nmr spectra of the deuterated samples with the analogous peaks in the nmr spectrum of undeuterated amine. For amine **1** the *N*-methyl singlet (3.0 H) was used as an internal standard. The ir spectra of the deuterated samples were taken neat.

(a) Amine **3**: ir 3400 (NH), 748 and 690 cm^{-1} (monosubstituted); nmr ($CDCl_3$) δ 4.73 (s, 2, $C_6H_5CH_2$), 6.4–79 (m, 10, aromatic); ratio of aromatic/lateral = 5.0.

(b) Deuterated **3** (ether metalation): ir 3410 (NH), 2540 (ND), 752 (broad), 730 and 690 cm^{-1} (predominantly monosubstituted); nmr ($CDCl_3$) 4.1 (s, 2, $C_6H_5CH_2$), 6.4–7.4 (m, 10, aromatic); ratio of aromatic/lateral = 5.0.

(c) Deuterated **3** (hexane metalation): ir 3410 (NH), 2540 (ND), 2230 (ring D), 776, 752, and 691 cm^{-1} (combination of ortho and monosubstituted); nmr ($CDCl_3$) δ 3.91 (s, 2, $C_6H_5CH_2$), 6.3–7.8 (m, 9.17, of aromatic); ratio of aromatic/lateral = 4.6.

Carbonyl Addition Reactions of Intermediate Dilithioamines 2.[20]—The respective dilithioamines were allowed to react with benzaldehyde and the various ketones. The resulting mixtures were neutralized after 30 min–12 hr with 50–100 ml of water. The aqueous layer was separated and then washed with 50 ml of ether. In the condensations with benzophenone and benzaldehyde, the combined ether fractions were extracted with 10% HCl. The resulting acidic fractions were made basic with NaOH, thus liberating the amine which was extracted into ether–methylene chloride (1:1). The organic solution was dried ($MgSO_4$), concentrated, and then worked up as described below.

In the condensations with cyclohexanone, acetophenone, and propiophenone, the acid–base work-up was omitted.

Condensation of 2 with Benzophenone. Formation of o-(N-Methylaminomethyl)triphenylcarbinol (6).—An ether solution of 6.36 g (0.035 mol) of benzophenone was added to the solution of lithioamine **2**. Following neutralization and normal work-up, hexane was added to the red liquid, and the resulting solution was cooled 10 hr and then filtered to give 5.0 g (50%) of pink-white solid, mp 172–180°. Recrystallization from absolute ethanol gave an analytical sample: mp 180–182°; ir (KBr) 3500 (OH), 3320 cm^{-1} (NH); nmr ($CDCl_3$) δ 2.28 (s, 3, NCH_3), 3.28 (s, 1.83, $PhCH_2$).

Cyclodehydration of 6 with 48% Hydrobromic Acid. Formation of 1,1-Diphenyl-2-methylisoindoline (8).—Into a 100-ml round-bottomed flask were placed 5.0 g (0.016 mol) of carbinolamine **6** and 50 ml of 48% hydrobromic acid. This solution was refluxed 1.5–2 hr, cooled, and then made basic with 6 *N* NaOH. The basic solution was extracted three times with 100-ml portions of methylene chloride. The combined organic extracts were dried ($MgSO_4$) and then concentrated to an oil which solidified on addition of ether to give 3.37 g (70%) of isoindoline (**8**), mp 128–136°. Recrystallization from absolute ethanol afforded an analytical sample: mp 135–137°; ir no NH or OH; nmr ($CDCl_3$) δ 2.13 (s, 3, NCH_3), 3.93 (s, 1.95, $PhCH_2$).

Cyclodehydration of 6 with 20% Sulfuric Acid.—Into a 100-ml round-bottomed flask were placed 5.0 g (0.016 mol) of **6** and 50 ml of 20% sulfuric acid. This solution was refluxed 2–3 hr, cooled, and then poured into an aqueous NaOH solution. When cool, the basic solution was extracted with 100-ml portions of ether–methylene chloride (1:1). The combined extracts were dried ($MgSO_4$) and then concentrated to an oil which was dissolved in absolute ethanol. Cooling gave a 75–85% yield of **8**, mp 133–137°.

Condensation of 2 with Benzaldehyde. Formation of o-(N-Methylaminomethyl)diphenylcarbinol (7).—An ether solution of 5.0 g (0.047 mol) of benzaldehyde was added to the solution of lithioamine **2**. After neutralization and normal work-up, the resulting yellow-red liquid was distilled at slightly reduced pressure to remove the TMEDA and unracted amine **1**. The higher boiling residue was then distilled, giving 4.71 g (63%) of yellow oil, bp 150–155° (0.18 mm). Further distillation afforded pure **7**: bp 139–142° (0.08 mm); ir (heat) 3320 cm^{-1} (NH); nmr ($CDCl_3$) δ 2.14 (s, 3, NCH_3), 3.30 (H_A), and 3.40 (H_B) (AB q, 1.94, $J_{AB_{app}}$ = 12 Hz, $PhCH_2$–), 5.7 (s, 0.88, >C(O–H).

Benzoylation of 7 with Benzoyl Chloride.[21]—Since attempts to crystallize **7** were unsuccessful, a solid dibenzoyl derivative was synthesized using the procedure described in ref 22 (pyridine method). Following this procedure, a 39% yield of the dibenzoyl derivative, mp 133–134°, was realized (note that recrystallization from hexane–ethanol require several days of cooling): ir (KBr) 1720 (–COO–), 1640 cm^{-1} (–CON<).

Cyclodehydration of 7 with 48% Hydrobromic Acid. Formation of 1-Phenyl-2-methylisoindoline (9).—Into a 100-ml round-bottomed flask were placed 5.35 g (0.0235 mol) of **7** and 40 ml of 48% HBr. Following the procedure described above, a yellow oil was isolated, which was distilled at reduced pressure to give 3.0 g (62%) of **9**, bp 110–112° (0.14 mm); the oil solidified on standing. Recrystallization of the white crystals from hexane gave an analytical sample, mp 57–58°.

It is important to note that refluxing **7** in 20% H_2SO_4 did not effect cyclodehydration; after 3–4 hr of refluxing **7** in 20% H_2SO_4, only **7** was recovered on work-up (80–90% recovery): ir (neat) no NH or OH; nmr ($CDCl_3$) δ 2.43 (s, 3, NCH_3), 3.69 (H_A), 4.32 (H_B), 4.49 (H_C) (ABC m, 2.8, $J_{AB_{app}}$ = 14 Hz, $J_{AC_{app}}$ = 3 Hz, $J_{CB_{app}}$ = 0.7–2.1 Hz, $ArCH_CNCH_3CH_AH_BAr$).

Metalation of N-Methylbenzylamine with Excess n-Butyllithium–TMEDA. Twofold Condensation with Benzaldehyde.—A solution of 3.9 g (0.0335 mol) of TMEDA in 60 ml of hexane was placed into a dry 500-ml round-bottomed flask. To this stirred solution was added 41 ml (0.0924 mol) of approximately 2.25 *M* *n*-butyllithium in hexane. After addition of the lithium reagent, stirring was continued 15 min; a white precipitate formed during the period. To this white suspension was added a hexane solution of 4.0 g (0.033 mol) of *N*-methylbenzylamine (the amine solution was added rapidly to the lithium reagent), and the mixture was stirred for 30 min. A solution of 7.0 g (0.066 mol) of benzaldehyde in 50 ml of hexane was added dropwise to the red-white suspension of the intermediate lithioamine. After addition of the aldehyde solution was complete, the resulting solution was stirred for 12 hr and then neutralized by adding 60 ml of water. The aqueous layer was separated and washed with 50 ml of ether. The combined organic fractions were dried ($MgSO_4$) and then concentrated to a yellow-red liquid. A solid precipitate formed on standing for 3–4 hr. This precipitate was initially triturated with hexane and filtered, yielding 6.31 g (65–75%) of white solid, mp 139–143°. Recrystallization from benzene–hexane and then absolute methanol afforded an analytical sample, mp 146–147°. It should be noted that this product was also isolated in varying yield when the other metalation procedures (see Table II) were employed in the benzaldehyde condensation reaction: ir (KBr) 3430 (OH), 762 and 740 (1,2,3 trisubstituted), 748 and 699 cm^{-1} (monosubstituted); nmr ($CDCl_3$) δ 1.93 (s, 3, NCH_3), AB q centered at 4.5 ($\Delta\nu$ = 46.6 Hz, AB q, 2, J = 15 Hz, $C_6H_5CH_2N$), 5.95 (s, 1, >CH), 6.08 (s, 1, >C(**H**)OH).

(20) Unless otherwise indicated, analyses were within acceptable limits for proof of structure.

(21) Solid dibenzoylated derivative of carbinolamine **7**.

(22) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1956, p 226.

Condensation of 2 with Cyclohexanone. Formation of 1-[o-(N-Methylaminomethyl)phenyl]cyclohexanol (12).—A ether solution of 4.0 g (0.0408 mol) of cyclohexanone was added to the solution of lithioamine **2** precooled in a Dry Ice–acetone bath. After neutralization and normal work-up, the resulting liquid was fractionated, initially at slightly reduced pressure to remove the TMEDA and cyclohexanone. Further distillation gave 35–40% recovered amine **1**, bp 65–70° (12–13 mm), and 3.53 g (51%) of **12**, bp 125–135° (0.14 mm). On cooling and mixing with hexane, the liquid solidified. Recrystallization of **12** from benzene–hexane and then petroleum ether gave an analytical sample, mp 73–75°.

When this condensation was effected at room temperature, a 39% yield of **12** was realized: ir (neat) 3320 (NH), 757 cm^{-1} (1,2 disubstituted); nmr ($CDCl_3$) δ 1.18–2.0 (m, 10.1, cyclohexyl CH_2), 2.41 (s, 2.88, NCH_3), 3.95 (s, 1.8, $PhCH_2$).

Dehydration of 12 with 48% Hydrobromic Acid. Formation of 1-[o-(N-Methylaminomethyl)phenyl]cyclohexene (15).—Into a 100-ml round-bottomed flask were placed 4.4 g (0.02 mol) of **12** and 50 ml of 48% HBr. Following the procedure described previously, a light red liquid was isolated. Distillation at reduced pressure afforded 3.0–3.1 g (75–77%) of colorless liquid **15**: bp 100–103° (0.17 mm); ir (neat) 3320 (NH), 1650 and 1823 cm^{-1} (trisubstituted olefin); nmr ($CDCl_3$) δ 1.48–2.3 (m, 8, cyclohexyl CH_2), 2.3 (s, 3, NCH_3), 3.62 (s, 1.9, $PhCH_2$), 5.5 (broad s, 0.8, $-CH_2=C<$).

Condensation of 2 with Acetophenone. Formation of 1,1-[N-Methylaminomethyl)diphenyl]ethanol (13).—An ether solution of 4.3 g (0.036 mol) of acetophenone was added to the solution of **2**, precooled in a Dry Ice–acetone bath. After neutralization and normal work-up, the resulting liquid was fractionated as described previously to give 3.15 g (40%) of yellow-red liquid **13**, bp 140–145° (0.14 mm). Dissolving this oil in hexane–ethanol (2:1) gave a white crystalline solid, mp 96–98°, on cooling. Further recrystallization from 95% ethanol gave an analytical sample, mp 97°–98°.

When this condensation was done at room temperature, a 33% yield of **13** was realized: ir (neat) 3300 cm^{-1} (NH); nmr ($CDCl_3$) δ 1.8 (s, 2.86, $>C(O^-)CH_3$), s, 2.9, NCH_3), 3.1 (s, 1.9, $PhCH_2$).

Dehydration of 13 with 48% Hydrobromic Acid. Formation of 1,1-[o-(N-Methylaminomethyl)diphenyl]ethylene (16)—Into a 100-ml round-bottomed flask were placed 3.8 g (0.057 mol) of **13** and 30 ml of 48% HBr. Following the procedure described previously, a light yellow liquid was isolated. Distillation under reduced pressure gave 2.71 g (77%) of colorless liquid **16**: bp 115° (0.1mm); ir (neat) 3320 cm^{-1} (NH); nmr ($CDCl_3$) δ 2.12 (s, 3, NCH_3), 3.51 (s, 1.9, $PhCH_2$), 5.2 (d, 1.0, J = 1.5 Hz, C=CHH), and 5.7 (d, 0.85, J = 1.5 Hz, >C=CHH).

Condensation of 2 with Propiophenone. Formation of 1,1-[o-(N-Methylaminomethyl)diphenyl]propanol (14)—An ether solution of 4.25 g (0.035 mol) of propiophenone was added to the solution of lithioamine **2**, precooled in an ice bath. After neutralization and normal work-up, the resulting liquid was fractionated as described previously to give 3.55 g (43%) of yellow oil **14**, bp 145–155° (0.14 mm); the oil solidified on standing. Recrystallization from ethanol–hexane gave an analytical sample: mp 93–95°; ir (neat) 3310 cm^{-1} (NH); nmr ($CDCl_3$) δ 0.8–1.2 (overlapping t and q, 4.5, J = 7 Hz, $-CH_2CH_3$), 2.3 (s, 3, NCH_3), 3.15 (s, 1.9, $PhCH_2$).

Dehydration of 14 with 48% Hydrobromic Acid. Formation of 1,1-[o-(N-Methylaminomethyl)diphenyl-2-methylethylene (17).—Into a 100-ml round-bottomed flask were placed 3.8 g (0.0149 mol) of **14** and 40 ml of 48% HBr. Following the procedure described previously, an orange liquid was isolated. Distillation under reduced pressure gave 2.5 g (70%) of colorless liquid **17**: bp 125–128°; ir (neat) 3305 (NH), 1595 cm^{-1} (C=C, conjugated); nmr ($CDCl_3$) δ 1.56 and 1.85 in a 3:1 ratio (2 d, 2.3, J = 7 Hz, $>C=C(CH_3)-$ (CH_3 group cis and trans)), 2.18 and 2.34 in a 3:1 ratio (2 s, 2.9, NCH_3), 3.47 and 3.70 in a 3:1 ratio (2 s, 2.0, $PhCH_2$), 6.28 (q, 0.8, J = 7 Hz, >C=CH). Presumably the product is a mixture of geometric isomers, the major isomer being present in 75–80% yield.

Anal. Calcd for C: 86.03. Found: 85.70.

Carbonyl Addition Reactions of Intermediate Dilithioamines (4).—Dilithioamine **4** was allowed to react with benzaldehyde and the various ketones. The resulting mixtures were inversely neutralized into an ether solution of acetic acid after 30 min–10 hr. After several minutes, 50 ml of water was added to the neutralized suspension. When the solid had dissolved, the aqueous layer was separated, and then washed with 50 ml of ether. The combined organic fractions were extracted with three 100-ml portions of 10% HCl; the solid HCl salt which formed was separated and then poured into an aqueous $NaHCO_3$ solution. After being stirred for 1 hr, the neutralized carbinolamine was collected by filtration. (In the benzaldehyde condensations, a viscous yellow oil was liberated on neutralization of the HCl salt. This oil was extracted into ether and then purified as described below.)

Condensation of Lithioamine 4 with Benzophenone. Formation of o-(N-Phenylaminomethyl)triphenylcarbinol (18).—An ether solution of 7.6 g (0.042 mol) of benzophenone was added to the suspension of lithioamine **4**. After the resulting mixture was stirred for 30 min–4 hr, neutralization and work-up gave 6.83 g (86%) of carbinolamine **18**, mp 149–151°. Several recrystallizations from CH_3CN afforded an analytical sample: mp 154–155.5°; ir (KBr) 3580 (OH), 3425 cm^{-1} (NH); nmr ($CDCl_3$) δ 3.95 (s, 1.9, $C_6H_5CH_2$), 5.2 (broad s, 1, OH), 5.7 (broad s, 1, NH).

Cyclodehydration of 18 with 20% Sulfuric Acid. Formation of 1,1,2-Triphenylisoindoline (21).—Into a 100-ml round-bottomed flask were placed 5.1 g (0.0143 mole) of carbinolamine **18** and 20 ml of 20% sulfuric acid. This mixture was refluxed 2–3 hr, cooled, and then poured into aqueous sodium hydroxide. After a 30-min period of stirring, the suspension was filtered, yielding 5.0 g of gray solid. This precipitate was dissolved in acetonitrile and on cooling gave 4.0 g (81%) of 1,1,2-triphenylisoindoline, mp 181–183°. Further recrystallization from acetonitrile–methanol (1:1) afforded an analytical sample: mp 182–183°; ir (KBr) no OH or NH, 745 (1,2 disubstituted), 730, and 690 cm^{-1} (monosubstituted); nmr ($CDCl_3$) δ 4.95 (s, 1.9, $PhCH_2$), 6.5–7.6 (m, 19.2, aromatic).

Condensation of 4 with Benzaldehyde. Formation of o-(N-Phenylaminomethyl)diphenylcarbinol (19).—A hexane solution of 6.3 g (0.0595 mol) of benzaldehyde was added to the suspension of **4**, and the mixture was stirred for 10 hr. The milky white suspension was neutralized and worked up as described above. The ether solution of **19** was dried ($MgSO_4$), concentrated, and then distilled under reduced pressure to give 4.2 g (72–75%) of a viscous yellow oil (**19**), bp 205–210–212° (0.06 mm). Repeated efforts to crystallize this oil were successful: ir (neat) 3590 (OH), 3320 cm^{-1} (NH); nmr ($CDCl_3$) 4.0 (s, 1.97, $PhCH_2-$), 5.86 (s, 1 $>C(O^-)H$).

Acylation of 19 with Acetic Anhydride.[23]—Approximately 2.0 g (0.007 mol) of carbinolamine **19** was placed into a 100-ml erlenmeyer flask, along with 15 ml of acetic anhydride. The resulting green mixture was heated (mild reflux) for 10–15 min, cooled, and then mixed with an equal amount of water. The viscous green oil which formed in cooling was extracted into ether. The combined ether extracts were washed with 30 ml of 10% hydrochloric acid, dried ($MgSO_4$), and then concentrated to a green oil. This residue was dissolved in 15 ml of methanol; cooling this solution with the addition of ice gave a white solid which was collected by filtration. Recrystallization from aqueous methanol afforded 0.7 g (30%) of white crystalline solid: mp 131°–132°; ir (KBr) 1750 (-COO-), 1680 cm^{-1} (-CON⁻–); nmr ($CDCl_3$) δ 1.85 (s, 2.8, $-COCH_3$), 2.0 (s, 2.9, $-COCH_3$), 4.76 (H_A), 5.14 (H_B) (AB q, 1.8, J_{AB} = 14 Hz, $PhCH_AH_B$), 5.9 (s, 0.5, >C-H).

Cyclization of Carbinolamine 19 with 20% Sulfuric Acid. Formation of 1,2-Diphenylisoindoline (22).—Into a 100-ml round-bottomed flask were placed 5.0 g (0.0172 mol) of carbinolamine **19** and 50 ml of 20% sulfuric acid. This mixture was refluxed 2–3 hr, cooled, and then poured into an aqueous sodium hydroxide solution. The resulting basic solution was stirred for 30 min and then an equal volume of ether was added. Stirring was continued until all the solid had dissolved. Then the aqueous portion was separated and washed with 100 ml of ether. The combined ether fractions were dried ($MgSO_4$) and then concentrated. The resulting residue was dissolved in acetonitrile–methanol (1:1); cooling this solution afforded solid product, mp 152–155°. Several recrystallizations from benzene–hexane afforded an analytical sample: ir (KBr) no OH or NH; nmr ($CDCl_3$) δ 4.74 (H_A),* 5.07 (H_B),* 5.82 (H_C)* (J_{AB}* = 13, J_{AC}* = 3, J_{BC}* = 0.5–1.1 Hz, $ArCH_CNC_6H_5CH_AH_BAr$) (the asterisk denotes approximate values).

Condensation of 4 with 9-Fluorenone. Formation of 9-[o-(N-Phenylaminomethyl)phenyl-9-fluorenol (20).—An ether solu-

(23) Solid diacylated derivative of carbinolamine **19**.

tion of 6.0 g (0.035 mol) of 9-fluorenone was added to the suspension of **4**, and the mixture was stirred for 1 hr. The yellow-green suspension was neutralized and worked up as described above to give 7.95 g (93–98%) of white solid, mp 154–156°. Recrystallization from benzene–hexane and then absolute EtOH afforded an analytical sample: mp 155–156°; ir (KBr) 3550 (OH), 3385 cm^{-1} (NH); nmr ($CDCl_3$) δ 2.3 (s, 2, $PhCH_2$), 3.6 (broad s, 0.9, OH), 3.9 (s, 1, NH).

Cyclodehydration of 20 with 20% Sulfuric Acid. Formation of Fluorene-9-spiro-1′-phenylisoindoline (23).—Into a 100-ml round-bottomed flask were placed 4.0 g (0.011 mol) of carbinolamine **20** and 60 ml of 20% sulfuric acid. This mixture was refluxed 4 hr, cooled, and then poured into a sodium hydroxide solution. The resulting white suspension was stirred for 30 min and then filtered, yielding 2.52 g (67%) of white solid. This precipitate was dissolved in absolute ethanol, cooled, and filtered, yielding a white solid, mp 174–176°. Addition of ice to the filtrate afforded a second crop of crystals. Further recrystallization from aqueous ethanol afforded an analytical sample: ir (KBr) no OH or NH; nmr ($CDCl_3$) δ 5.18 (s, 1.9, $PhCH_2$), 6.2–7.9 (m, 17, aromatic).

Condensation of 4 with Acetophenone. Formation of 1,1-[o-(*N*-Phenylaminomethyl)diphenyl]methanol (24).—A hexane solution of 3.4 g (0.028 mol) of acetophenone was added to the suspension of **4** precooled in an ice bath for 15 min. After a stirring period of 30–45 min, the yellow-white solution was neutralized and worked up as described above to give 0.9 g (10%) of white solid, mp 139–142°. (Amine **3** was recovered in 65–75%.) Attempts to improve the yield of **24** by condensing lithioamine **4** at −80 were unsuccessful; ir (KBr) 3430 (OH), 3285 cm^{-1} (NH); nmr ($CDCl_3$) δ (1.85 (s, 2.7, $>C(O^-)CH_3$), 3.7 (H_A), 3.9 (H_B) (AB q, 2, $J_{AB_{app}}$ = 12 Hz, $PhCH_2$).

Carbonation of Lithioamine 4. Formation of o-(*N*-Phenylaminomethyl)benzoic Acid (25).—To the magnetically stirred yellow-white suspension of lithioamine **4** were added small pieces of carbon dioxide over a 15-min period. The resulting milky white slurry was stirred for 30 min and then poured into 50 ml of 10% hydrochloric acid. The acidic solution was stirred for 5 min, 100 ml of ether was added, and stirring was continued another 30 min. The light-red acid layer was separated from the organic layer. The organic fraction was dried ($MgSO_4$) and then concentrated to give 0.3–0.4 g (8%) of 2-phenylphthalimidine (**26**), mp 157–160°. Recrystallization from absolute methanol afforded a white crystalline solid, mp 159–161°.

The acid layer was made basic with sodium hydroxide pellets; when cool, the basic aqueous solution was stirred with an equal volume of ether for 30 min. The ether layer was separated and then washed with 50 ml of 10% sodium hydroxide. The combined basic fractions were carefully acidified to pH 5 with concentrated hydrochloric acid. Cooling and scratching afforded 3.0 g (61%) of green-white solid which was collected by filtration. The solid acid did not melt but decomposed between 103 and 107° to form the lactam, which melted at 158–161°: ir (KBr) 3020–2780 (broad) (OH), 1680 (>C=O), 1400 and 1252 (OH and C–O), 867 cm^{-1} (OH).

Thermal Cyclization of Amino Acid (25). Formation of 2-Phenylphthalimidine (26).—The solid amino acid **25** was placed in a 250-ml beaker and heated on a hot plate until all the solid had melted. The beaker was cooled and then the solid was dissolved in methanol; the solvent was slowly removed by gentle heating. The resulting solid was again dissolved in methanol, cooled, and filtered, yielding 2.4–2.5 g (90%) of crystalline white solid, mp 160–162°. One recrystallization from absolute methanol gave a white crystalline solid: mp 162–163° (lit.[24] mp 162–163°); ir (KBr) 1690 (five-membered lactam); nmr ($CDCl_3$) δ 4.75 (s, 1.8, $C_6H_5CH_2$–), 6.9–8.3 (m, 9.3, aromatic).

Registry No.—TMEDA, 110-18-9; *n*-butyllithium, 109-72-8; **1**, 103-67-3; **3**, 103-32-2; **6**, 28504-92-9; **7**, 15496-39-6; **7** (dibenzoylated derivative), 28504-94-1; **8**, 28504-95-2; **9**, 28504-96-3; **10**, 28504-97-4; **12**, 28504-98-5; **13**, 28504-99-6; **14**, 28505-00-2; **15**, 28505-01-3; **16**, 28505-02-4; *cis*-**17**, 28505-03-5; *trans*-**17**, 28505-04-6; **18**, 28505-05-7; **19**, 28505-06-8; **19** diacetate, 28505-07-9; **20**, 28519-58-6; **21**, 28607-62-7; **22**, 28519-59-7; **23**, 28519-60-0; **24**, 28519-61-1; **25**, 28519-62-2; **26**, 5388-42-1.

(24) J. R. A. Pollock and R. Stevens, Ed., "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965, p 2711.

A Direct Preparation of Amidines. The Reaction of Tetrakis(dimethylamino)titanium with N–H Carboxamides

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Tetrakis(dimethylamino)titanium reacts with N-monosubstituted carboxamides to give free trisubstituted amidines. Benzamide is converted to a mixture of benzonitrile and *N,N*-dimethylbenzamidine, and 1*H*-2-pyridones yield 2-dimethylaminopyridines. This reaction appears to be the first direct conversion of amides to trisubstituted amidines. Nmr spectral data are presented for the amidines prepared.

Although we know of many reactions which lead to amidinium salts,[1] conversion to their conjugate bases, amidines, cannot always be achieved in good yield.[2] Previous reports from this laboratory have described the reactions of various carboxylic acid derivatives with tetrakis(dimethylamino)titanium (**1**) by which reaction carboxylic anhydrides, *N,N*-dialkylamides, and esters are all converted to alkylidene bis(dialkylamines).[5] Thus it was of interest to study the reactions of **1** with a series of N–H amides to see (1) whether carbon and titanium can undergo nitrogen–nitrogen ligand exchange reactions similar to the carbon-bound oxygen for titanium-bound nitrogen exchanges previously observed,[5] and (2) if amidines can be directly prepared this way. We report our results here.

(1) (a) P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. 1, W. A. Benjamin, New York, N. Y., 1965, pp 182–194.

(2) This is particularly true for the smaller, aliphatic amidines. Thus Short and his coworkers consistently obtained lower yields of aliphatic than aromatic amidines in their extensive research in the area.[3] Similar results were reported by Pettit and Garson.[4]

(3) P. Oxley and W. F. Short, *J. Chem. Soc.*, 147 (1946), 382 (1947), and subsequent publications.

(4) G. R. Pettit and L. R. Garson, *Can. J. Chem.*, **43**, 2640 (1965).

(5) H. Weingarten and W. A. White, *J. Amer. Chem. Soc.*, **88**, 850 (1966); H. Weingarten and W. A. White, *J. Org. Chem.*, **31**, 2874 (1966).

Results and Discussion

The reactions of several N-monosubstituted amides with tetrakis(dimethylamino)titanium were observed; the products and their physical properties are presented in Table I. In general, the reactions appear to follow eq 1 although no quantitative reactions were observed. The conditions employed were generally similar to those previously employed:[5] the reagents were mixed, either