A Comparison of the Synthetic Utility of *n*-Butyllithium and Lithium Diisopropylamide in the Metalations of *N,N*-Dialkyltoluamides[1a]

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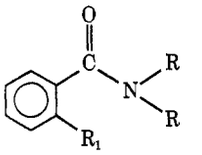
N,N-Diisopropyl-*o*-toluamide (1) underwent side-chain metalation using either *n*-butyllithium or lithium diisopropylamide as the lithium reagent. Evidence for the presence of lithiated *N,N*-diisopropyltoluamide was obtained by quenching studies and by using condensation reactions with benzophenone and *n*-butyl bromide. The analogous meta and para *N,N*-diisopropyltoluamides underwent predominantly a carbonyl addition reaction with *n*-butyllithium, giving the cleavage products on hydrolysis. In contrast, lithium diisopropylamide metalated both these toluamides at the respective side chain methyl in good to excellent yields. The corresponding *N,N*-diethyl-*o*-, *m*-, and *p*-toluamides were also metalated at the respective side chain positions using lithium diisopropylamide in fair to good yields.

Metalations and subsequent condensations at the methyl group of *N,N*-dimethyl-*p*-toluenesulfonamide by means of sodium amide in liquid ammonia[3] and at the ortho position of *N,N*-dimethylbenzenesulfonamide with *n*-butyllithium[4] have been observed. Unlike the sulfonamides, which are stable to nucleophilic addition and cleavage by *n*-butyllithium, *N,N*-dialkylbenzenecarboxamides undergo addition reactions with Grignard[5] and lithium reagents,[6] leading to the formation of ketones. For example, valerophenone was obtained in 70% yield when *N,N*-dimethylbenzamide was treated with *n*-butyllithium in tetrahydrofuran (THF)–hexane.[7] However, ortho and side-chain metalations have been observed when N-substituted benzamides[7] and *o*-toluamides[8] were treated with 2 equiv of *n*-butyllithium. Apparently, the initial N-metalation of the amino hydrogen deactivates the carbonyl group to attack by the base.

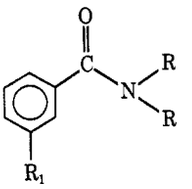
It was of initial interest during this investigation to determine if carbonyl addition of the lithium reagent to the *N,N*-dialkyltoluamides could be eliminated or significantly reduced by increasing the steric requirements of the *N,N*-dialkyl substituents; that is, could the carbonyl addition reaction be reduced or eliminated by steric factors rather than by electronic deactivation as shown by the dimetalation of N-substituted amides[7,8] described above. Secondly, the synthetic value of metalating *N,N*-dialkyltoluamides by different lithium reagents was investigated.

Results

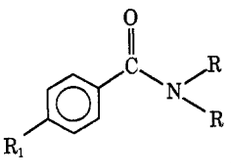
The findings of the present study show that ortho toluamide **1** (R = isopropyl) will undergo preferential side-chain metalation with *n*-butyllithium in THF at 0°, whereas para toluamide **3** (R = isopropyl), under the same metalating conditions, apparently undergoes more carbonyl addition with *n*-butyllithium than metalation.



1, R = $CH(CH_3)_2$; $R_1 = CH_3$
4, R = $CH(CH_3)_2$; $R_1 = CH_2COH(C_6H_5)_2$
7, R = $CH(CH_3)_2$; $R_1 = (CH_2)_4CH_3$
7′, R = $CH(CH_3)_2$; $R_1 = CH(C_4H_9)_2$
10, R = CH_2CH_3; $R_1 = CH_3$
13, R = C_2H_5; $R_1 = CH_2COH(C_6H_5)_2$
16, R = C_2H_5; $R_1 = (CH_2)_4CH_3$
16′, R = C_2H_5; $R_1 = CH(C_4H_9)_2$



2, R = $CH(CH_3)_2$; $R_1 = CH_3$
5, R = $CH(CH_3)_2$; $R_1 = CH_2COH(C_6H_5)_2$
8, R = $CH(CH_3)_2$; $R_1 = (CH_2)_4CH_3$
11, R = CH_2CH_3; $R_1 = CH_3$
14, R = CH_2CH_3; $R_1 = (CH_2)COH(C_6H_5)_2$
17, R = CH_2CH_3; $R_1 = (CH_2)_4CH_3$



3, R = $CH(CH_3)_2$; $R_1 = CH_3$
6, R = $CH(CH_3)_2$; $R_1 = CH_2COH(C_6H_5)_2$
9, R = $CH(CH_3)_2$; $R_1 = (CH_2)_4CH_3$
12, R = CH_2CH_3; $R_1 = CH_3$
15, R = CH_2CH_3; $R_1 = CH_2COH(C_6H_5)_2$
18, R = CH_2CH_3; $R_1 = (CH_2)_4CH_3$

Evidence of this difference in the site of attack by *n*-butyllithium in toluamides **1** and **3** was obtained initially by glpc analysis of the respective reaction mixtures, obtained by adding *n*-butyllithium dropwise to a THF solution of the respective toluamide at 0°. The glpc data of the quenched toluamides (*cf.* Table I,

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(2) (a) This work represents part of the research of J. S. G., partially fulfilling the requirements for the Ph.D. degree at Duke University; (b) Undergraduate participant in NSF–COSIP program at VMI; (c) Deceased, January 6, 1970.

(3) F. H. Rash and C. R. Hauser, *J. Org. Chem.*, **32**, 3379 (1967).

(4) H. M. Watanabe, unpublished data, 1970.

(5) See E. E. Royals, "Advanced Organic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1954, p 582.

(6) V. Boekelheide and R. J. Windgassen, *J. Amer. Chem. Soc.*, **86**, 2020 (1958).

(7) W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964).

(8) R. L. Vaulx, W. H. Puterbaugh, and C. R. Hauser, *J. Org. Chem.*, **29**, 3514 (1964).

SCHEME I

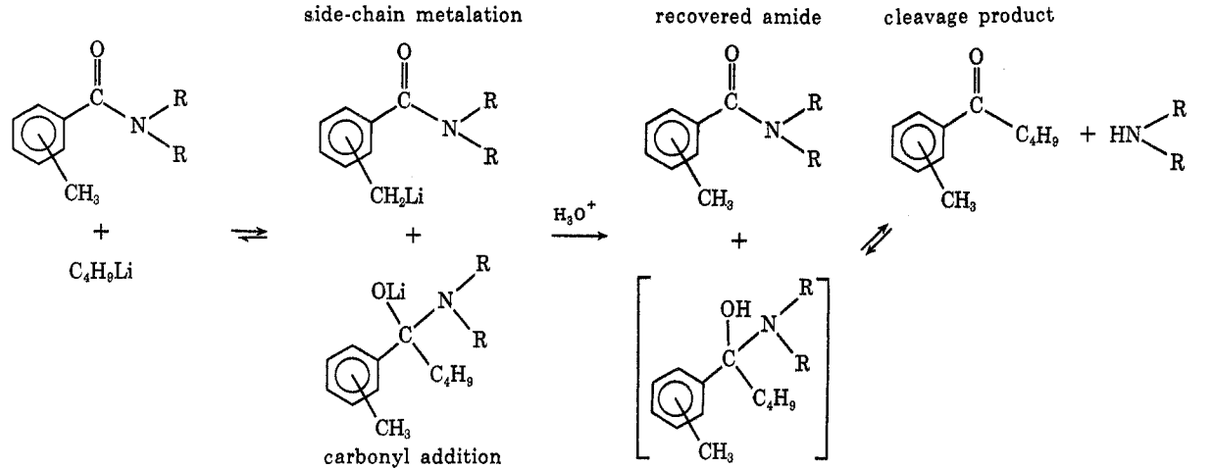

TABLE I

COMPOSITION OF THE REACTION MIXTURES[a] OF THE METALATED *N,N*-DIALKYLTOLUAMIDES WHEN QUENCHED WITH WATER

Expt	Toluamide	Metalating conditions	Carboxamide,[b] %	Ketone,[c] %	Other,[d] %
1	1	*n*-C_4H_9Li–Hexane; THF 0°	92–94	0–2	4
2	2	*n*-C_4H_9Li–Hexane; THF 0°	42	45	13
3	3	*n*-C_4H_9Li–Hexane; THF 0°	25–40	75–50	0–10
4	3	$LiN[CH(CH_3)_2]_2$; THF 0°	98	1	
5	10	*n*-C_4H_9Li–Hexane; THF 0°	68–70	20–23	8–10
6	11	*n*-C_4H_9Li–Hexane; THF 0°	20	70	10
7	12	*n*-C_4H_9Li; THF 0°	0–10	80–90	0–10

[a] Glpc analysis *via* ratio of peak areas found by integration. [b] While this term includes both unchanged carboxamide as well as the hydrolyzed side-chain metalated product, a comparison of these data to the yield data for the benzophenone and butylation reactions (Tables II and III) gives a good indication of the extent to which side-chain lithiation is occurring in the respective toluamides. [c] This term gives good indication of the extent of carbonyl addition which is occurring in the respective toluamides by the *n*-butyllithium. [d] No attempt was made to isolate or identify the "other" components of the glpc analysis, though in most cases the "other" was a single high-boiling component.

expt 1 and 3) clearly show that no *o*-tolyl butyl ketone, the expected cleavage product, was present when the intermediate lithiated toluamide of **1** was quenched. Conversely, the ketone resulting from the attack of the lithium butyl at the carbonyl of toluamide **3** was the major product recovered when lithiated **3** was quenched.

Using the identical metalating conditions, *N,N*-diethyl-*o*-toluamide (**10**) showed a metalation–carbonyl addition reactivity ratio with *n*-butyllithium which was intermediate between that of toluamides **1** and **3** (*cf.* Table I, expt 5), while the corresponding *N,N*-diethyl-*p*-toluamide (**12**) underwent an exclusive carbonyl addition reaction, as indicated by the absence of toluamide **12** in the glpc of the quenched reaction mixture.

Supporting evidence for this difference in the site of attack by *n*-butyllithium in toluamides **1**, **3**, **10**, and **12** at 0° was afforded from the varying yields obtained when the respective lithiated toluamides were condensed with benzophenone. Whereas toluamide **1** afforded an 80–85% yield of adduct **4** and toluamide **10** gave a 15–25% yield of adduct **13**, no benzophenone adduct was isolated using the identical experimental conditions with either lithiated toluamide **3** or **12**.

These results indicate that sufficient steric requirements in the *N,N*-dialkyl substituents, as in toluamide **1** and to a smaller degree in toluamide **10**, will inhibit cleavage of the amide linkage by the *n*-butyllithium and allow metalation, at least in the side chain, to occur. However, in most cases *n*-butyllithium cannot be used as a metalating reagent in preparing side-chain or ortho lithio-*N,N*-dialkyltoluamides as synthetic intermediates because of the undesirable carbonyl addition by the base with subsequent cleavage of the amide bond on hydrolysis (see Scheme I).

Since lithium diisopropylamide, $LiN[CH(CH_3)_2]_2$, has been shown to be an effective metalating reagent of *o*-, *p*-, and *m*-toluic acids,[9] metalations of the corresponding *N,N*-dialkyltoluamides were attempted using this lithium reagent. With $LiN[CH(CH_3)_2]_2$ as the metalating reagent, toluamide **1** was lithiated, then condensed with benzophenone to give carbinolamide **4** in yields varying from 80 to 95%. The intermediate lithioamide of **1** was also alkylated with *n*-butyl bromide (see Table II), yielding both mono- and di-side

TABLE II

THE CARBONYL ADDITION AND ALKYLATION REACTIONS OF THE LITHIATED *N,N*-DIISOPROPYLTOLUAMIDES. COMPARISON OF THE YIELDS[a] IN ALKYLATION REACTION USING THE STEPWISE[b] AND DIRECT[c] METHOD

Expt	Toluamide	Lithiating reagent	Electrophile	Product	Yield, %
1	1	*n*-C_4H_9Li, THF 0°	$(C_6H_5)_2C{=}O$	4	75–85
2	1	*n*-C_4H_9Li, THF 15–20°	$(C_6H_5)_2C{=}O$	4	45–50
3	1	$LiN[CH(CH_3)_2]_2$, THF 0°	$(C_6H_5)_2C{=}O$	4	80–90
4[b]	1	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	7	70
				7′	14
4′[c]	1	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	7	72
				7′	11
5	2	$LiN[CH(CH_3)_2]_2$, THF 0°	$(C_6H_5)_2C{=}O$	5	3–10
6[b]	2	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	8	66
6′[c]	2	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	8	77
7	3	*n*-C_4H_9Li, THF 0°	$(C_6H_5)_2C{=}O$	6	0–5
8	3	$LiN[CH(CH_3)_2]_2$, THF 0°	$(C_6H_5)_2C{=}O$	6	80–100
9[b]	3	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	9	93
9′[c]	3	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	9	87–92

[a] By glpc analysis by integration of peak areas. [b] Formation of lithioamide followed by treatment with 1-bromobutane. [c] Addition of base to a mixture of toluamide and 1-bromobutane.

(9) P. L. Creger, *J. Amer. Chem. Soc.*, **92**, 1396 (1970).

chain alkylated products, **7** and **7'**. Using the same metalating conditions *p*-toluamide **3** was metalated at the *p*-methyl group as evidenced by benzophenone condensation of the intermediate lithiated amide to give carbinolamide **6** (85–95%), and by butylation to give substituted toluamide **9** (see Table II).

Carbinolamines **4** and **6** were readily isolated from the respective reaction mixtures (see Experimental Section). However, when *m*-toluamide **2** (R = isopropyl) was metalated using $LiN[CH(CH_3)_2]_2$, then condensed with benzophenone under the exact conditions which gave carbinolamides **4** and **6** in >85% yield, only a small amount of solid product, identified as carbinolamide **5**, was isolated. This seemed to indicate that either metalation of **2** was not occurring, or that the resulting lithioamide did not condense as readily with benzophenone as did the *o*- and *p*-*N*,*N*-diisopropyltoluamides. Presumably, the latter explanation is more correct than the former, since butylation of the intermediate meta-lithiated toluamide of **2** gave 60–70% of alkylated amide **8**.

As the metalations of *N*,*N*-diisopropyltoluamides **1**, **2**, and **3** proceeded satisfactorily using $[(CH_3)_2CH]_2NLi$ as the metalating reagent, metalations of the analogous *N*,*N*-diethyltoluamides **10**, **11**, and **12** were attempted using the same lithium reagent. Under these conditions, **10** was successfully metalated at the 2-methyl position, as shown by the 50–60% yield of benzophenone adduct **13** and the 70–75% yield of mono- and di-side chain butylated amides **16** and **16'**. Similarly, *N*,*N*-diethyltoluamides **11** and **12** were successfully metalated at the respective side-chain methyl groups, with the resulting lithiated intermediates being condensed with benzophenone and/or alkylated with *n*-butyl bromide. The results are summarized in Table III.

TABLE III

THE CARBONYL ADDITION AND ALKYLATION REACTIONS OF THE LITHIATED *N*,*N*-DIETHYLTOLUAMIDES. COMPARISON OF THE YIELDS[a] IN ALKYLATION REACTIONS USING THE STEPWISE[b] AND DIRECT[c] METHODS

Expt	Toluamide	Lithiating reagent	Electrophile	Product	Yield, %
1	**10**	*n*-C_4H_9Li, THF 0°	$(C_6H_5)_2C{=}O$	**13**	15–25
2	**10**	$LiN[CH(CH_3)_2]_2$, THF 0°	$(C_6H_5)_2C{=}O$	**13**	50–60
3[b]	**10**	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	**16**	42
				16'	25
3'[c]	**10**	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	**16**	75
				16'	12
4	**11**	$LiN[CH(CH_3)_2]_2$, THF 0°	$(C_6H_5)_2C{=}O$	**14**	42
5[b]	**11**	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	**17**	75
5'[c]	**11**	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	**17**	75
6	**12**	$LiN[CH(CH_3)_2]_2$, THF 0°	$(C_6H_5)_2C{=}O$	**15**	28–40
7[b]	**12**	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	**18**	80
7'[c]	**12**	$LiN[CH(CH_3)_2]_2$, THF 0°	*n*-C_4H_9Br	**18**	71

[a] By glpc analysis *via* integration of peak areas. [b] Formation of lithioamide followed by treatment with 1-bromobutane. [c] Addition of base to a mixture of toluamide and 1-bromobutane.

Discussion

Both the quenching experiments (Table I) and the yields of the side-chain benzophenone adducts (Tables II and III) indicate that a greater amount of side-chain metalation is occurring in the ortho *N*,*N*-dialkyltoluamides than in either of the corresponding meta or para isomers when *n*-butyllithium is used as the lithium reagent. Furthermore, the yield of the benzophenone adduct of the *o*-toluamide was much higher when R = isopropyl (**1**) than when R = ethyl (**10**). Thus, similar to some sterically hindered ketones which do not undergo carbonyl addition reactions with *n*-butyllithium,[10] it appears that a sufficiently large *N*,*N*-dialkyl group can, at least in the ortho isomers, reduce the amount of carbonyl addition by the lithium reagent and increase the amount of side-chain metalation which occurs. Closer inspection of the data (Table II, expt 1 and 2) shows that in addition to the steric factor, the temperature at which the metalation is run also determines the reaction which occurs between the lithium butyl and the toluamide. For example, at 0° the yield of the benzophenone adduct of toluamide **1** using *n*-butyllithium as the metalating reagent was 75–85%, while at >20° the yield of the addition product under otherwise identical conditions dropped to 45–50%.

Confirmation that the steric factors do play the major role in preventing carbonyl addition is supported by the ir and nmr spectra of these toluamides and their respective benzophenone addition products. Siddall and Garner have shown that increased ortho substitution in the benzene ring attached to the carbonyl causes slower rotation about the amide bond (higher coalescence temperature).[11] That is, because of this steric inhibition of resonance, substitution decreases the effect of cross conjugation of the benzene ring with the carbonyl group, and thereby increases the double-bond character of the amide bond; note the ν O=CN< of the ortho toluamides in Table IV, especially that of benzophenone adduct **4** (ν O=CN< 1591 cm^{-1}).

In addition to these low ir absorption frequencies for the amide bond, further confirmation of the greater steric crowding in the ortho toluamides can be seen by examination of the nmr spectra of the respective toluamides. For example, the nmr study of Siddall and Garner showed two methine sets of absorptions and three methyl sets of absorptions for the *N*,*N*-diisopropyl groups in the nmr spectrum of **1** at 40°,[11] while in the present study the nmr spectrum of **4** indicates that all four methyls of the *N*,*N*-diisopropyl groups are in different chemical environments (see Experimental Section). Apparently, there is sufficient steric interaction between the *N*,*N*-diisopropyl groups and the ortho side chain substituent in **4**, owing to the reduced rotation about the carbon–nitrogen–amide bond, to hinder rotation within both *N*-isopropyl groups.

Evidence that this unusual steric interaction is a combination of the two large *N*,*N*-dialkyl groups, the ortho side-chain substituent, and the amide linkage can be seen from the following data: (1) the nmr spectra of the side-chain benzophenone adduct of *N*-isopropyl-*o*-toluamide shows a single doublet (6 H), J = 6.2 Hz, centered at δ 1.1, assigned to the two methyls of the isopropyl group; (2) the nmr spectra of the corresponding *N*,*N*-dialkyl meta and para side-chain benzophenone adducts each show a single doublet, J = 6 Hz, for all the methyls of the *N*,*N*-diisopropyl groups; (3) the nmr spectrum of the side chain benzophenone adduct of *N*,*N*-diisopropyl-*o*-toluidine at 40° shows a single doublet for all the methyls of the *N*,*N*-diisopropyl groups.

(10) (a) R. C. Fuson and J. R. Larsen, *J. Amer. Chem. Soc.*, **81**, 2149 (1959); (b) R. C. Fuson, W. C. Hammann, and P. R. Jones, *ibid.*, **79**, 928 (1957).

(11) T. H. Siddall and R. H. Garner, *Can. J. Chem.*, **44**, 2387 (1966).

TABLE IV
CARBOXAMIDE INFRARED SPECTRAL DATA[a] OF THE *N,N*-DIALKYLTOLUAMIDES

Substituent	Toluamide	R_1CH_2–C(=O)–NR'_2 cm^{-1}	Toluamide	CH_2R_1–C(=O)–NR'_2 cm^{-1}
$R' = R = C_2H_5$; $R_1 = H$	**13**	1611	**10**	1618
$R' = R = C_2H_5$; $R_1 = C(OH)(C_6H_5)_2$	**15**	1610	**4**	1595
$R = R_1 = H$; $R' = CH(CH_3)_2$				1647
$R = H$; $R_1 = C(OH)(C_6H_5)_2$; $R' = CH(CH_3)_2$				1636
$R' = R = CH(CH_3)_2$; $R_1 = H$	**3**	1623	**1**	1615
$R' = R = CH(CH_3)_2$; $R_1 = C(OH)(C_6H_5)_2$	**6**	1614	**4**	1591

[a] Data recorded on the Beckman IR-20 spectrophotometer using *ca.* 0.1 *M* chloroform solutions.

Though to a lesser extent, a similar nonequivalence in the *N,N*-dialkyl groups can be seen in the nmr spectra of toluamide **10**[11] and its side-chain benzophenone adduct **13** (see Experimental Section).

Summary

While *n*-butyllithium cannot be used as a general reagent to successfully metalate *N,N*-dialkyltoluamides, the results of this study do show that the use of lithium diisopropylamide as the metalating reagent does provide a good synthetic alternative. Though the intermediate lithiotoluamides prepared using the latter metalating reagent have been condensed only with benzophenone and alkylated only with butyl bromide, it is assumed that other electrophiles and alkylating reagents should undergo the same type of reactions with the lithiated amines.

It is also important to point out that the alkylation reactions of the respective lithiated toluamides were carried out using both a stepwise and a direct metalation procedure (see Experimental Section). The results are summarized in Tables II and III.

Both the stepwise and direct method have advantages. Somewhat higher yields of products generally resulted from the stepwise method; however, greater selective control of the product ratios was possible with the direct method by adding more alkylating reagent and base as needed.

Experimental Section

All melting points were taken in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. All boiling points are uncorrected. Infrared spectra were obtained on Perkin-Elmer Model 137 and 237 spectrophotometers and a Beckman IR-20A spectrophotometer, using potassium bromide pellets (KBr) or chloroform solutions for solids, and sodium chloride plates (neat) or chloroform solutions for liquids. Nmr spectra were obtained on a Varian T-60 spectrometer using deuteriochloroform as solvent. All chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane (TMS) standard. Gas–liquid partition chromatography (glpc) was carried out with an F & M Model 700 chromatograph, using helium as the carrier gas and a thermal conductivity detector, with 0.25 in. × 6 ft, 3% SE-30 on 60/80 Gas Chrom Q columns. The measurement of peak areas was done with a Disc integrator attached to the recorder. Measured molar response factors, determined from known mixtures of authentic materials, agreed within ±5% of the integrated peak areas. Analyses were performed by M-H-W Laboratories, Garden City, Mich. Tetrahydrofuran (THF) was freshly distilled from lithium aluminum hydride immediately before use. The *n*-butyllithium in hexane was obtained from both Foote Mineral Co., Exton, Pa., and Alfa Inorganics, Inc., Beverly, Mass., and used as supplied. The toluyl chlorides and *N,N*-diethyl-*m*-toluamide were obtained from Aldrich Chemical Co., Cedar Knolls, N. J.

The metalation reactions were done either in a 300-ml round-bottomed flask, equipped with a side arm for nitrogen inlet, or in a 500-ml round-bottomed 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 Claisen adapter. In both instances, the apparatus was predried and the reactions were performed under a positive nitrogen pressure.

Preparation of the *N,N*-Diisopropyltoluamides (1–3).—One mole of the appropriate toluyl chloride in 100 ml of THF was added at room temperature to a rapidly stirred solution of 5–6 mol of diisopropylamine in 800 ml of THF. After the suspension had been stirred for 20 min, the solid amine hydrochloride was collected by suction filtration. The THF and excess amine were removed from the filtrate under reduced pressure and the resulting crude *N,N*-diisopropyltoluamide was recrystallized twice from benzene–hexane and dried before use. The following toluamides were prepared using this procedure.

N,N-Diisopropyl-*o*-toluamide (**1**) had mp 100–102°; nmr ($CDCl_3$) δ 7.20–7.00 (m, 4 H, ArH), 3.97–3.03 (m, 2 H, NCH), 2.30 (s, 3 H, $ArCH_3$), 1.57, 1.05 (2 d, 12 H, $CHCH_3$) (see ref 11).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.58; H, 9.71; N, 6.26.

N,N-Diisopropyl-*m*-toluamide (**2**) had mp 59–61°; nmr ($CDCl_3$) δ 7.25–7.00 (m, 4 H, ArH), 3.67 (sp, 2 H, NCH), 2.35 (s, 3 H, $ArCH_3$), 1.32 (d, 12 H, $CHCH_3$).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.71; H, 9.68; N, 6.29.

N,N-Diisopropyl-*p*-toluamide (**3**) had mp 85–86°; nmr ($CDCl_3$) δ 7.20–7.00 (m, 4 H, ArH), 3.68 (sp, 2 H, NCH), 2.30 (s, 3 H, $ArCH_3$), 1.33 (d, 12 H, $CHCH_3$).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.50; H, 9.61; N, 6.31.

Preparation of the *N,N*-Diethyltoluamides (10–12).—One mole of the appropriate toluyl chloride in 100 ml of THF was added to a rapidly stirred solution (0°) of 5–6 mol of diethylamine in 800 ml of THF. After the suspension had been stirred for 20 min, the solid amine hydrochloride was collected by suction filtration. The THF and excess amine were removed from the filtrate under reduced pressure and the resulting crude *N,N*-diethyltoluamide was purified by distillation.

Using the above procedure, *N,N*-diethyl-*o*-toluamide (**10**), bp 118–120° (1.5 mm) [lit. bp 160° (24 mm)],[12] *N,N*-diethyl-*m*-toluamide (**11**), bp 94° (0.2 mm) [lit. bp 160° (19 mm)],[12] and

(12) N. N. Maxim, *Bull. Soc. Chim. Romania*, **11**, 29 (1929); *Chem. Abstr.*, **24**, 94 (1930).

N,N-diethyl-*p*-toluamide (**12**), bp 100° (0.2 mm), mp 57–58° [lit. bp 163° (17 mm)][12] were prepared. (Spectroscopic data of these ethyl toluamides corresponds to that found in ref 11.)

Metalation of *N,N*-Dialkyltoluamides Using *n*-Butyllithium in THF.—To a solution of 2.2 g (0.01 mol) of the *N,N*-diisopropyltoluamide in 150 ml of THF, precooled to 0° in an ice bath for 45–60 min, was added 8 ml (0.013 mol) of approximately 2.25 *M* *n*-butyllithium in hexane. The resulting solution was stirred for 30–60 min, then treated with either benzophenone or *n*-butyl bromide or quenched with water.

Preparation of Lithium Diisopropylamide.—To a THF solution of 2.6 g (0.026 mol) of diisopropylamine, precooled to 0°, was added 13 ml (0.026 mol) of approximately 2.0 *N* *n*-butyllithium. The resulting clear yellow solution was stirred for 30 min; it was then assumed to contain ~0.26 mol of lithium diisopropylamide.

Metalations of *N,N*-Dialkyltoluamides Using Lithium Diisopropylamide. A.—A THF solution of 4.38 g (0.02 mol) of *N,N*-diisopropyltoluamide was added dropwise to a stirred solution of 0.026 mol of lithium diisopropylamide in THF at 0°. The resulting mixture was stirred for 30–60 min and then treated with either benzophenone or *n*-butyl bromide or quenched with water.

Using this procedure the following characteristic colors were observed for the respective lithiated toluamides: ortho, deep red solution; para, deep green solution; meta, brown solution.

B.—A THF solution of 3.82 g (0.02 mol) of *N,N*-diethyltoluamide was added dropwise to a stirred solution of 0.026 mol of lithium diisopropylamide in THF at 0°. The resulting mixture was stirred for 15–90 min and then treated with either benzophenone or *n*-butyl bromide or quenched with water.

Quenching of Intermediate Lithioamides with Water or Dilute HCl.—The magnetically stirred solutions of the respective lithiotoluamides were quenched by pouring them directly onto either ice–water or equal amounts (by weight) of ice and 3 *N* HCl. The layers were separated and the aqueous layer was extracted with several 50-ml portions of ether. The combined organic layers were dried ($MgSO_4$) and then concentrated to an oil which solidified in several instances on cooling. The solids were recrystallized (benzene–hexane) and shown by mixture melting point to be recovered starting material. The oils were analyzed by glpc (Table I) and distilled under reduced pressure to give recovered toluamides and the side-chain methyl valerophenones. Using *n*-butyllithium as the lithiating reagent, the following methylvalerophenones were isolated: 2′-methylvalerophenone, bp 84° (0.6 mm) [lit. bp 97–98° (2.0 mm)];[13] 3′-methylvalerophenone, bp 85° (0.25 mm), 2,4-dinitrophenylhydrazone mp 139–140° (lit. mp 141–142°);[14] and 4′-methylvalerophenone, bp 144° (15 mm), semicarbazone mp 198–199° (lit. mp 199–201°).[15] The yields are summarized in Table I.

Condensation of the *N,N*-Diisopropyl Side Chain Lithiotoluamides with Benzophenone.—A THF solution of 4.0 g (0.022 mol) of benzophenone was added dropwise to the respective lithiated toluamide at 0°. The resulting clear yellow solution was stirred for 30 min, then inversely neutralized onto ice. Stirring was continued until the THF had evaporated, leaving a white precipitate which was filtered, weighed, and then recrystallized. The filtrate was extracted with several 50-ml portions of ether. The combined ether extracts were combined, dried ($MgSO_4$), and then concentrated to an oil which was subjected to glpc analysis.

Preparation of Carbinol Amide 4.—Using the general procedure described above, *ca.* 8 g of white solid was obtained on evaporation of the THF. Recrystallization from benzene–hexane gave 6.0–6.4 g (75–80% yield) of carbinol amide **4**, mp 159–161°. Further recrystallization from benzene–hexane gave an analytical sample: mp 161.5–162°; ir ($CHCl_3$) 1595 cm^{-1} (–NC=O); nmr ($CDCl_3$) δ 6.2–7.8 (m, 14 H, aromatic), 6.5 (s, 1 H, –OH), 3.2–4.0 [m, 3.84, $PhCH_2$ and $2HC(CH_3)_2$], 1.5 [d of d, J = 6.0 Hz, 6 H, $HC(CH_3)_2$], and 1.1 [d of d, J = 6.0 Hz, 6 H, $HC(CH_3)_2$] (see ref 11).

When this reaction was run at 15–20°, rather than at 0°, the yield of **4** dropped to ~3.9 g (~50%) crude product.

Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78; N, 3.49. Found: C, 80.68; H, 7.81; N, 3.38.

Preparation of Carbinol Amide 6.—Using the general procedure described above using *n*-butyllithium as the metalating agent, no solid product was obtained when the THF evaporated. In contrast, the reaction using $LiN(i\text{-}Pr)_2$ as the metalating reagent afforded nearly 10 g of crude brown-white solid. One recrystallization from benzene–hexane gave 6.3–7.3 g (78–93%), mp 196–198°. Further recrystallization from benzene–hexane gave an analytical sample: mp 197–198°; ir ($CHCl_3$) 1614 cm^{-1} (–NC=O); nmr ($CDCl_3$) δ 6.8–7.5 (m, 14 H, aromatic), 3.3–3.9 [m, 2 H, 2 $HC(CH_3)_2$], 3.6 (s, 2 H, $PhCH_2$–), 2.6 (s, 1 H, OH), 1.3 [d, J = 6 Hz, 12 H, 2 $HC(CH_3)_2$].

Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78; N, 3.49. Found: C, 80.83; H, 7.69; N, 3.48.

Preparation of Carbinol Amide 5.—Using the general procedure described above using only lithium diisopropylamide as the metalating agent, no solid product was obtained when THF evaporated. The resulting aqueous layer was extracted with several 50-ml portions of chloroform. The combined organic extracts were concentrated to give a yellow oil. This oil was washed with several portions of petroleum ether (bp 30–60°) at room temperature to remove excess benzophenone. Crystallization occurred after the oil was allowed to stand for several days. Two recrystallizations of the solid from benzene–hexane gave 2.0 g (12%) of white, crystalline *m*-(2-hydroxy-2,2-diphenylethyl)-*N,N*-diisopropylbenzamide (**5**): mp 160–161°; ir (KBr) 1613 cm^{-1} (–NC=O); nmr ($CDCl_3$) δ 6.7–7.6 (m, 14.3 H, aromatic), 3.78 (s, ~2 H, $PhCH_2$–), 3.2–4.0 [m, ~2 H, 2 $HC(CH_3)_2$], 2.70 (s, 1 H, –OH), 1.25 [d, J = 6 Hz, 11.9 H, 2 $HC(CH_3)_2$].

Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78; N, 3.49. Found: C, 81.07; H, 7.76; N, 3.42.

Alkylation of Lithioamide 1′ with 1-Bromobutane (Stepwise Method).—A solution containing 12 g (0.088 mol) of 1-bromobutane in 40 ml of THF was added during 30 min to a stirred solution (0°) containing 0.060 mol of lithioamide 1′. After it had been stirred for 1 hr, the yellow solution was poured on a mixture of ice and 3 *N* HCl. The layers were separated, and the aqueous layer was extracted with several 50-ml portions of chloroform. The combined extracts were concentrated to give 16.0 g of a light yellow oil. A glpc analysis of this oil indicated a ratio of toluamide **1** to two product peaks of 16:70:14.

Purification was effected by a two-step distillation. The oil was first refluxed in a 19-cm column under reduced pressure (0.2 mm). The toluamide **1** solidified at the top of the column, and refluxing was continued until a glpc analysis of the material in the distillation flask indicated that no toluamide **1** remained. Distillation of the remaining oil with a spinning-band column gave 10.1 g (62%) of colorless *N,N*-diisopropyl-*o*-pentylbenzamide (**7**), bp 108° (0.2 mm), and 1.9 g (10%) of *N,N*-diisopropyl-*o*-(1-butylpentyl)benzamide (**7′**): mp 123–125° (0.2 mm); mp 73°; ir (neat) 1629 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 7.1–7.4 (m, 3.7 H, aromatic), 3.52 and 3.75 [m, 2 H, centers of two septets of 2 $HC(CH_3)_2$], 2.65 (t, 2 H, $PhCH_2$–), 0.67–2.0 [m, ~9 H, $-(CH_2)_3CH_3$], 1.58 [d, J = 6 Hz, 12 H, 2 $HC(CH_3)_2$].

Anal. (of **7**). Calcd for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.72; H, 10.71; N, 5.14.

7 had ir (KBr) 1621 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 7.0–7.4 (m, 3.9 H, aromatic), 3.5 and 3.75 (m, 2 H, centers of two septets of 2 $HC(CH_3)_2$], 2.75 [m, 1 H, $PhHC(CH_2-)_2$], 0.3–1.9 [m, 18 H, $2-(CH_2)_3CH_3$], 1.58 [d, J = 6 Hz, 12 H, 2 $HC(CH_3)_2$].

Anal. (of **7′**). Calcd for $C_{22}H_{37}NO$: C, 79.70; H, 11.25; N, 4.23. Found: C, 79.57; H, 11.46; N, 4.16.

Alkylation of *N,N*-Diisopropyl-*o*-toluamide (1) by Metalation in the Presence of 1-Bromobutane (Direct Method).—To a stirred solution containing 2.19 g (0.010 mol) of *N,N*-diisopropyl-*o*-toluamide (**1**) and 2.05 g (0.015 mol) of 1-bromobutane in 50 ml of THF at 0° was added during 10 min 0.010 mol of lithium diisopropylamide in THF. As the base was added to the stirred solution a red color was produced, but was rapidly discharged. A glpc analysis of an acid-neutralized sample of the reaction mixture, taken 20 min after the start of the addition of base, indicated that the solution contained toluamide **1**, monoalkylation product **7**, and dialkylation product **7′** in a ratio of 17:72:11, respectively. Addition of an extra 0.005 mol of base to the reaction mixture changed this ratio (glpc) to 5:75:20.

Alkylation of Lithioamide 2′ with 1-Bromobutane (Stepwise Method).—Following the stepwise procedure outlined above,

(13) P. L. Pickard and S. H. Jenkens, Jr., *J. Amer. Chem. Soc.*, **75**, 5899 (1953).

(14) E. A. Evans, *Chem. Ind. (London)*, 1596 (1957).

(15) J. H. Simons, D. I. Randall, and S. Archer, *J. Amer. Chem. Soc.*, **61**, 1795 (1939).

a light yellow oil was isolated on concentration of the organic extracts. Purification was effected by a two-step distillation (see above), giving a 64% yield of colorless *N,N*-diisopropyl-*m*-pentylbenzamide (**8**): bp 128–130° (0.2 mm); ir (neat) 1634 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 7.15 (m, 3.8 H, aromatic), 3.7 [m, 2 H, 2 $HC(CH_3)_2$], 2.62 (t, 2 H, $PhCH_2$–), 0.43–2.3 [m, 9H, $-(CH_2)_3CH_3$], 1.3 [d, J = 6 Hz, 12 H, 2 $HC(CH_3)_2$].

Anal. Calcd for $C_{18}H_{29}NO$: C, 78.49; H; 10.61; N, 5.09. Found: C, 78.36; H, 10.74; N, 5.01.

Alkylation of *N,N*-Diisopropyl-*m*-toluamide (2) by Metalation in the Presence of 1-Bromobutane (Direct Method).—Following the direct procedure described above, the reaction mixture was stirred for 2 hr, when a glpc analysis of an acid-neutralized sample of the reaction mixture indicated that the solution contained toluamide **2** and alkylation product **8** in a ratio of 33:66. Treatment of the reaction mixture with an additional 0.0075 mol of base and 0.0075 mol of 1-bromobutane changed the ratio to 23 (**2**):77 (**8**) after 2 hr.

Alkylation of Lithioamide 3′ with 1-Bromobutane (Stepwise Method).—Using the stepwise procedure described above gave a light yellow oil, glpc analysis of which showed that it contained toluamide **3** and another component in a ratio of 6:93. Purification of this crude product using two-step distillation gave an 84% yield of colorless *N,N*-diisopropyl-*p*-pentylbenzamide (**9**): bp 130–133° (0.2 mm); ir (neat) 1629 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 7.2 (m, 3.7 H, aromatic), 3.72 [m, 2 H, 2 $HC(CH_3)_2$], 2.62 (t, 2 H, $PhCH_2$–), 0.5–2.23 [m, 9 H, $-(CH_2)_3CH_3$], 1.3 [d, J = 6 Hz, 12 H, 2 $HC(CH_3)_2$].

Anal. Calcd for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.58; H, 10.85; N, 5.06.

Alkylation of *N,N*-Diisopropyl-*p*-toluamide (3) by Metalation in the Presence of 1-Bromobutane (Direct Method).—Following the direct procedure described above, the reaction mixture was stirred for 2 hr, when a glpc analysis of an acid-neutralized sample of the reaction mixture indicated that the solution contained toluamide **3** and alkylation product **9** in a ratio of 13:87. Treatment of the reaction mixture with an additional 0.0075 mol of base and 0.0075 mol of 1-bromobutane changed this ratio to 8 (**3**):92 (**8**).

Results with *N,N*-Diethyl-*o*-toluamide (10). Neutralization of the Lithio Intermediate with H_2O–HCl.—Using the quenching procedure described above, a light orange oil was recovered when lithium diisopropylamide was used. A glpc analysis of this oil showed the ratio of toluamide **10** to a major product to be 3:95. The major product was tentatively identified by spectral evidence as 2-(*o*-*N,N*-diethylcarbamoylphenyl)-2′-methylacetophenone: ir (neat) 1635 (amide C=O), 1705 cm^{-1} (ketone C=O); nmr ($CDCl_3$) δ 8.00–6.22 (m, 7.9 H, ArH), 4.34 (s, 1.8 H, CH_2CO), 3.42, 3.25 (12 q, 4.4 H, CH_2N), 2.45 (s, 2.7 H, $ArCH_3$), and 1.02 (t, 6.3 H, $-CH_2CH_3$).

The 2,4-dinitrophenylhydrazone derivative of this keto amide was prepared according to standard procedure[16] and recrystallized twice from ethanol–ethyl acetate to give yellow solid: mp 174–176°; nmr ($CDCl_3$) 8.3–6.8 (m, 10 H, ArH), 4.03 (s, 2 H, CH_2CO), 3.52, 2.87 (2 q, 4 H, NCH_2), 2.10 (s, 3 H, $ArCH_3$), 1.02, 0.93 (2 t, 6 H, CH_2CH_3).

Anal. (of 2,4-DNP). Calcd for $C_{26}H_{27}N_5O_5$: C, 63.79; H, 5.56; N, 14.31. Found: C, 63.60; H, 5.47; N, 14.30.

Using *n*-butyllithium as the lithiating reagent gave recovered **10** and 2′-methylvalerophenone, as shown in Table I.

Condensation of the *N,N*-Diethyl Side Chain Lithiotoluamide with Benzophenone. Preparation of Carbinol Amide 13.—Using the general procedure described above for the preparation of **4**, the reaction mixture of **10′**, after the addition of benzophenone, was stirred for 1 hr, then inversely neutralized onto ice. Using lithium diisopropylamide as the metalating reagent, *ca.* 4.2 g of crude **13** was collected on filtration after the quenched reaction mixture had been heated with a benzene–hexane solution. One recrystallization from benzene–hexane (1:2) gave a 56% yield of **13**, mp 135–136°.

Using *n*-butyllithium as the metalating reagent, the yield of carbinol amide **13** was reduced to *ca.* 20%: ir ($CHCl_3$) 1611 cm^{-1} (–NC=O); nmr ($CDCl_3$) δ 6.2–7.7 (m, 14 H, aromatic), 6.45 (s, 1 H, OH), 3.6 (s, 1.9 H, $PhCH_2$–), 3.2 and 3.57 (q, J = 7.5 Hz, ~2 H, centers of two overlapping "q" of the 2 $>NCH_2CH_3$), 1.08 and 1.2 (t, J = 7.5 Hz, 3 H, centers of two overlapping "t" of the two, $>NCH_2CH_3$) (see ref 11).

Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.39; H, 7.29; N, 3.75. Found: C, 80.25; H, 7.40; N, 3.48.

Alkylation of Lithioamide of 10 (Stepwise Method).—Following the stepwise procedure described above, a yellow oil was isolated on concentration of the dried organic extracts. A glpc analysis of this oil indicated that the ratio of recovered toluamide **10** to two product peaks was 33:42:25.

Distillation of this oil at reduced pressure with a spinning-band column gave 5.8 g (38%) of colorless *N,N*-diethyl-*o*-pentylbenzamide (**16**), bp 102–104° (0.2 mm), and 3.5 g (20%) of colorless *N,N*-diethyl-*o*-(1-butylpentyl)benzamide (**16′**): bp 123° (0.2 mm); ir (neat) 1631 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 6.9–7.2 (m, 4 H, aromatic), 3.08 and 3.53 (q, 2 H, centers of two overlapping "q" of the 2 $>NCH_2CH_3$), 2.6 (t, 2 H, $PhCH_2$–), 0.7–2.0 (m, 14.8 H, $(CH_2)_3CH_3$ and 2 $>NCH_2CH_3$).

Anal. (of **16**). Calcd for $C_{18}H_{29}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.75; H, 10.46; N, 5.84.

16 had ir (neat) 1637 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 7.0–7.5 (m, 4 H, aromatic), 2.5–4.2 [m, 5 H, $PhHC(CH_2)_2$ and 2 amido methylenes], 0.6–2.0 [m, 24 H, two $-(CH_2)_3CH_3$ and two NCH_2CH_3].

Anal. (of **16′**). Calcd for $C_{29}H_{33}NO$: C, 79.15; H, 11.14; N, 4.62. Found: C, 79.14; H, 11.14; N, 4.82.

Alkylation of *N,N*-Diethyl-*o*-toluamide by Metalation in the Presence of 1-Bromobutane (Direct Method).—To a stirred solution containing 1.91 g (0.010 mol) of *N,N*-diethyl-*o*-toluamide and 2.05 g (0.015 mol) of 1-bromobutane in 50 ml of THF at 0° was added during 10 min 0.010 mol of lithium diisopropylamide in THF. A red color was produced as the base was added to the stirred solution, but was rapidly discharged. A glpc analysis of an acid-neutralized sample of the reaction mixture, taken 20 min after the start of the addition of base, indicated that the solution contained toluamide **10**, monoalkylation product **16**, and dialkylation product **16′** in a ratio of 13:75:12, respectively. Treatment of the reaction mixture with an additional 0.005 mol of base changed this ratio to 2:76:22 after 10 min.

Results with *N,N*-Diethyl-*m*-toluamide (11). Neutralization of the Lithio Intermediate(s) with H_2O–HCl.—Using the quenching procedure described above, an orange oil was recovered when lithium diisopropylamide was used. A glpc analysis of this oil showed the ratio of toluamide **11** to the product peak to be 3:97. Distillation of the oil gave 8.0 g (86%) of 2-(*m*-*N,N*-diethylcarbamoylphenyl)-3′-methylacetophenone: bp 190° (0.25 mm); ir (neat) 1621 (amide C=O), 1675 cm^{-1} (ketone C=O); nmr ($CDCl_3$) δ 8.12–7.03 (m, 8 H, ArH), 4.23 (s, 2 H, CH_2CO), 3.35 (q, 4 H, NCH_2), 2.32 (s, 3 H, $ArCH_3$), 1.10 (t, 6 H, CH_2CH_3).

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.48; H, 7.51; N, 4.61.

Using *n*-butyllithium as the lithiating reagent gave recovered **11** and 3′-methylvalerophenone, as shown in Table I.

Condensation of the Lithio Intermediate with Benzophenone. Preparation of Carbinol Amide 14.—A solution of 14.56 g (0.080 mol) of benzophenone in 50 ml of THF was added during 15 min to a stirred solution (0°) of the lithio intermediate. Normal work-up of the reaction mixture gave a yellow oil which was dissolved in benzene. Crystallization occurred after the solution was allowed to stand for several days and 8.5 g (42%) of a white, crystalline solid was collected. Two recrystallizations from benzene gave an analytical sample of *m*-(2-hydroxy-2,2-diphenylethyl)-*N,N*-diethylbenzamide (**14**): mp 181–183°; ir (KBr) 1618 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 6.8–7.7 (m, 13.9 H, aromatic), 3.62 (s, 2 H, $PhCH_2$), 2.9–3.65 (broad m, 3.9 H, overlapping amido methylenes), 2.62 (s, 1 H, –OH), 1.07 (t, 6.1 H, two NCH_2CH_3).

Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.39; H, 7.29; N, 3.75. Found: C, 80.20; H, 7.29; N, 3.58.

Alkylation of the Lithio Intermediate with 1-Bromobutane (Stepwise Method).—Following the stepwise procedure described above, the reaction mixture was stirred for 9 hr at room temperature, quenched, and then worked up to give a yellow oil. A glpc analysis of this oil showed that it contained toluamide **11** and one other peak in a ratio of 25:75. Distillation of the oil gave 8.8 g (60%) of colorless *N,N*-diethyl-*m*-pentylbenzamide (**17**): bp 121–122° (0.2 mm); ir (neat) 1634 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 7.18 (m, 3.8, aromatic), 3.38 (q, J = 7.5 Hz, 4 H, two N-CH_2CH_3), 2.63 (t, J = 7.0 Hz, 2.1 H, $PhCH_2$–), 0.5–2.3 [m, 15.2 H, $-(CH_2)_3CH_3$ and two $>NCH_2CH_3$].

(16) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1965, p 253.

Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.50; H, 10.38; N, 5.56.

Alkylation of *N,N*-Diethyl-*m*-toluamide (11) by Metalation in the Presence of 1-Bromobutane (Direct Method).—A solution of 0.040 mol of lithium diisopropylamide was added during 10 min to a stirred solution (0°) of 5.74 g (0.030 mol) of *N,N*-diethyl-*m*-toluamide (11) and 5.48 g (0.040 mol) of 1-bromobutane in 50 ml of THF. After it had been stirred for 3 hr, a glpc analysis of an acid-neutralized sample of the reaction mixture indicated the presence of toluamide **11** and alkylation product **17** in a ratio of 25:75.

Results with *N,N*-Diethyl-*p*-toluamide (12). Neutralization of the Lithio Intermediates with H_2O–HCl.—Using the quenching procedure described above, a copious white precipitate formed immediately when lithium diisopropylamide was employed. The solvents were removed from the mixture at reduced pressure, and the white solid was collected by vacuum filtration. The filter cake was broken up and stirred with H_2O for 5 min, and the white solid was again collected by vacuum filtration. The solid was extracted with two 200-ml portions of benzene to remove the lower molecular weight components of the mixture. After removal of the solvent, the benzene fraction gave 2.7 g of white solid. Sublimation of the solid (100°, 0.2 mm) gave 1.4 g (30%) of white, crystalline 2-(*p*-*N,N*-diethylcarbamoylphenyl)-4′-methylacetophenone: mp 110–112°; ir (KBr) 1623 (amide C=O), 1675 cm^{-1} (ketone C=O); nmr ($CDCl_3$) δ 8.17–6.90 (m, 8 H, ArH), 4.30 (s, 2 H, CH_2CO), 3.40 (q, 4 H, NCH_2), 2.38 (s, 3 H, $ArCH_3$), 1.13 (t, 6 H, CH_2CH_3).

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.78; H, 7.59; N, 4.42.

After sublimation of the monoself-condensation product, the remaining solid was recrystallized twice from acetone to give 0.9 g (21%) of white crystalline 2-(*p*-*N,N*-diethylcarbamylphenyl)-4′-(*p*-methylphenacyl)acetophenone: mp 166–169°; ir (KBr) 1629 (amide C=O), 1678 cm^{-1} (ketone C=O); nmr (acetone-d_6) δ 8.22, 7.12 (m, 12 H, ArH), 4.47, 4.40 (2 s, 4 H, CH_2CO), 3.38 (q, 4 H, NCH_2), 2.40 (s, 3 H, $ArCH_3$), 1.10 (t, 6 H, CH_2CH_3); mass spectrum M^+ *m/e* 427.

Anal. Calcd for $C_{28}H_{29}NO_3$: C, 78.66; H, 6.84; N, 3.28; *m/e* 427.2147. Found: C, 78.78; H, 6.71; N, 2.94; *m/e* 427.2150.

Using *n*-butyllithium as the lithiating reagent gave recovered **12** and 4′-methylvalerophenone as shown in Table I.

Condensation with Benzophenone. Preparation of Carbinol Amide 15.—Using the general procedure described above for the preparation of **4**, the reaction mixture of **12′**, after the addition of benzophenone, was stirred for 45 min, then inversely neutralized onto ice. Using lithium diisopropylamide as the metalating reagent, 2.3–3.0 g of crude **15** were collected on filtration after the quenched reaction mixture had been heated with a benzene–hexane solution. Recrystallization from benzene–hexane (1:2) gave a 28–40% yield of **15**, mp 153–154°.

Using *n*-butyllithium as the metalating reagent, no carbinol amide **15** was isolated.

15 had ir ($CHCl_3$) 1610 cm^{-1} (–NC=O); nmr ($CDCl_3$) 6.8–7.5 (m, 14 H, aromatic), 3.69 (s, 2 H, $PhCH_2$–), 3.0–3.55 (broad m, 3.9 H, two NCH_2CH_3), 2.8 (s, 0.9 H, OH), 1.1 (t, 6 H, J = 7 Hz, two NCH_2CH_3).

Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.39; H, 7.29; N, 3.75. Found: C, 80.52; H, 7.32; N, 3.52.

Alkylation of the Lithio Intermediates with 1-Bromobutane (Stepwise Method).—Following the stepwise procedure described above, the reaction mixture was stirred for 6 hr at room temperature, quenched, and then worked up to give a yellow oil. A glpc analysis of this oil indicated that the ratio of toluamide **12** to a product peak was 20:80.

Distillation of the oil at reduced pressure gave 9.8 g (66%) of colorless *N,N*-diethyl-*p*-pentylbenzamide (**18**): bp 121° (0.2 mm); ir (neat) 1629 cm^{-1} (>NC=O); nmr ($CDCl_3$) δ 7.0–7.5 (m, 3.8 H, aromatic), 3.35 (q, J = 7.5 Hz, 4 H, NCH_2CH_3), 2.6 (t, J = 7 Hz, 2 H, $PhCH_2$–), 0.62–2.1 (m, 15.2 H, $-(-CH_2-)_3CH_3$ and NCH_2CH_3).

Anal. Calcd for $C_{15}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.89; H, 10.40; N, 4.89.

Alkylation of *N,N*-Diethyl-*p*-toluamide by Metalation in the Presence of 1-Bromobutane (Direct Method).—To a stirred solution containing 1.91 g (0.010 mol) of *N,N*-diethyl-*p*-toluamide (**12**) and 2.05 g (0.015 mol) of 1-bromobutane in 50 ml of THF at 0° was added during 10 min 0.010 mol of lithium diisopropylamide. After the solution had been stirred for 1 hr a glpc analysis of an acid-neutralized sample showed that the reaction mixture contained toluamide **12** and alkylation product **18** in a ratio of 29:71.

Registry No.—**1**, 6641-72-1; **2**, 5448-36-2; **3**, 6937-52-6; **4**, 38630-83-0; **5**, 38630-83-0; **6**, 38630-85-2; **7**, 38630-86-3; **7′**, 38630-87-4; **8**, 38630-88-5; **9**, 38630-89-6; **10**, 2728-04-3; **11**, 134-62-3; **12**, 2728-05-4; **13**, 38631-12-8; **14**, 38631-13-9; **15**, 38631-14-0; **16**, 38631-15-1; **16′**, 38631-16-2; **17**, 38631-17-3; **18**, 38631-18-4; *n*-butyllithium, 109-72-8; lithium diisopropylamide, 4111-54-0; *o*-toluyl chloride, 933-88-0; *m*-toluyl chloride, 1711-06-4; *p*-toluyl chloride, 874-60-2; diisopropylamine, 108-18-9; diethylamine, 109-89-7; benzophenone, 119-61-9; 1-bromobutane, 109-65-9; 2-(*O-N,N*-diethylcarbamaylphenyl)-2′-methylacetaphenone, 38631-19-5, 38631-20-8 (2,4-DNPH); 2-(*m*-*N,N*-diethylcarbamoylphenyl)-3′-methylacetophenone, 38631-21-9; 2-(*p*-*N,N*-diethylcarbamoylphenyl)-4′-methylacetophenone, 38631-22-0; 2-(*p*-*N,N*-diethylcarbamoylphenyl)-4′-(*p*-methylphenacyl)acetophenone, 38631-23-1.