The Effect of Tetramethylethylenediamine on the Metalation of o-and p-N,N-Dimethyltoluidines with n-Butyllithium. Deuteration and Electrophilic Condensation of Intermediate Lithioamines[1]

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When compared with n-butyllithium alone, n-butyllithium-N,N,N',N'-tetramethylethylenediamine (TMEDA) reagent was shown to be better for effecting the lithiation of o- and p-N,N-dimethyltoluidine. Upon treatment with n-butyllithium in ether-hexane, N,N-dimethyl-o-toluidine (1) undergoes metalation predominantly in the 2-methyl position to form lithioamine 2; small amounts of ring metalation were also detected. When n-butyllithium-TMEDA in hexane was used as a metalating agent, a more rapid and selective metalation of 1 occurred to give a better yield of intermediate lithioamine 2. With the same reagent, N,N-dimethyl-p-toluidine (26) undergoes only *ortho* ring metalation to give lithioamine 27. Positions and extent of metalation were determined by deuteration and by condensation with electrophilic compounds. These results indicate a n-butyllithium-TMEDA complex sufficiently electrophilic so that the neighboring nitrogen still influences the site of metalation. The synthetic advantages of TMEDA as a butyllithium activator in metalations influenced by a neighboring tertiary aromatic amine are also presented.

The use of nitrogen as a neighboring heteroatom to effect selective metalations with n-butyllithium has been widely investigated.[2-7] Benzyldimethylamine undergoes exclusive *ortho* ring metalation with n-butyllithium, as evidenced by condensation with electrophilic compounds in excellent yields.[2-3] Similarly, 2-methylbenzyldimethylamine has been shown to undergo exclusive 2-methyl (side chain) metalation to afford lithioamine 3, which was condensed with electrophiles in excellent yields.[4] N,N-Dimethylaniline has been metalated with alkyllithium reagents,[5,6] but the yields were low, possibly owing to some delocalization of the free electron pair on nitrogen decreasing the coordination ability of the nitrogen and also decreasing the acidity of the ring protons. It was anticipated that N,N-dimethyl-o-toluidine (1) should undergo metalation with n-butyllithium at the 2-methyl position, since the 2-methyl protons are more acidic than the ring protons and a five-membered intermediate (2) could be formed.

1 2 3
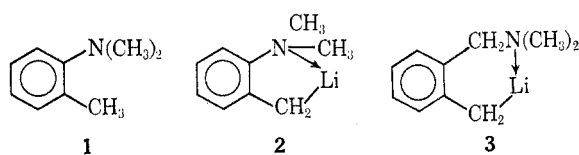
Metalation of N,N-Dimethyl-o-toluidine with n-Butyllithium in Ether-Hexane.

—We have found that N,N-dimethyl-o-toluidine (1) undergoes preferential metalation at the 2-methyl position with n-butyllithium in ether-hexane to form mainly lithioamine 2, as shown by deuteration and condensation studies. Some ring metalation also occurs, presumably at the *ortho* position,[8] although this does not necessarily arise by direct metalation of amine 1 (see below).

Deuteration of the metalation mixtures was conducted to determine the site and extent of lithiation in amine 1. The results (see Table I) show that, when 1 equiv or an excess of reagent was employed in ether-hexane, the ratio of side-chain to ring deuterium incorporation varied from 3.1:1 to 1.5:1 (expt 1-4) and, more significantly, that this ratio decreased as the metalation period was increased (*cf.* expt 1 and 2, and 3 and 4). This decrease in ratio with time might be explained in one of the following three ways: (A) by isomerization of side-chain lithio derivative 2 to form the o-lithio derivative 5; (B) by a slower competitive direct *ortho* metalation of 1 to give intermediate lithioamine 5; or (C) by further metalation of the monolithioamine 2 to give dilithioamine 7. The first explanation seems unlikely, since the amount of 2-methyl metalation did not decrease with time (see Table I). Moreover, not only is the carbanion in 2 probably a weaker base than in 5,[9] but the five-membered ring in 2, having lithium coordinated with nitrogen, should be more stable than the corresponding four-membered ring that might be assumed in 5. Such a side-chain to ring isomerization has been observed previously with α-lithiobenzyldimethylamine to form o-lithiobenzyldimethylamine,[7] but this was accompanied by the formation of a relatively stable five-membered ring.

4 5

6 7

No direct evidence was found to distinguish between the latter two possibilities.

(1) Supported by the U. S. Army Research Office (Durham) and by the Public Health Service Research Grant No. CA04455-11 from the National Cancer Institute.

(2) F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963).

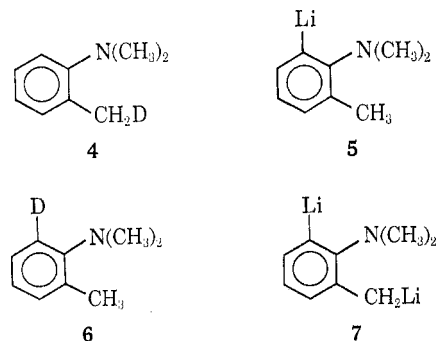(3) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *ibid.*, **28**, 3461 (1963).

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

(5) A. R. Lepley, W. A. Khan, A. B. Guimanini, and A. G. Guimanini, *ibid.*, **31**, 2047 (1966).

(6) G. Wittig and W. Merkie, *Chem. Ber.*, **75**, 1491 (1942).

(7) W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **85**, 2467 (1963).

(8) The results only establish that some ring metalation occurred in the case of N,N-dimethyl-o-toluidine. Since ring metalation of the *para* isomer was proven unequivocally to be in the *ortho* position, it is assumed that the ring metalation in amine 1 was also in the *ortho* position.

(9) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York and London, 1965, p 19.

TABLE I

METALATION OF N,N-DIMETHYL-o-TOLUIDINE WITH n-BUTYLLITHIUM AT 25–30° AND
DEUTERATION WITH DEUTERIUM OXIDE

Expt no.	Ratio of C_4H_9Li to amine 1	Solvent	Metalation time, hr	Extent of deuteration Total	At CH_3-2	On ring	Ratio of 2-CH₃ to ring
1	1:1	Ether–hexane	11	0.49	0.37	0.12	3.1:1
2	1:1	Ether–hexane	20	0.63	0.39[a]	0.24	1.6:1
3	2:1	Ether–hexane	12	0.68	0.45[a]	0.23	2.0:1
4	2.5:1	Ether–hexane	40	0.94	0.57[a]	0.37	1.5:1
5[b]	2.5:1	Ether–hexane	40	0.45	0.15	0.30	1:2[c]
6	1.5:1	Hexane–TMEDA[d]	4	0.88	0.80[e]	0.08	10:1
7	2.5:1	Hexane–TMEDA	4	1.11	1.01[e]	0.10	10:1
8	3.0:1	Hexane–TMEDA	18	1.02	0.72[f]	0.30	2.4:1
9	3.0:1	Hexane–TMEDA	40	1.1	0.85[f]	0.26	3.3:1

[a] In the nmr spectrum of this sample, the peak for the side-chain methyl does show some splitting, although the best description would be a broad singlet. [b] Reaction mixture quenched with less than 1 equiv of deuterium oxide, rather than the usual excess. [c] The accuracy of the estimation of deuterium incorporation is presumably 0.1–0.2 D; the measurement is accurate enough to show that the extent of deuterium incorporation into the ring in expt 5, relative to the deuteration of the 2-methyl group, is markedly greater than was observed in expt 4. [d] N,N,N′,N′-Tetramethylethylenediamine. [e] In the nmr spectrum of this sample, the peak for the side-chain methyl is clearly a triplet ($J = 2$ cps). [f] In the nmr spectrum of this sample, the signal for the side-chain methyl appears as a quartet ($J = 2$ cps).

TABLE II

METALATION OF N,N-DIMETHYL-o-TOLUIDINE WITH n-BUTYLLITHIUM.
CONDENSATION AT THE 2-METHYL GROUP OF AMINE 1 WITH BENZOPHENONE TO FORM CARBINOLAMINE 8

Expt no.	Ratio of LiC_4H_9 to 1	Solvent	Temp, °C	Metalation time, hr	Ratio of $(C_6H_5)_2CO$ to 1	Yield of 8, %
1	1.1:1	Ether–hexane	25–30	18–20	1.1:1	47–50
2	1.5:1	Ether–hexane	25–30	30	1.5:1	51
3	2.0:1	Ether–hexane	25–30	40[a]	2.0:1	59–62
4	2.0:1	Hexane	69	72	2.0:1	71
5	1.5:1	Hexane–TMEDA	25–30	4	1.5:1	65–71
6	2.0:1	Hexane–TMEDA	25–30	3	2.0:1	90–94
7	1.1:1	Hexane–THF[b]	25–30	10–20	1.1:1	0

[a] One equivalent of reagent was added initially. After the solution had been stirred for 20 hr, a second equivalent was introduced (see Experimental Section). [b] Tetrahydrofuran.

When the metalation mixture produced under the conditions of Table I, expt 5, was treated with only 50 mol % deuterium oxide (instead of the usual excess), so that presumably preferential deuteration of the more basic site would occur, the ratio of side-chain to ring deuterium incorporation was much less (only 1:2) than that observed (1.5:1) when the metalated amine mixture was treated with excess deuterium oxide. Either dilithioamine 7 or a mixture of lithioamines 2 and 5 would be consistent with these deuteration results.

Table II summarizes the yields of carbinolamine 8 obtained when amine 1 was metalated with n-butyllithium in ether–hexane under various conditions and the resulting lithioamine 2 was treated with excess benzophenone. This table shows that carbinolamine 8 was obtained in fair to good yields (47–71%) when the metalation of amine 1 was effected in ether–hexane or hexane alone (expt 1–4). In Table II, expt 3, the crude reaction product was indicated by tlc to consist of two components with radically different retention ratios. The compound with the higher R_f value was shown to be adduct 8, which was isolated in 62% yield. The other component, not positively identified, was shown by its mass spectrum to have a much higher molecular weight than adduct 8, and is thought to be diadduct 9, arising from twofold condensation of dilithioamine 7 with the ketone. No benzophenone adduct arising from lithioamine 5 was ever isolated or detected in any experiment. The absence of such an adduct leads us to believe that the third possibility

(see above), formation of dilithioamine 7, best accounts for the observation of deuterium incorporation into the ring of amine 1 with longer metalation periods.
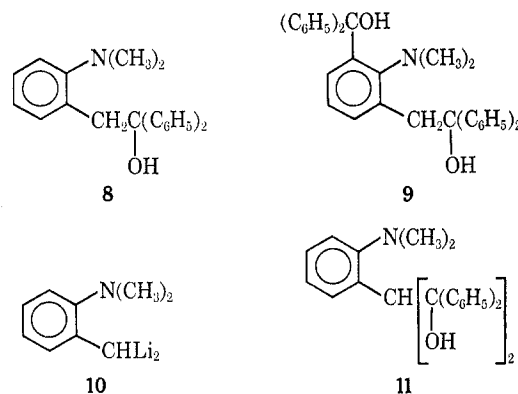
Metalation of N,N-Dimethyl-o-toluidine with n-Butyllithium–TMEDA in Hexane.

Since the discovery that certain tertiary amines greatly increase the activity of n-butyllithium, many aromatic hydrocarbons known to be inert to n-butyllithium alone have been metalated in good to excellent yield by the use of the proper tertiary amine catalyst.[10–12] However, this technique seems to have had limited application in effecting metalations of compounds containing

(10) J. F. Eastham and C. G. Screttas, *J. Amer. Chem. Soc.*, **87**, 3276 (1965).
(11) G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964).
(12) A. W. Langer, Jr., *Trans. N. Y. Acad. Sci.*, **27**, 1741 (1965).

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TABLE III

CONDENSATIONS AT THE 2-METHYL GROUP OF N,N-DIMETHYL-o-TOLUIDINE (1) WITH ELECTROPHILIC
COMPOUNDS (E) IN ETHER–HEXANE (METHOD A) AND IN TMEDA–HEXANE (METHOD B)

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Electrophilic compd (E)	Method A[a] Ratio of E to 1	Product	Yield, %	Method B[b] Ratio of E to 1	Direct method Product	Yield, %	Indirect method Product	Yield, %
Benzophenone	2:1	8	47–61	1.5:1	8	50–70	8	90–94
Benzaldehyde	1.5:1	12	41–48	1:1, 1.5:1	12	25–30	12	78–79
					15b	10–15	15b	0–5
Phenylisocyanate	1:1	13	30	...	...	...	...	...
Benzonitrile	1:1	14[c]	41–43	1:1	14[c]	45–48	14	48–54
					16	5–10	10	15–20
Methyl benzoate	1:2	14	48–52	1:2	14	47	14	32
					17	18–20	17	28
Benzyl chloride	1:1	21	16–17	2:1	21	41	21	33–42
	2:1	21	33					
Benzyl bromide	2:1	21	36–38	...	...	...	...	...
1,4-Dibromo-	1:2	22	42					
butane		23	...	1:2	22	5–14	22	10–15
					23	50	23	45–50

[a] Metalation time 40 hr in ether–hexane. [b] Metalation time 3–4 hr in TMEDA–hexane. [c] Ketone obtained after acid hydrolysis of the crude reaction mixture.

heteroatoms;[13,14] in many instances the use of such catalysts is unnecessary.

When N,N-dimethyl-o-toluidine was treated with n-butyllithium–TMEDA in hexane, not only did metalation occur much more rapidly and selectively than with n-butyllithium alone, but the overall yield was also increased (see Tables I and II). For example, in Table I, expt 7, 1.1 equiv of deuterium was incorporated into the molecule on quenching with deuterium oxide after only 4 hr of metalation. Moreover, the ratio of side-chain to ring deuterium incorporation had increased to 10:1. The incorporation of more than 1 equiv of deuterium is direct evidence of some dilithiation. In this instance, though, we believe the dilithio intermediate to be 10, rather than 7. Evidence for the presence of 10 was afforded by the nmr spectrum of the deuterated samples of Table I, expt 8 and 9, which showed very complex splitting for the side-chain methyl signal. Chemical evidence for the α,α'-dilithio intermediate is presented in the next section. Similar dilithio intermediates have been postulated in related instances.[15]

The synthetic advantages of using TMEDA are apparent from the condensation results with benzophenone (Table II). By employing short metalation periods, indicated by deuteration studies to give the best selectivity, 90–94% yields of adduct 8 were realized (see Table II, expt 6).[16] In the o-toluidine system TMEDA can be utilized to give more active n-butyllithium, which not only metalates more quickly and in better overall yield than the lithium reagent alone, but also exhibits increased selectivity, a trait uncommon in a more reactive reagent.

We believe that the results employing TMEDA support the conclusions drawn in the preceding section, namely, that metalation of amine 1 occurs initially at the 2-methyl group to form lithioamine 2 and not on

the ring to give 5. It also appears that 2 may undergo further metalation to afford a dilithioamine, possibly 7 or 10; the results suggest that dilithiamine 7 is formed preferentially when n-butyllithium in ether–hexane is the metalation reagent (Table I, expt 5), whereas 10 is the predominant dilithio intermediate with n-butyllithium–TMEDA in hexane.

Condensation of Lithioamine 2 with Various Electrophilic Compounds. Synthetic Methods.—As a result of the observations discussed in the previous sections, two general procedures were employed in the study of the condensation of lithioamine 2 with various electrophilic compounds. These involved (A) metalation of amine 1 with the lithium reagent in ether–hexane for 40 hr (method A), and (B) metalation with n-butyllithium–TMEDA in hexane for 3–4 hr (method B). It should be noted that there were two methods of mixing the reagents in method B: the direct method, adding premixed n-butyllithium–TMEDA to amine 1, and the indirect method, adding amine 1 to n-butyllithium–TMEDA. Most of the condensations were carried out using both of these metalation procedures. However, only in the case of the carbonyl addition reactions was a difference in yields noted (Table III) between the direct and indirect procedures of method B (see Experimental Section).

Early reports on the use of n-butyllithium–TMEDA claimed that a 1:1 mol ratio of these components was necessary to give maximum yields of the condensation products.[11] Other workers, though, have shown that the extent of metalation was the same with a 4:1 and 1:1 mol ratio of n-butyllithium to TMEDA.[15] In the present study, a 4:1 mole ratio was found to give best results. Not only were the yields of the condensation products the same as when a 1:1 ratio of these reagents was employed, but also purification of the desired product was easier with less TMEDA in the reaction mixture.

The yields of the condensation products of lithioamine 2 with the various electrophilic compounds employing methods A and B are summarized in Table III.

Lithioamine 2 underwent addition reactions not only with benzophenone to form carbinolamine 8, but also

(13) D. J. Peterson, *J. Organometal. Chem.*, **8**, 199 (1967).
(14) E. J. Corey and D. Seebach, *J. Org. Chem.*, **31**, 4097 (1966).
(15) R. West and P. C. Jones, *J. Amer. Chem. Soc.*, **90**, 2656 (1968).
(16) In Table II, expt 5, the crude reaction product was indicated by tlc to consist of three components. The compound with the highest R_f value was adduct **8**, which was isolated in 65–71% yield. The other two compounds had much lower R_f values, similar to the compound detected by tlc in Table II, expt 3. Though neither compound was positively identified, possible structures would be diadducts **9** and **11**.

with benzaldehyde, phenyl isocyanate, and benzonitrile to give carbinolamine 12, amide amine 13, and keto amine 14 (after hydrolysis of intermediate imine),

12   13   14
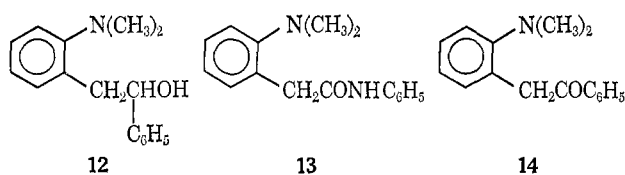
respectively. Carbinolamines 8 and 12 were dehydrated with acid to afford olefin amines 15a and 15b, respectively. Part of carbinolamine 12 produced by method B was also converted into olefin amine 15b during the condensation reaction or work-up (see Table III). Beside keto amine 14, some diimine (15–20%) 16 was obtained from benzonitrile in method B (see Table III). The formation of 16 affords further evidence for the presence of α,α-dilithioamine 10.[17]

15a, R = C₆H₅
b, R = H   16
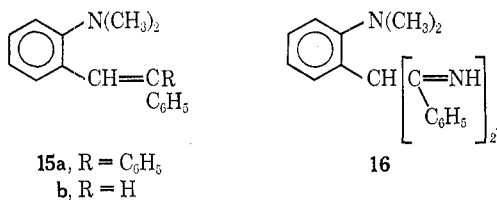
Lithioamine 2 underwent benzoylation with methyl benzoate to form mainly keto amine 14, a relatively small amount of which reacted further with 2 to give carbinoldiamine 17. This arresting of the reaction at the ketone stage presumably occurs because much of the ketone is converted into its enolate 18 by lithioamine 2, thereby minimizing the amount of ketone or its lithium methoxide addition complex available for further conversion into carbinoldiamine 17 (Scheme I).

SCHEME I
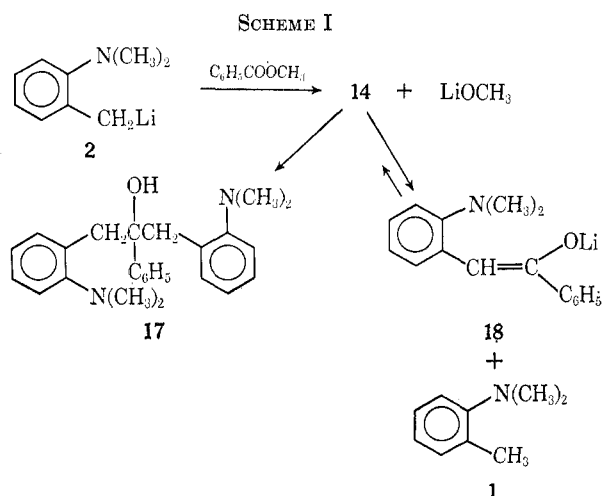
This result is to be contrasted with the reaction of lithioamine 19 with methyl benzoate, which has been observed to afford carbinolamine 20 under similar conditions; none of the keto amine corresponding to 14 was isolated.[3]

19   20
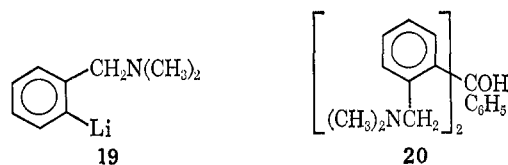
Lithioamine 2 underwent alkylation with benzyl chloride to form benzyl derivative 21. When a 1:1 mol ratio of amine 1 to benzyl chloride was used, the yield of 21 was only 16%. When a 1:2 mol ratio of these reagents was used, a 34% yield of alkylated product was realized. In an attempt to further improve the yield of 21, lithioamine 2 was alkylated with benzyl bromide, but the change in halogen increased the yield only to 36–38%. Lithioamine 2 also underwent alkylation with 1,4-dibromobutane to give halo amine 22 and the bis derivative 23. Interestingly, 22, which still contains bromine, was the main product in method A, whereas the main product in method B was 23 (see Table III).

21   22

23
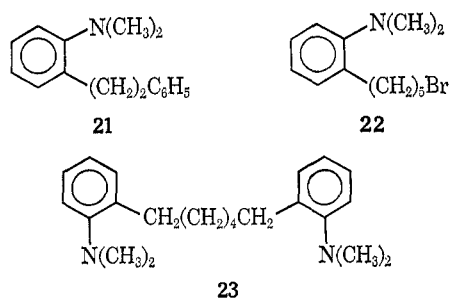
Halo amine 22 reacted as an alkylating agent when added to disodiophenylacetamide (24) in liquid ammonia to form amide amine 25; disodio salt 24 was prepared from phenylacetamide and sodium amide.[18]

24   25
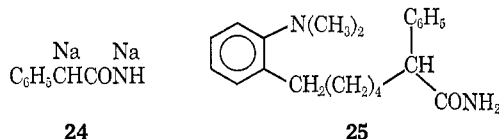
All of the products described above are new. Their structures were supported by analyses and absorption spectra. For example, the nmr spectra of carbinolamine 8 has a singlet at δ 2.72 (6 H) assigned to the N-methyl protons and another singlet at δ 3.62 (2 H)

(17) A rapid two-step condensation might be postulated to account for the formation of 16. Such a sequence appears unlikely, since an excess of benzonitrile was quickly added to the metalation mixture.
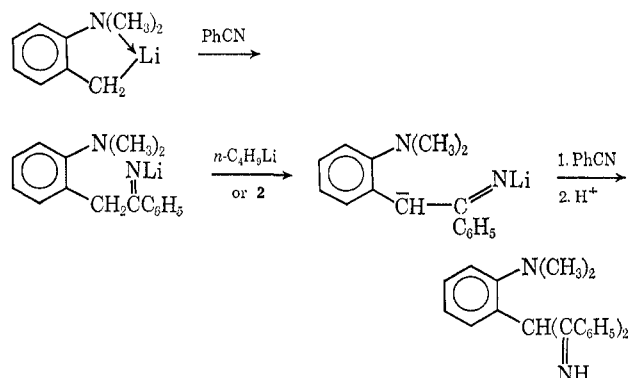

(18) S. D. Work, D. R. Bryant, and C. R. Hauser, *J. Org. Chem.*, 29, 722 (1964).

assigned to the benzylic methylene protons. The 3:1 integration ratio confirms structure **8** and eliminates the other possibility, the *o*-benzophenone adduct from lithioamine **5**. Also, special attention should be given to the nmr spectra of mono- and bisalkylated amines **22** and **23**. In each of these nmr spectra, the triplet assigned to the benzylic methylene protons is hidden for the most part under the large singlet of the N-methyl protons. The N-methyl "singlet" at δ 2.62 integrates for eight protons in the nmr spectrum of **22**, and that in the nmr spectrum of **23** (δ 2.6) integrates for 16.2 protons. The structure of the diimine adduct **16** was established from the nmr spectrum, which showed a one-proton singlet at δ 6.2 assigned to the methine proton along with the expected N-methyl and aromatic peaks (see Experimental Section). Also, the ir spectrum of **16** does not have any absorption bands corresponding to 1,2,3 trisubstitution. Thus the diadduct was established as structure **16** arising from dilithio compound **10** and not from reaction of dilithio amine **7**.

Based on the results of Table III, it must be concluded that, when the major products were the same in methods A and B, the latter method is generally preferable, since not only did it usually afford better yields, but the lithiation was complete in much less time. However, as shown in the alkylation reaction with 1,4-dibromobutane, metalation under the conditions of method A is still useful.

Metalation of N,N-Dimethyl-*p*-toluidine.—The foregoing section showed that the metalation of amine **1** (method A) occurred in fair yield at the 2-methyl position, as shown by deuteration and condensation studies. More significant, it was shown that the use of the TMEDA-activated reagent (method B) not only greatly facilitated the rate of metalation of amine **1**, but also enhanced the ratio of side-chain to ring metalation (see Table I).

In contrast to amine **1**, which underwent preferential metalation at the 2-methyl group, amine **26** was found to undergo exclusive ring metalation with either *n*-butyllithium or its TMEDA complex, as shown by deuteration and condensation with benzophenone to form deuterioamine **28** and carbinolamine **29**, respectively.
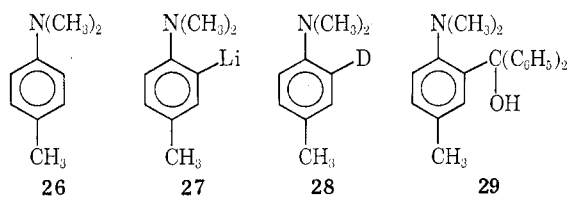
That the deuterium was incorporated into the ring, presumably *ortho* to the dimethylamino group, was supported by ir and nmr spectra. Similarly, the structure of the benzophenone adduct **29** was supported by elemental analysis and absorption spectra.

In view of the proposed coordination mechanism for similar metalation reactions of tertiary amines,[19] it seems improbable that either deuterium or benzophenone was incorporated *ortho* to the *p*-methyl group of amine **26**. However, the analysis and absorption spectra used to verify structure **29** would also be consistent with the structure of the product which would have resulted from the condensation of amine **26** with

(19) K. P. Klein and C. R. Hauser, *J. Org. Chem.*, **32**, 1479 (1967).

benzophenone *ortho* to the *p*-methyl group. In order to verify the proposed structure of adduct **29**, then, this carbinolamine was synthesized by another method (Scheme II). Thus bromo amine **31**, obtained by methylating commercially available 2-bromo-4-methyl-

SCHEME II
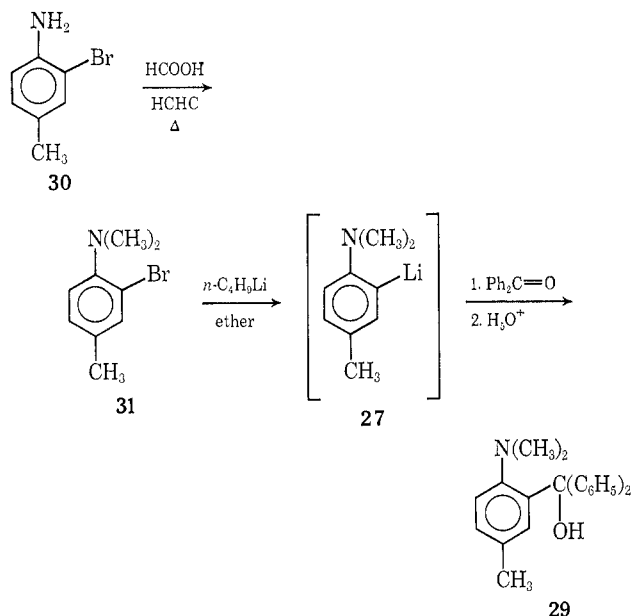
aniline (**30**) with excess formic acid and formaldehyde,[20] was treated with 3 molar equiv of *n*-butyllithium in ether, and then with excess benzophenone.[21] The product was shown to be identical with carbinolamine **29** by mixture melting point and spectral data. Again, metalation of amine **26** with the TMEDA-activated reagent provided a better yield of adduct **29** in much less time than did metalation and condensation of amine **26** with *n*-butyllithium alone; metalation of amine **26** in refluxing hexane for 72–80 hr with *n*-butyllithium alone gave a 60% yield of **29**, while metalation with TMEDA–*n*-butyllithium for 3–4 hr afforded nearly an 80% yield of this carbinolamine.

The above results indicate that amine **26** is being lithiated only in the *ortho* position. However, it is possible that **26** was metalated initially at the *p*-methyl position followed by isomerization to form *o*-lithioamine **27** or that with longer metalation times **27** might isomerize to form the *p*-methyl lithio derivative. When the metalation reaction of amine **26** with *n*-butyllithium–TMEDA in hexane was quenched with deuterium oxide after 30 min, the nmr spectrum of the deuterated amine showed very little deuterium incorporation; less than 0.1 D was present at the *p*-methyl position and a maximum of 0.24 D was present in the ring. When the same reaction was quenched with D$_2$O after 36 hr, the nmr showed *ca.* 0.8 D in the ring and essentially no deuterium at the *p*-methyl position. These deuterations further substantiate that amine **26** is metalated nearly exclusively in the *ortho* position. No significant *p*-methyl metalation was detected.

Based on the good yields of metalation observed in the *o*- and *p*-dimethyltoluidines, it was of interest to

(20) R. N. Icke, B. B. Wisegarver, and G. A. Alles, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 723.
(21) F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 701 (1962).

apply the TMEDA method to N,N-dimethylaniline (**32**) to determine whether or not *ortho* derivatives could be attained in better yields than previously reported. Treatment of amine **32** with *n*-butyllithium–TMEDA in hexane for 3–4 hr followed by condensation with benzophenone afforded carbinolamine **33** in 71% yield. The best yield of adduct **33** previously obtained with *n*-butyllithium alone was 40% (56% crude).[5]

32   **33**
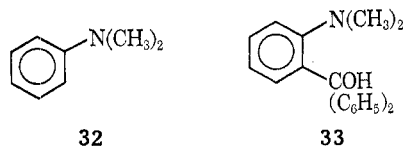
Summary.—The *n*-butyllithium–TMEDA complex has been shown in this study to be a better metalating reagent of N,N-dimethyl tertiary aromatic amines than *n*-butyllithium alone. The complex is not only an effectively stronger base, as suggested by better yields and shorter metalation periods, but also, unexpectedly, a more selective base, as shown by the results with N,N-dimethyl-*o*-toluidine (**1**).

In the metalation of the *p*-amine **29**, no comparison of selectivities is possible, since both reagents give only *ortho* metalation. Since the *n*-butyllithium–TMEDA complex metalates toluene nearly quantitatively in the α position,[11] some metalation at the 4-methyl position of amine **26** might be expected; yet with amine **29** only *ortho* metalation is observed. This clear-cut preference indicates that the *n*-butyllithium–TMEDA complex is apparently still sufficiently electrophilic to coordinate with the free electron pair of nitrogen in the aromatic amine. Such a coordination complex between the reagent and the amine would form an intermediate in which the potential *n*-butyl carbanion is directed to a methyl hydrogen in amine **1**, but to an *ortho* hydrogen in amine **26**, as indicated in **34** and **35**, respectively.

34   **35**
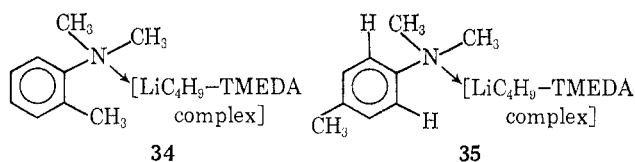
Thus, although a protophilic mechanism does probably operate to form a weaker base in both cases, the potential lithium cation must play an important role in determining the site of metalation.[22] If initial coordination of the TMEDA complex was not an important factor in directing the site of metalation, it is difficult to explain why the more acidic 4-methyl group of amine **26** was not metalated preferentially.

Synthetically, the TMEDA method has been shown to be excellent for effecting substitution at the 2-methyl position of N,N-dimethyl-*o*-toluidine and at the *ortho* positions of N,N-dimethyl-*p*-toluidine and N,N-dimethylaniline. Currently, studies are underway to apply this method to other systems.

(22) A. A. Morton has long stressed the influence of the metallic cation in the mechanism of metalations: A. A. Morton, "Solid Organoalkali Reagents," Gordon and Breach, Inc., New York, N. Y. 1964.

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 Janssen Pharmaceutica, Beerse, Belgium, and by M–H–W Laboratories, 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 a Varian A-60 spectrometer. All chemical shifts are reported in parts per million downfield from a tetramethylsilane standard.

Vpc analysis was done with an F & M Model 700 vapor phase chromatograph using a 6-ft column packed with 10% SE-30 on 80–100 Diataport S. Mass spectra were measured at the Research Triangle Institute for Mass Spectrometry, Durham, N. C., on a MS-902 mass spectrometer.

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

The various metalation conditions are described below. However, only one procedure will be described for the condensation reactions of lithioamine **2** with the different reagents, unless different products were obtained in method A and method B metalations (see Table II and III for yields). Analytical and spectral data for the condensation products are summarized in Tables IV and V.

TABLE IV

ANALYSES FOR CONDENSATION PRODUCTS AND DERIVATIVES

Compd	Molecular formula	Calcd, %			Found, %		
		C	H	N	C	H	N
8	$C_{22}H_{23}NO$	83.24	7.30	4.41	83.03	7.40	4.48
12	$C_{16}H_{19}NO$	79.63	7.94	5.81	79.47	7.95	5.86
13	$C_{16}H_{18}N_2O$	75.65	7.10	11.02	76.04	7.40	11.13
14	$C_{16}H_{17}NO$	80.40	7.12	5.80	79.95	7.07	5.93
15a	$C_{22}H_{21}N$	88.30	7.02	4.68	88.13	7.21	4.70
15b	$C_{16}H_{17}N$	86.08	7.63	6.28	85.84	7.85	6.27
16	$C_{23}H_{23}N_3$	80.90	6.79	12.30	80.61	6.71	12.58
17	$C_{25}H_{30}N_2O$	80.20	8.08	7.48	80.05	8.07	7.18
21	$C_{16}H_{19}N$	85.40	8.44	6.22	85.32	8.48	6.21
22	$C_{13}H_2ONBr$	57.95	7.41	5.18	58.17	7.53	5.10
23	$C_{22}H_{32}N_2$	81.43	9.94	8.63	81.14	10.19	8.48
25	$C_{21}H_{28}N_2O$	77.8	8.64	8.64	77.78	8.47	8.60
29	$C_{22}H_{23}NO$	83.24	7.30	4.41	83.42	7.50	4.48

Preparation of Lithioamine 2 from N,N-Dimethyl-*o*-Toluidine in Ether. Method A.—A solution of 5.0 g (0.038 mol) of N,N-dimethyl-*o*-toluidine in 200–250 ml of anhydrous ether was placed into a 500-ml, round-bottomed flask. To this stirred solution was syringed 27 ml (0.038 mol) of *ca.* 1.55 *M* *n*-butyllithium in hexane. This mixture was stirred under a nitrogen atmosphere for 20 hr, when another 27 ml (0.038 mol) of *n*-butyllithium was syringed into the yellow solution. Stirring of this mixture was continued for another 20–25 hr before deuteration or condensation with the designated electrophile. Lithioamine **2** usually precipitated from the ether medium over this latter period of stirring.

Preparation of Lithioamine 2 from N,N-Dimethyl-*o*-Toluidine Using TMEDA. Method B. Direct Method.—A solution of 5.0 g (0.038 mol) of N,N-dimethyl-*o*-toluidine in 150 ml of dry hexane was placed into a 500-ml, round-bottom flask. Next a solution of 2.2–8.7 g (0.019–0.075 mol) of TMEDA in 20–30 ml of dry hexane was placed in the dropping funnel. To this TMEDA solution was syringed 25–33 ml (0.056–0.075 mol) of *ca.* 2.25 *M* *n*-butyllithium in hexane. The resulting cloudy solution was allowed to stand for 10–15 min, during which time the *n*-butyllithium–TMEDA complex usually precipitated. The premixed solution was then added to the stirred hexane solution of amine **1**. Stirring of the resulting mixture was continued for 3–4 hr before deuteration or condensation. Lithioamine **2** usually precipitated from the hexane medium during the metalation period.

Preparation of Lithioamine 2 from N,N-Dimethyl-*o*-Toluidine Using TMEDA. Method B. Indirect Method.—A solution of 2.2 g (0.019 mol) of TMEDA in 100 ml of dry hexane was placed

TABLE V

SPECTRAL PROPERTIES OF CONDENSATION PRODUCTS AND DERIVATIVES

Compd	N(CH₃)₂[b] stretching	ortho substitution	Mono-aromatic substitution	Other	N(CH₃)₂ (type, integration)	Aromatic (type, integration)	Other[c] (assignment) (type, integration)
8[d]	1060 935	767	756		2.71 (s, 5.9 H)	7.0–7.5 (m, 14.1 H)	3.62 (PhCH₂) (s, 2 H) 6.54 (OH) (broad s, 1.1 H)
12	1065 939	773	759 700	3350 (OH)	2.38 (s, 6 H)	6.7–7.2 (m, 9.1 H)	2.86 (PhCH₂) (d,[e] 2.1 H) 4.67 (CHOH) (t,[f] 0.91 H) 5.54 (OH) (broad s, 0.97 H)
13	1045 943	770	755 690	3310 (NH), 1652 (amide I) 1610 (amide I)	2.74 (s, 6 H)	6.8–7.55 (m, 10.3 H)	3.65 (PhCH₂) (s, 2 H)
14	1050 950	768	756 690	1682 (C=O)	2.45 (s, 6 H)	6.9–8.0 (m, 9 H)	4.18 (PhCH₂) (s, 1.83 H)
15a	1050 946	770	755 697	...	2.78 (s, 6 H)	7.05–7.45 (m, 13.5 H)	6.4–6.6 [Ph(C=)H] (m, 1 H)
15b	1052 948	763	758 692	...	...[g]		
16[d]	1032 947	763	750 697	3410 and 1565 (NH imine) 1640 (C=N)	2.79 (s, 6 H)	6.7–7.9 (m, 16 H)	6.23 (methine) (s, 0.96 H)
17[d]	1052 945	770	765 705	3380 (OH)	2.58 (s, 12 H)	6.7–7.45 (m, 14.3 H[h])	2.97 and 3.28 [CH₂C(OH)CH₂] (AB pattern,[i] 4.1 H)
21	1045 945	764	749 697		2.55 (s, 6.1 H)	7.0–7.2 (m, 9 H)	2.88 (PhCH₂CH₂) (s, 3.9 H)
22	1050 947	768	...		2.62 (broad s, 8 H)	6.9–7.1 (m, 4 H)	1.27–1.95 (CH₂) (m, 5.94 H) 3.3 (CH₂Br) (t,[j] 1.93 H)
23	1048 950	768	...		2.6 (broad s 16.2 H)[k]	6.82–7.17 (m, 8.2 H)	1.32–1.87 (CH₂) (m, 8 H)
25	1048 950	763	748 702	3420 and 3210 (NH), 1650 (amide I) 1605 (amide II) 1415 (amide III)	2.58 (broad s, 8 H)[k]	6.6–7.6 (m, 9.8 H)[l]	1.0–2.8 (CH₂) (m, 8.8 H[l]) 3.23 (methine) (t, 1.1 H[m])
29	...[n]	...	...	3350 (OH)	2.29 (s, 6 H)	6.95–7.4 (m, 12.6 H)	2.21 (p-CH₃) (s, 2.96 H) 6.45 (OH) (broad s, 1 H)
31[o]	915	...	...	870 and 812 (1,2,4-trisubstitution)	2.63 (s, 6 H)	6.88 and 7.35 (two broad s, 1.98 and 0.85 H)	2.11 (p-CH₃) (s, 3.1 H)

[a] Nmr spectra determined in carbon tetrachloride unless noted otherwise. [b] A. R. Katritzky and R. A. Jones, *J. Chem. Soc., C*, 3674 (1959). [c] Ph = o-N,N-dimethylaminophenyl. [d] Nmr solvent deuteriochloroform. [e] J = 5.5 Hz. [f] J = 5.5 Hz. [g] Nmr spectrum not determined. [h] Aromatic integration includes hydroxyl proton. [i] AB_{obsd} = 14 Hz. [j] J = 6–8 Hz. [k] Peak and integration also include PhCH₂ protons. [l] Integration was not accurate enough to determine position of protons on amide nitrogen. [m] J = 7 Hz. [n] Unable to determine correlations. [o] Nmr spectrum determined on neat liquid.

into a 500-ml, round-bottom flask. To this stirred solution was syringed 33 ml (0.075 mol) of *ca.* 2.25 *M* n-butyllithium in hexane. This mixture was stirred for 10–15 min, during which time the TMEDA–n-butyllithium complex usually precipitated. Then a hexane solution of 5.0 g (0.038 mol) of N,N-dimethyl-o-toluidine was added *via* the dropping funnel over a 2–10 min interval. Stirring of the resulting mixture was continued for 3 hr. Lithiomine 2 precipitated during this time affording a yellow-white suspension.

Deuteration of Lithioamine 2 with Deuterium Oxide.—To the stirred yellow-white suspension of lithioamine 2 was added a 2–3 molar excess of deuterium oxide (99.8% deuterium) *via* the dropping funnel. (In one instance, less than 1 molar equiv of deuterium oxide was employed; see Table 1, expt 5.) Stirring was continued until a clear yellow solution resulted (5–60 min). The organic layer was filtered free of the solid which had separated, dried (MgSO₄), and concentrated to give deuterated amine 1. The recovery of undistilled deuterated amines was 75–100%. The crude liquids were fractionated at reduced pressure through a 15-cm Vigreux column [65–70° (12–13 mm), a midcut being collected for deuterium analysis (see Table I).

The TMEDA employed in certain metalations was distilled at atmospheric pressure and 120–123° or at slightly reduced pressure.

Deuteration of Lithioamine 2 with Less than 1 Equiv of Deuterium Oxide (See Table I, Expt 5.)—To the stirred yellow-white suspension of lithioamine 2 was added 0.4 g (0.020 mol) of deuterium oxide (99.8% deuterium) *via* the dropping funnel. After the solution had been stirred for 1 hr, excess water was added and stirring was continued until a clear yellow solution resulted. Subsequent work-up of the deuterated sample was the same as described above.

The nmr spectra of the deuterated amines were run either neat or as carbon tetrachloride solutions. The integration data was obtained by comparing the integrating areas of the signal in the nmr spectra of the deuterated samples with the analogous absorption peaks in the nmr spectrum of undeuterated amine 1. In each instance, the dimethylamino singlet (6 H) was used as an internal standard. The ir spectra of the deuterated samples were taken neat.

Condensation of Lithioamine 2 with Benzophenone.—To the yellow suspension of 2 was added an ethereal solution of 13.4

g (0.075 mol) of benzophenone, dropwise, over a 15-min interval. The resulting green solution was stirred for 5–30 min and then poured into a solution of 5.0 g (0.083 mol) of glacial acetic acid in 30 ml of ether. After the solution had been stirred for several minutes, 50 ml of water was added. The resulting suspension was filtered, affording a white, crystalline solid, yield 0.0–11.0 g, mp 149–152°. The filtrate was extracted with 10% hydrochloric acid (solid hydrochloric salt of product precipitated). The resulting aqueous suspension was made basic with NaOH pellets, liberating the solid free amine, which was collected by filtration to give up to 7.91 g of crude benzophenone adduct **8**, mp 148–151°. (This solid was subjected to tlc analysis.) One recrystallization from benzene–hexane gave 6.85 g of white needles, mp 151.5–154°. The basic filtrate was extracted with ether, and the combined ether extracts were dried (MgSO₄) and concentrated. Distillation of this oil gave 0–0.8 g (16% recovery) of **1**, bp 35° (0.25 mm). Cooling the high-boiling residue gave 0.8 g of adduct **8**, mp 148–151°. The total yield of pure adduct **8** was 60–94%. Further recrystallization of **8** from benzene–hexane afforded an analytical sample, mp 153–155°.

Dehydration of Benzophenone Adduct 8 with 20% Sulfuric Acid.—Into a 100 ml, round-bottom flask were placed 3.17 g (0.01 mol) of **8** and 20 ml of 20% sulfuric acid. This solution was refluxed for 2 hr, cooled in an ice bath, and then carefully poured into a precooled solution of 8 g of NaOH in 20 ml of water. The basic solution was extracted with ether; the combined ether extracts were dried (MgSO₄) and concentrated to a yellow oil which solidified on standing overnight. Recrystallization of the crude product from petroleum ether (bp 30–60°) gave 2.0 g (70%), mp 73–75°, of olefin amine **15a**. Further recrystallizations from petroleum ether gave an analytical sample, mp 75–77°.

Dehydration of Benzophenone Adduct 8 with Acetic Acid–Sulfuric Acid.—Into a 100-ml, round-bottom flask were placed 4.0 g (0.0126 mol) of carbinolamine **8** along with 45 ml of glacial acetic acid. Stirring was initiated until all the solid had dissolved. Then 5 ml of concentrated sulfuric acid were added with immediate development of red color. After stirring for 2 min, the reaction mixture was poured into ice contained in a 250-ml beaker. The resulting slurry was neutralized with NaOH pellets, liberating a gummy, yellow solid which was taken up in petroleum ether. Cooling and scratching afforded 3.35 g (88%) of white solid (**15a**), mp 74–76°.

Condensation of 2 with Benzaldehyde.—To the milky yellow slurry of lithoamine **2** was added 8.0 g (0.075 mol) of benzaldehyde–hexane. After stirring for 30 min, the clear yellow solution was inversely neutralized into acetic acid–ether. Following usual acid–base work-up procedure, the ether layer was dried (MgSO₄) and concentrated to a yellow oil which was distilled under reduced pressure, yielding 2.45 g of yellow liquid, bp 105–125° (0.35 mm), and 7.07 g (78–79%) of yellow oil (**12**), bp 155–160° (0.35 mm). The yellow liquid was a mixture of a TMEDA–*n*-butyllithium condensation adduct and a smaller amount of the dehydrated benzaldehyde adduct (**15b**). Treatment of the yellow oil **12** with hexane afforded a white, crystalline solid, mp 66–68°.

Dehydration of Carbinolamine 12 with 20% Sulfuric Acid.—Into a 200-ml, round-bottom flask were placed 1.4 g (0.006 mol) of carbinolamine **12** and 20 ml of 20% sulfuric acid. After refluxing for 2 hr, the solution was cooled and then treated in the same manner as in the dehydration of carbinolamine **8**. The concentrated ether layer was distilled under reduced pressure to give 0.68 g (50%) of a light yellow liquid (**15b**), bp 130–135° (0.2 mm). Two further distillations gave a colorless liquid, bp 130–132° (0.2 mm). In contrast to carbinolamine **12**, the dehydrated product **15b** does not solidify when treated with hexane.

Condensation of 2 with Phenyl Isocyanate.—To the milky yellow slurry of **2** was added an ether solution of 6.7 g (0.055 mol) of phenyl isocyanate. After the initial exothermic reaction had subsided, the semiclear solution was refluxed for 4 hr and then inversely neutralized into an acetic acid–ether solution. This solution was washed with sodium bicarbonate, and then the ether layer was dried (MgSO₄) and concentrated. Distillation of the ether residue (complicated by the presence of a subliming white solid) gave 1.0 g of **1** and sublimed white solid and 1.5 g of unidentified yellow oil, bp 100–105° (0.3 mm) (also contaminated with white solid). The resulting high boiling point residue was taken up in hexane–ether, which on cooling gave 7.0 g of yellow-white precipitate, mp 74–84°. This precipitate was dissolved in ether and extracted with 10% hydrochloric acid. The acid washings were neutralized with NaOH pellets and extracted with

ether. Evaporation of the ether gave a residue which was taken up in absolute ethanol. Cooling afforded 3.2 (33%) of white solid (**13**), mp 103–105°. Recrystallization from acetonitrile gave an analytical sample, mp 104–105°, of amido amine **13**.

Condensation of 2 with Benzonitrile.—To the yellow-white slurry of **2** was added 4.65 g (0.045 mol) of benzonitrile–hexane. After the resulting mixture had been stirred for 3 hr, the light orange solution was neutralized directly with 100 ml of water. As neutralization proceeded, a white precipitate formed. The solid was filtered and then recrystallized from absolute ethanol, yielding 1.0 g (10%), mp 168–172°, of amine diimine **16**. The filtrate was extracted with 10% hydrochloric acid. The combined acid extracts were then heated under reflux for 45–240 min, cooled, and then neutralized with NaOH pellets, liberating a yellow oil. This oil was extracted into ether, dried (MgSO₄), concentrated, and distilled under reduced pressure to give 3.42 g (48%) of keto amine **14**, bp 130–140° (0.2 mm). Further distillation of keto amine **14** afforded an analytical sample.

When the solid was determined to be diimine amine **16**, a longer metalation period, 16 hr, employing 2.5 equiv of *n*-butyllithium and 0.6 mol of TMEDA, was used in order to maximize the yield of the diadduct. Following the above procedures, a 15–20% yield of diadduct **16** was realized, along with 48–54% of keto amine **14**, after hydrolysis of the intermediate monoimine adduct. Recrystallization of diimine adduct **16** from benzene–hexane afforded an analytical sample as white needles, mp 167.5–169.5°.

Benzoylation of 2 with Methyl Benzoate.—To the yellow-white slurry of **2** was added 2.6 g (0.019 mol) of methyl benzoate in ether. After the resulting mixture had been stirred for 35 min, the orange-yellow suspension was inversely neutralized into acetic acid in ether. Following the usual acid–base work-up, the resulting yellow liquid was distilled under reduced pressure, giving 2.5–2.6 g (50%) of recovered amine **1**, 1.42 g (32%) of keto amine **14**, bp 150–165° (0.075 mm), and 1.41 g of carbinoldiamine **17**, bp 180–195° (0.075 mm). The high-boiling point residue was dissolved in petroleum ether and afforded 0.7 g of yellow-white solid. This solid was dissolved in 95% ethanol along with the liquid distilled at 180–195°. Cooling gave 2.0 g (28%) of white solid (**17**), mp 103–105°.

Alkylation of 2 with Benzyl Chloride.—To the yellow-white slurry of **2** was added 9.0 g (0.071 mol) of benzyl chloride–hexane. After this mixture had been stirred at room temperature for 2 hr (or refluxed for 4 hr), the white slurry was neutralized with 60 ml of water. After work-up in the usual manner, distillation of the resulting yellow liquid afforded 1.3 g (26%) of recovered amine **1**, 2.84 g (34%) of alkylated amine **21**, bp 114–120° (0.1 mm), a yellow oil, bp 135–150° (0.1 mm), and a viscous liquid, bp 175–185° (0.1 mm). The yellow oil fraction was found by vpc analysis to contain three components, of which one was the alkylated product **21**. Of the two other components, the larger one may be a 1,1 diadduct similar to that isolated in the condensation with benzonitrile. The retention time of the minor component was the same as that for the viscous liquid. Neither of these two compounds was purified sufficiently for identification.

Alkylation of 2 with 1,4-Dibromobutane. Method A.—To the milky yellow suspension of **2** was added an ether solution of 8.1 g (0.0375 mol) of 1,4-dibromobutane, dropwise, over a 5–10-min period. During this addition, mild reflux was initiated and continued throughout the reaction. After *ca*. 20 min, the yellow-white solution cleared but became cloudy as refluxing continued. After 7 hr, the solution was neutralized and worked up in the usual manner, giving 1.3 g (26% recovery) of **1**, 4.22 g (42%) of colorless liquid **22**, bp 110–113° (0.22 mm), and 1.0 g of high-boiling residue. Using the same procedure with either 4.0 g (0.019 mol) or 2.0 g (0.0094 mol) of 1,4 dibromobutane, only the monoalkylated product **22** and recovered **1** were isolated.

When the reaction was neutralized after only 30 min of ether reflux, less than 10% **22** was isolated, whereas, after 1 hr of refluxing, the yield of isolated **22** was increased to 21%.

Alkylation of 2 with 1,4-Dibromobutane. Method B.—To the yellow-white slurry of **2**, prepared using a 1:1 mol ratio of *n*-butyllithium to TMEDA (1.5 equiv), was added 4.12 g (0.079 mol) of 1,4-dibromobutane in hexane. After stirring for 6 hr, the resulting mixture was neutralized by adding 100 ml of water. Following the usual work-up procedure, the yellow liquid was distilled under reduced pressure, yielding 1.63 g (26%) of recovered amine **1**, 0.75 g (14%) of monoadduct **22**, and 3.03 g (49.2%, based on moles of dihalide used) of alkylated product **23**, bp 160–

165–180° (0.25 mm). Further distillations gave an analytical sample as a yellow liquid, bp 160–163° (0.2 mm).

Formation of the Dipotassium Salt of Phenylacetamide.[18] Alkylation of Haloamine 22.—To a stirred solution of 0.033 mol of potassium amide in 300 ml of liquid ammonia was added 2.0 g (0.015 mol) of solid phenylacetamide. The resulting dark green solution was stirred for 30 min, when an ether solution of 4.0 g (0.0148 mol) of 22 was added during 1.5 min. After stirring for 20 min, the yellow solution was neutralized with excess ammonium chloride. The ammonia was replaced by ether, and the resulting ether layer was filtered and then extracted with 10% hydrochloric acid. Normal work-up gave a light yellow oil which was taken up in benzene–hexane. After the solution had been cooled to room temperature, the solid which had formed was removed by filtration to give 0.62 g of crystalline solid, mp 155–160° (31% recovery of phenylacetamide). Cooling the filtrate in an ice bath, with scratching, gave 3.0 g (63%) of white, powdery solid (25). Recrystallization from acetonitrile gave a white, crystalline solid, mp 79–81°.

Lithiation of Amine 26 by n-Butyllithium in Refluxing Hexane. Condensation with Benzophenone.—Into a 500-ml, round-bottom flask were placed 5.0 g (0.0375 mol) of N,N-dimethyl-p-toluidine dissolved in 250 ml of dry hexane. To this stirred solution was syringed 25 ml (0.037 mol) of ca. 1.55 M n-butyllithium in hexane. This mixture was stirred with mild refluxing for 24 hr, when 25 ml (0.037 mol) of n-butyllithium was syringed into the dropping funnel and added dropwise to the reaction mixture. Stirring with mild reflux was continued for 72 hr, when an ether solution of 9.1 g (0.05 mol) of benzophenone was introduced dropwise over a period of 15 min. This mixture was stirred for 4 hr, and then the dark blue reaction mixture was inversely neutralized into acetic acid in ether. This neutralized solution was extracted with three 50-ml portions of 10% hydrochloric acid. The combined acid extracts were made basic with sodium hydroxide pellets, liberating a solid which was collected by filtration, yield 6.4 g (52%), mp 169–173°. The basic filtrate was extracted with ether, which was dried over MgSO₄ and then concentrated to give 0.85 g (8%) of solid, mp 163–170°. Recrystallization of the combined product from benzene–hexane gave a white, crystalline solid, mp 171.5–172.5°.

Lithiation of Amine 26 by n-Butyllithium–TMEDA in Hexane.—Using the previously described apparatus, 4.0 g (0.0296 mol) of N,N-dimethyl-p-toluidine was dissolved in 250 ml of dry hexane and then placed in a 500-ml, round-bottom flask. To this stirred solution was added a premixed (10–15 min) suspension of 5.2 g (0.045 mol) of TMEDA and 20 ml (0.045 mol) of ca. 2.25 M n-butyllithium in hexane. The resulting mixture was stirred for 4 hr.

Deuteration of Lithioamine 27.—Quenching the lithioamine prepared as described above with deuterium oxide was done in the same manner as described for deuteration of lithioamine 2. Undistilled deuterated amine 26 was recovered in greater than 90% yield. The crude amine was distilled under reduced pressure through a 15-cm Vigreux column [54–56° (0.4 mm)], a midcut being collected for deuterium analysis. The three experimental conditions are outlined below.

A. **Metalation for 30 min** resulted in the following data: ir (neat) identical with that of undeuterated amine 26; nmr (neat) δ 2.2 (s, 2.9, C₆H₅–CH₃), 2.62 [s, 6.0, N(CH₃)₂], and 6.4–7.1 (AB quartet, 3.76, $J = 4$ Hz, aromatic).

B. **Metalation for 3 hr** resulted in the following data: ir (neat) 2300 (ring D), 950 [N(CH₃)₂], and 878 and 806 cm⁻¹ (1,2,4-triaromatic substitution); nmr (neat) δ 2.21 (s, 2.98, p-C₆H₅CH₃), 2.60 [s, 6, N(CH₃)₂], and 6.4–7.2 (m, 2.94, aromatic).

C. **Metalation for 36 hr** resulted in the following data: ir (neat) 2290 (ring D), 951 and 1054 [N(CH₃)₂], and 808 and 878 cm⁻¹ (1,2,4-triaromatic substitution); nmr (neat) δ 2.21 (s,

2.96, p-C₆H₅CH₃), 2.61 [s, 6.0, N(CH₃)₂], and 6.4–7.1 (m, 3.2, aromatic).

Condensation with Benzophenone.—To a stirred solution of lithioamine 27 was added an ether solution of 8.2 g (0.045 mol) of benzophenone. Stirring was continued for 20 min after addition of benzophenone. Then the clear yellow solution was inversely neutralized into acetic acid–ether. Normal acid–base work-up afforded 6.92 g (74%) of white solid, mp 160–172°, on neutralization with sodium hydroxide. Concentration of the ether washings afforded another 0.6 g (6.5%) of carbinolamine 29. The total yield was 80%.

Independent Synthesis of Alcohol Amine 29. Methylation of 2-Bromo-p-toluidine.[23]—A 3.38-g sample (0.675 mol) of 90% formic acid was placed in a 500-ml, three-necked, round-bottom flask. Then 25 g (0.135 mol) of 2-bromo-p-toluidine was added to the acid with stirring. After the solution had been stirred for 5 min, 30.5 ml (0.405 mol) of 37% formaldehyde solution was added cautiously, resulting in vigorous gas evolution. After addition was complete, the flask was introduced into an oil bath (90–100°). The reaction mixture was kept at 95–100° for 8 hr and then cooled. After the mixture had cooled to room temperature, 69 ml of 4 M hydrochloric acid was introduced into the reaction mixture. The resulting mixture was concentrated on Buchi Rota-Vac to ca. 30 ml of orange-red liquid plus some white precipitate. Next, 50 ml of water was added and then 30 g of sodium hydroxide in 60 ml of water. The resulting solution was extracted with ether and benzene; the organic extracts were dried (MgSO₄), concentrated, and distilled at reduced pressure. The desired product was collected as a light yellow liquid at 90–93° (1.5 mm), leaving a higher boiling, yellow-orange liquid which solidified on cooling. The yield of halo amine 31 was 35–38%.

Lithiation, *via* Metal–Halogen Exchange, of Halogen Amine 31.[20] Condensation with Benzophenone.—Into a 500-ml, round-bottom flask fit with a Claisen adapter were placed 4.28 g (0.02 mol) of 2-bromo-N,N-dimethyl-p-toluidine and 150 ml of anhydrous ether. To this stirred solution was syringed 27 ml (0.06 mol) of ca. 2.25 M n-butyllithium in hexane. The resulting solution was stirred for 1 hr, when an ether solution of 7.5 g (0.04 mol) of benzophenone was added dropwise to the light yellow solution. After stirring at room temperature for 1.5 hr, the red-brown solution was inversely neutralized into an ether solution of acetic acid. Normal acid–base work-up afforded an orange-white solid, which was dissolved in absolute ethanol. After cooling, the suspension was filtered to give 5.5 g (74%) of crystalline, white solid, mp 169–172°. No depression of melting point occurred on admixture with carbinolamine 29.

Lithiation of Amine 34 by n-Butyllithium–TMEDA in Hexane. Condensation with Benzophenone.—A solution of 4.0 g (0.033 mol) of N,N-dimethylaniline in 250 ml of hexane was placed into the 500-ml, round-bottom flask. To this stirred solution was added a premixed (10–15 min) suspension of 7.68 g (0.066 mol) of TMEDA and 31 ml (0.069 mol) of ca. 2.25 M n-butyllithium in hexane. The resulting mixture was stirred for 4 hr, when an ether solution of 9.1 g (0.05 mol) of benzophenone was added over a 5-min interval. After stirring for 30 min, the reaction mixture was inversely neutralized into an ether solution of acetic acid. Normal acid–base work-up afforded 7.1 g (71%) of crystalline carbinolamine 35, mp 157–160° (lit.[4] mp 160.5–161.5°).