17827-41-7; XXIIc, 17827-42-8; XXIIa, 17827-43-9; XXIId, 17827-44-0; XXIIe, 17827-45-1; XXIII, 17827-56-4; XXVI, 17827-46-2; XXVIII, 17827-47-3; XXIX, 17827-48-4; XXXI, 2397-62-8; 2-methyl-2-(2-methyl-1-propenyl)-1,4-naphthalenediol diacetate, 17827-58-6; XXXIIa, 17827-59-7; XXXIIb (*cis*), 17831-10-6; XXXIIb (*trans*), 17831-11-7; XXXIIc (*cis*), 17831-12-8; XXXIIc (*trans*), 17831-13-9; 2-pentyltriphenylphosphonium bromide, 17827-53-1; 3-pentyltriphenylphosphonium bromide, 7333-53-1; XXXIIe, 17827-51-9; XXXIIf (*cis*), 17831-25-3; XXXIIf (*trans*), 17831-15-1; 2-octanone-1,1,1,3,3-d_5, 17827-52-0; XXXIIg (*cis*), 17831-26-4; XXXIIg (*trans*), 17831-27-5; 1,4-dihydroxy-α,2-dimethyl-3-naphthaleneacrylic acid δ-lactone 1-propionate, 17838-75-4; 1,4-dihydroxy-α,2-naphthaleneacrylic acid δ-lactone, 17838-76-5; XXXIIIa (*cis*), 17831-16-2; XXXIIIa (*trans*), 17831-17-3; XXXIIIb (*cis*), 17831-18-4; XXXIIIb (*trans*), 17831-19-5; XXXIIIc, 17827-50-8; XXXIIId (*cis*), 17831-09-3; XXXIIId (*trans*), 17831-08-2; XXXIIIe (*cis*), 17838-74-3; XXXIIIe (*trans*), 17831-14-0; XXXIV chloride, 17866-64-7; XXXVII, 17827-55-3; XXXIX, 17831-20-8; XL, 17831-21-9; XLI, 17831-22-0; XLII, 17831-24-2; XLIII, 17831-23-1

N-Alkyl Substituents as Competition Reaction Sites in the α Alkylation of Tertiary Amines[1a]

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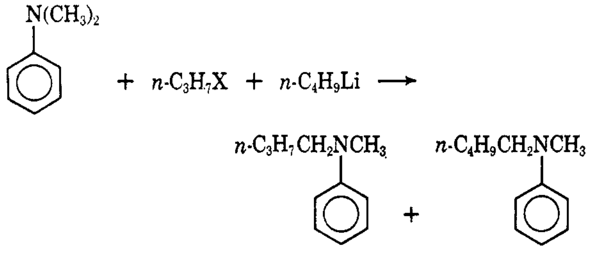
The direct α butylation of tertiary amines with *n*-butyllithium and 1-iodobutane was investigated by inter- and intramolecular competition reactions. Structure changes at the α position in the reacting amine were used as the competition variables. The intermolecular competition of N,N-dimethylaniline with N,N-diethylaniline, N-methyldiphenylamine, N-methyl-N-ethylaniline, triethylamine, or triethylenediamine showed that reactivity per α hydrogen was significantly greater for methyl than for ethyl groups. This effect of alkyl structure was much greater than the conjugative or resonance effects caused by increasing or decreasing the number of aromatic rings attached to nitrogen. Intramolecular competition in N-methyl-N-ethylaniline and in N-methyl-N-(2-butyl)aniline extended the reactivity order to methyl > ethyl > *sec*-butyl or primary > secondary > tertiary. The quantitative alkyl reactivity ratios closely parallel hydrocarbon acidities and σ^* values for cumulative inductive effects. A model is therefore suggested for the reaction transition state which is compatible with previous α alkylation results and with two other simultaneously occurring reactions, halogen–metal interchange and Wurtz coupling.

The direct α-carbon alkylation of tertiary amines takes place when these amines are used as solvents for the reaction of organolithium reagents with alkyl or aryl halides[2] (eq 1). Either the bromo- or iodoalkanes



(1)

will participate in the reaction, but the former are less reactive while the latter also undergo extensive halogen-metal interchange.[3]

Trialkylamines[4] as well as N-alkylanilines[2,3,5] can undergo substitution. However, the reaction is limited to an α-alkyl position as demonstrated with triethylamine[4] and N,N-diethylaniline.[5]

These observations seemed to be in agreement with a simple mechanism involving metalation of the amine at an α-alkyl site followed by a "Wurtz" coupling with the available halide. Metalation studies of both N,N-dimethylaniline[6] and triethylamine[4] failed to confirm such a pathway, although the aniline reactivity was in reasonable agreement with hydrogen–deuterium exchange data.[7] A second route for product formation, amine quaternization with a subsequent Stevens rearrangement, was also eliminated in these same studies.

Although the reaction is described as a *direct* α alkylation because of the initial lack of a cogent mechanism, it seemed desirable to attempt to clarify this situation. Since steric effects and the relative reactivity of alkyl groups are closely related in many cases to the type of species involved as intermediates or in transition states, we have investigated the competition of α reaction sites in direct alkylation of tertiary amines. In order to ascertain comparability of steric factors as well as group reactivity, both inter- and intramolecular competition reactions were considered.

Results

The direct α-substitution reaction of tertiary amines was carried out on compounds or mixtures of compounds in which two nonequivalent positions were available for competitive alkylation. *n*-Butyllithium and 1-iodobutane were used so that the alkyl group

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[1] (a) Presented in part before the Division of Organic Chemistry, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, Abstracts S161; A. R. Lepley and W. A. Khan, *Chem. Commun.*, 1198 (1967). This work was supported by U. S. Public Health Grants GM-09136 and GM-13987 from the National Institute of General Medical Sciences. (b) Department of Chemistry, Marshall University, Huntington, W. Va. (c) Department of Chemistry, Queen's University of Belfast, Belfast 9, Northern Ireland.

[2] A. R. Lepley and A. G. Giumanini, *Chem. Ind.* (London), 1035 (1965).

[3] A. R. Lepley and W. A. Khan, *J. Org. Chem.*, **31**, 2064 (1966).

[4] A. R. Lepley and W. A. Khan, *ibid.*, **31**, 2061 (1966).

[5] A. R. Lepley and A. G. Giumanini, *ibid.*, **31**, 2055 (1966).

[6] A. R. Lepley, W. A. Khan, A. B. Giumanini, and A. G. Giumanini, *ibid.*, **31**, 2047 (1966).

[7] A. I. Shatenshtein and Y. I. Ranneva, *J. Gen. Chem. USSR*, **31**, 1317 (1961).

substituting for an α hydrogen was limited to butyl in all reactions; *cf.* eq 1. Gas chromatography (gc) of the ice-quenched reaction mixtures was used to determine product retention ratios and to isolate preparative samples. The gc data were compared with retention ratio values of available or independently synthesized compounds to establish tentative product identifications, Table I. The final product structural assignments were based on the infrared spectra and proton magnetic resonance (pmr) chemical shifts, Table II, of the materials separated by preparative gc. The quantitative evaluation of relative and absolute product yields was made by gc, using an internal standard method,[8] and from pmr integral ratios, Table III.

TABLE I

GAS CHROMATOGRAPHIC RETENTION RATIOS[a] OF REACTANTS, PRODUCTS, AND STANDARDS IN THE INTER- AND INTRAMOLECULAR COMPETITIVE TERTIARY AMINE α-ALKYLATION REACTIONS

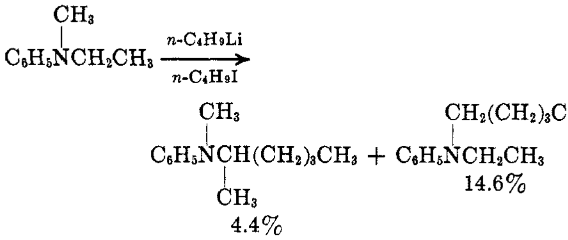
	Retention ratios		
	Calibration, deg		Reaction
Compound	100	185	products
Triethylamine	0.194		
Octane	0.400		0.402
Aniline[b]	1.000[c]		
N,N-Diethyl-2-hexylamine	1.42		1.42
N,N-Dimethylaniline	2.04	0.146	
N-Methyl-N-ethylaniline		0.194	
N,N-Diethylaniline		0.208	
N-Methyl-N-(2-butyl)aniline		0.330	
N-Methyl-N-(1-pentyl)aniline		0.524	0.525
N-Ethyl-N-(1-pentyl)aniline		0.615	0.618
N-Methyl-N-(2-hexyl)aniline		0.622	0.618
N-Ethyl-N-(2-hexyl)aniline[d]		0.694	0.695
N-Methyldiphenylamine		0.946	
N-(2-Butyl)-N-(1-pentyl)aniline		0.961	0.959
Benzhydryldimethylamine[b]		1.00[e]	
o-(Diethylamino)biphenyl[d]		1.27	
N-(1-Pentyl)diphenylamine		2.70	2.73

[a] 0.25 in. × 10 ft column of 20% GE-SF96 on 40–60 mesh Chromosorb W, 160–170 cc/min of He flow at indicated temperatures; retention ratio variation ±0.2–1% of reported values. [b] Standard for quantitative analysis. [c] Standard for retention ratio at 100°; retention time, 9.1 ± 0.4 min; peak width at half-height, 0.86 ± 0.03 min. [d] Alternate standards for quantitative analysis and retention ratios; values measured with respect to these compounds are scaled to benzhydryldimethylamine as a primary standard. [e] Standard for retention ratio at 185°; retention time, 14.6 ± 0.7 min; peak width at half-height, 1.07 ± 0.05 min.

The several tertiary amines needed for product identification were synthesized in 30–40% yield by the reaction of a secondary amine and an alkyl halide. N-Methylaniline reacted with 2-bromobutane or 2-bromohexane to form N-methyl-N-(2-butyl)aniline[9] and N-methyl-N-(2-hexyl)aniline, respectively. N-Ethyl-N-(1-pentyl)aniline was prepared from N-ethylaniline and 1-bromopentane, while the more sterically hindered N-(2-butyl)-N-(1-pentyl)aniline was formed from N-(2-butyl)aniline and 1-bromopentane.

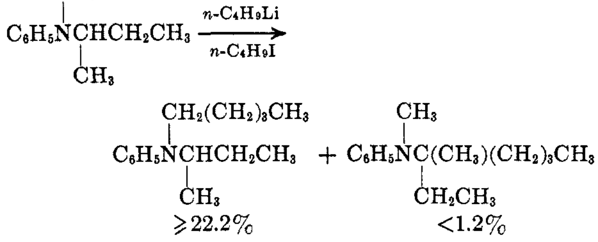
Intermolecular competition in the α-alkylation reaction was run with a mixture of N,N-dimethylaniline and of an equimolar amount of a second tertiary amine acting as the solvent and reactants, Table III. The gc of the reaction mixture showed two products in all cases except that of triethylenediamine, where only the product of N,N-dimethylaniline butylation was observed. Gc retention ratios on these products were generally adequate for identification as confirmed by the infrared and pmr spectra. However, with N-methyl-N-ethylaniline, the isomeric products were not separated but their distribution was determined by pmr analysis of the product from the intermolecular competition reactions; see below. The over-all yields of α-tertiary amine alkylation were determined by comparison with a known amount of added gc standard. The relative amounts of the competition products were determined by the ratios of peak areas. All data were reduced to absolute yields and compared both on the basis of products from each amine and in terms of the number of α protons for the individual reactants, Table III.

Intramolecular competition reactions were carried out with N-methyl-N-ethylaniline or N-methyl-N-(2-butyl)aniline. In both cases only a single peak for products was evident from gc. As before, no other peaks were evident from other reactions with the amine nor was there a multiplicity of peaks in the region of interest. Thus the product mixture was readily collected. In the case of N-methyl-N-ethylaniline (eq 2), the difference in retention ratios for N-methyl-N-(2-hexyl)aniline and N-ethyl-N-(1-pentyl)aniline was much less than that required for peak resolution;[3] *cf.* Table I. However, quantitative analysis of the two product mixture was possible by pmr or preparative gc samples. The methyl and methine on nitrogen peaks of the first of the compounds was adequately separated from the overlapping methylene on nitrogen bands of the second to give readily determined integral ratios which allowed calculation of the yields.



$$C_6H_5\overset{\overset{CH_3}{|}}{N}CH_2CH_3 \xrightarrow[n\text{-}C_4H_9I]{n\text{-}C_4H_9Li} \underset{4.4\%}{C_6H_5\overset{\overset{CH_3}{|}}{N}\underset{\underset{CH_3}{|}}{C}H(CH_2)_3CH_3} + \underset{14.6\%}{C_6H_5\overset{\overset{CH_2(CH_2)_3CH_3}{|}}{N}CH_2CH_3} \quad (2)$$

N-Methyl-N-(2-butyl)aniline gave predominantly N-(2-butyl)-N-(1-pentyl)aniline on α alkylation, eq 3.



$$C_6H_5\overset{\overset{CH_3}{|}}{N}\underset{\underset{CH_3}{|}}{C}HCH_2CH_3 \xrightarrow[n\text{-}C_4H_9I]{n\text{-}C_4H_9Li} \underset{\geqslant 22.2\%}{C_6H_5\overset{\overset{CH_2(CH_2)_3CH_3}{|}}{N}\underset{\underset{CH_3}{|}}{C}HCH_2CH_3} + \underset{<1.2\%}{C_6H_5\overset{\overset{CH_3}{|}}{N}\underset{\underset{CH_2CH_3}{|}}{C}(CH_3)(CH_2)_3CH_3} \quad (3)$$

The over-all yield of products was 23.4% for the reaction. Qualitative features of the pmr and ir spectra from preparative gc samples were essentially identical with those of N-(2-butyl)-N-(1-pentyl)aniline except for a very weak pmr singlet at 2.65 ppm. Such a pmr singlet is characteristic[10] of a NCH_3 group on an aniline with steric inhibition of conjugation

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(8) A. R. Lepley, *Anal. Chem.*, **34**, 2365 (1962).

(9) T. C. van Hoek, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.*, **77**, 559 (1958).

(10) A. R. Lepley and V. C. Dohm, *Proc. W. Va. Acad. Sci.*, **39**, 382 (1967).

TABLE II

PROTON MAGNETIC RESONANCE SPECTRA OF TERTIARY AMINES ASSOCIATED WITH THE INTER- AND INTRAMOLECULAR COMPETITIVE α-ALKYLATION REACTIONS

		Chemical shift^a							
		CH_3		CH_2			CH		H
Compound	Registry no.	C	NAr	C, C	C, N	C, NAr	C, C, N	C, CN	ArN Ar
N-(2-Butyl)-N-(1-pentyl)aniline	17692-89-6	1.11 m (16)^b		1.11 m (16)^b		3.05 m (2)		3.71 q^c (1)	6.69 m (3) 7.14 m (2)
N,N-Diethylaniline	91-66-7	1.08 t (6)				3.21 q (4)			6.53 m (3) 7.01 m (2)
N,N-Dimethylaniline	121-69-7		2.78 s (6)						6.61 m (3) 7.09 m (2)
N,N-Diethyl-2-hexylamine	17692-90-9	0.97 t 1.05 m (18)^b		1.05 m (18)^b	2.41 m (5)^e		2.41 m (5)^e		
N-Ethyl-N-(2-hexyl)aniline	3299-40-9	1.10 t 1.15 m (15)^b		1.15 m (15)^b		3.16 q (2)		3.7 m (1)	6.62 m (3) 7.03 m (2)
N-Ethyl-N-(1-pentyl)aniline	17693-26-4	1.08 t 1.17 m (12)^b		1.17 m (12)^b		3.28 q 3.18 m (4)^d			6.59 m (3) 7.08 m (2)
N-Methyl-N-(2-butyl)aniline	17693-27-5	1.02 m (8)^b	2.61 s (3)	1.01 m (8)^b				3.71 q^c (1)	6.66 m (3) 7.07 m (2)
N-Methyldiphenylamine	91-00-9		3.16 s (3)						6.96 m (10)
N-Methyl-N-ethylaniline	613-97-8	1.05 t (3)	2.78 s (3)			3.29 q (2)			6.60 m (3) 7.09 m (2)
N-Methyl-N-(2-hexyl)aniline	17693-29-7	1.10 m (12)^b	2.59 s (3)	1.10 m (12)^b				3.78 m (1)	6.63 m (3) 7.05 m (2)
N-Methyl-N-(1-pentyl)aniline	3299-39-6	1.30 m (9)^b	2.82 s (3)	1.30 m (9)^b		3.21 t (2)			6.58 m (3) 7.06 m (2)
Triethylamine	121-44-8	0.93 t (9)			2.43 q (6)				
Triethylenediamine	280-57-9				2.60 s (12)				

^{a} All shifts are δ values relative to tetramethylsilane in parts per million (ppm); splitting, s singlet, t triplet, q quartet, m multiplet; J values are 6.9 ± 0.1 cps unless otherwise indicated; values in parentheses are relative integrated peak ratios in compound. ^{b} Total of CH_3 and CH_2 protons attached only to other carbon atoms in particular compound. ^{c} Probably sextet inadequately amplified, more complex splitting not evident. ^{d} Total of all CH_2 protons attached to NAr in a particular compound. ^{e} Total of all CH_2 and CH proton attached to N of aliphatic amine; *cf.* ref 4.

TABLE III

INTERMOLECULAR COMPETITION IN α BUTYLATION OF N,N-DIMETHYLANILINE WITH OTHER TERTIARY AMINES

		Competition product yields				Yield/α-H		
Competing amine	Over-all % yield	% A^a	% B^b	Ratio of B/A	α-H in B,^{b} N	% A/6	% B/N	Ratio of (B/N)/(A/6)
Triethylenediamine (TED)	5.8	5.8	<0.1		12	0.97		
Triethylamine	22.0	13.1	8.9	0.69	6	2.2	1.5	0.68
N,N-Diethylaniline	21.1	15.2	5.9	0.39	4	2.5	1.5	0.58
N-Methyl-N-ethylaniline	31.0	18.8	12.2^c	0.65	5	3.1	2.4	0.78
N-Methyldiphenylamine	29.6	19.5	10.1	0.52	3	3.3	3.4	1.04

^{a} A, N-methyl-N-(1-pentyl)aniline from reaction with N,N-dimethylaniline. ^{b} B, product from reaction with the competing amine. ^{c} N-Ethyl-N-(1-pentyl)aniline plus N-methyl-N-(2-hexyl)aniline; relative amounts of the two products were determined in intramolecular competition experiments; see text.

between nitrogen and the aromatic ring. Although we were unsuccessful in attempts to synthesize N-methyl-N-(3-methyl-3-heptyl)aniline, the pmr band at 2.65 ppm was quite reasonable for this product. Further support of this assignment was seen in the 2.61-ppm location for the NCH_3 singlet of N-methyl-N-(2-butyl)aniline, which was absent in the separated products as determined by gc. Analysis of the pmr integrals for the products indicated a maximum possible yield of 1.2% for N-methyl-N-(3-methyl-3-heptyl)-aniline which corresponded to a minimum of 22.2% for N-(2-butyl)-N-(1-pentyl)aniline.

The several intramolecular competition yields were converted to a comparable scale by dividing the yields by the number of α hydrogens per group and normalizing them with respect to the methyl hydrogen value. This gave the relative values 1.0, 0.45, and <0.16 for the methyl, ethyl, and *sec*-butyl groups, respectively.

Discussion

Several factors influencing the α alkylation of tertiary amines were apparent from the chosen set of compounds for inter- and intramolecular competition. These include group reactivity at the α position, steric effects in this position and in the tertiary amine as a whole, and conjugative effects on the amine nitrogen. These qualitative and quantitative factors and the mechanisms of analogous reactions aided in the formulation of a model for the transition state of α-amine alkylation. In particular, comparisons of measured yields were made with the ease of carbanion formation from hydrocarbons and with carbene insertion selectivity on hydrocarbons. These results, in conjunction with reaction routes in metalation, Wurtz coupling, and halogen–metal interchange were used in model development.

Complexes readily form between tertiary amines and organolithium reagents.[11] The insolubility of the triethylenediamine–*n*-butyllithium complex[12] probably accounts for the very low yields in the competition reaction involving this amine.

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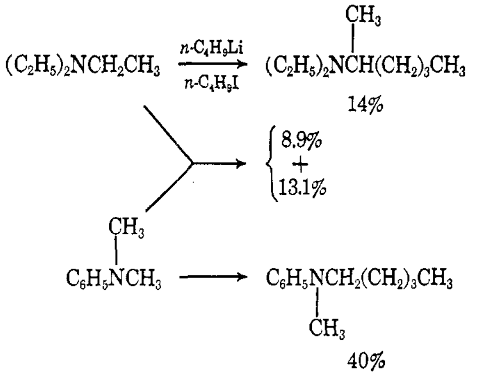
(11) J. F. Eastham and G. W. Gibson, *J. Amer. Chem. Soc.*, **85**, 2171 (1963); Z. K. Cheema, G. W. Gibson, and J. F. Eastham, *ibid.*, **85**, 3517 (1963); F. A. Settle, M. Hagerty, and J. F. Eastham, *ibid.*, **86**, 2076 (1964); T. L. Brown, R. L. Gerteis, D. A. Bafus, and J. A. Ladd, *ibid.*, **86**, 2135 (1964).

(12) C. G. Screttas and J. F. Eastham, *ibid.*, **87**, 3276 (1965).

Triethylamine alone[4] undergoes α alkylation much less readily than dimethylaniline,[5] eq 4. The larger value for competition may well be associated with the milder reaction in dialkylanilines[3,5] than in triethylamine, where significantly higher yields, up to 25%, were achieved when lower temperatures were used to control the vigorous initial reaction.[4]



(4)

A comparison of compounds with equal numbers of ethyl and methyl groups as in N,N-diethylaniline and N,N-dimethylaniline decreased the ratio of A/B seen with triethylamine by 0.30. This change was small with respect to the exponentially related effect in steric requirements with thermodynamic stabilities in going from an ethyl to a phenyl group.[13] A distinct major variation normally observed in conjunction with these two groups is decreased basicity with conjugation. A factor of 6 decrease in pK_b occurs when going from a trialkylamine to the comparable dialkylaniline.[14] The availability of the lone pair on nitrogen is directly associated with organolithium–amine complex formation. Participation of base in related organometallic reactions including Wurtz coupling has recently been reported in tetrahydrofuran solutions involving an RLi–solvent complex.[15] The extent of structural effects on complexes or other reaction intermediates should be clearly distinguishable from normal statistical variations in the number of each type of reaction site as given by the yield per equivalent α hydrogen; see Table III.

Methyl group reactivity with structure variation was evident from the methyldiphenylamine and dimethylaniline competition. The yields per α hydrogen were within 0.1. In the range 3.3–3.4, this represents 3% which is comparable with the gc reproducibility and hence the optimum precision. It should be noted, however, that a 1:1 reactivity ratio occurred in this case where a pK_b decrease from phenyl to diphenyl is to the order of 4.[16]

Yields per α hydrogen for N,N-diethylaniline and triethylamine remained significantly lower than the competitive methyl results. The normalized ratio displayed an increased reactivity for the all alkyl compound.

Intramolecular competition in N-methyl-N-ethylaniline helped to place the intermolecular competition of this compound with dimethylaniline in perspective, eq 2. The ratio of reaction, although similar to the previous B/A value, was slightly less than that of diethylaniline *vs.* dimethylaniline. Reduction of these values to the per cent α H gave 2.5 and 1.1 for methyl and ethyl, respectively.[17] Both these absolute ethyl and methyl yields and their ratio, B/A = 0.45, were lower than in the intermolecular experiments. Application of the intramolecular reaction distribution to the intermolecular competition with dimethylaniline gave the distribution from N-methyl-N-ethylaniline alone of % B/N as 3.1 on methyl and 1.4 on ethyl. Since a 3.1% A/6 value for dimethylaniline was also obtained in this experiment, a 1:1 ratio for methyl group reactivity in the two compounds was maintained and ethyl results were consistent with other ethyl substituted compounds.

The 2-butyl group was compared only in intramolecular competition, eq 3. Per cent yield per α hydrogen for the methyl group in this case gave B/3 of 3.7.[17] The very low value for the 2-butyl group might be cause for suggesting appreciable steric hindrance at this tertiary carbon atom. However, the methyl reactivity is quite comparable with that in most of the intermolecular experiments. Since there is no obvious reason to assume that the alkylation reaction process differs in mechanism for the methyl and ethyl groups, it may well be considered to be similar in this case as well. Based on the statistical α-hydrogen activity as normalized to 1.0 for methyl, the order of substitution ease for the three groups was methyl > ethyl > *sec*-butyl or more generally primary > secondary > tertiary.

For irreversible reactions, the relative reactivities of groups from competition processes are equivalent to the ratios of rate constants when comparable ratios of product yields are present at all times; *i.e.*, the reaction orders are the same. The intramolecular values normalized to the methyl group then compose a short set of relative rates, k/k^0. *Qualitatively*, the order (decreasing) of structural class reactivities is not comparible with carbene insertion (increasing) reactions,[18] but is comparable with hydrocarbon acidities.[19]

Although dimethylaniline ring and alkyl group acidities have been studied,[7] the alkyl carbon attached to nitrogen has such a low acidity that in general only the effect of nitrogen on aromatic ring protons has been considered. Alkyl structural effects are more completely available, particularly with respect to the groups of interest, for the α positions of alkyl-

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[13] The relative values from cyclohexane conformer studies are ΔG^* of 1.8 and 3.1 for ethyl and phenyl, respectively: E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 44.

[14] D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworth and Co. Ltd., London, 1965.

[15] C. G. Screttas and J. F. Eastham, *J. Amer. Chem. Soc.*, **88**, 5668 (1966).

[16] N-Alkyldiphenylamines have not been reported, but the decrease from aniline or N-alkylated anilines to diphenylamine is of this order of magnitude.[14]

[17] Since only a single tertiary amine was employed in the reaction mixture for intramolecular competition and yet the same quantities of n-butyllithium and 1-iodobutane were used as in the intermolecular cases, it was necessary to divide B/N values by 2 to obtain these values which are comparable with those in Table III.

[18] α dehydrohalogenation of the alkyl halide participating in the reaction could give a carbene; however, the order of CH insertions called for by the reactivity ratios is the reverse of that required for this reaction: J. Hine, "Divalent Carbon," Ronald Press Co., New York, N. Y., 1964, Chapter 7; W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 252.

[19] A. I. Shatenshtein, *Tetrahedron*, **18**, 95 (1962).

benzenes.[19,20–23] While the absolute magnitude of these values greatly exceeds that of CH_3 in N,N-dimethylaniline, the qualitative order primary > secondary > tertiary is in agreement both for lithium[20,21] and cesium[22,23] cyclohexylamides.

The quantitative α-alkylation results are in best agreement with the more ionic cesium base as an attacking reagent in hydrogen abstraction, Table IV. As suggested by Streitwieser and Young,[23] results of this type should be predominantly carbanionic in character. Inductive effects must then play a major role and the log k/k^0 may well relate to σ^* for the collective groups if the C_6H_5N effect is assumed to be constant. Although the three groups considered here constitute too small a set for statistical treatment, a quantitative direct proportionality with the inductive constant does seem to hold.

TABLE IV

α-PROTON EXCHANGE IN ALKYLBENZENES AND RELATIVE REACTION RATES OF α ALKYLATION IN TERTIARY ANILINES

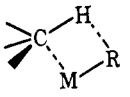
	Alkylbenzenes[a]		N-Alkylanilines[b]		
Group	Li$^+$, k/k^0	Cs$^+$, k/k^0 [d]	k/k^0	Log k/k^0	σ^* [c]
CH_3	1.0[e]	1.0	1.0	0.0	0.0
CH_2	0.11[f]	0.49	0.45	−0.35	−0.10
CH	0.008[g,h]	0.13[g]	>0.16	>−0.79	−0.20[g,i]

[a] From proton-exchange studies using lithium or cesium cyclohexylamide. [b] α-Alkylation data from this work. [c] Calculated by additivity of inductive effects neglecting NC_6H_5 and/or C_6H_5 as constants in the reactions considered; *cf.* J. E. Leffler and E. Grunwald, "Rates and Equilibria in Organic Reactions," John Wiley & Sons, Inc., New York, N. Y., 1963, pp 222, 224. [d] Reference 23. [e] Reference 20. [f] Reference 21. [g] Value for isopropyl. [h] *sec*-Butyl value may be calculated as 0.003 from the data of ref 22, assuming the same primary isotope effect as in ref 21. [i] *sec*-Butyl value is −0.215 by the method in footnote *c*.

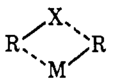
Previous alkylation studies,[3–5] metalation experiments,[6] and the measured acidities in dimethylaniline[7] indicate that metalation is not important on the N-alkyl group. The current structural data and their relationship to carbanionic character are not in conflict with this evidence. A carbanionic intermediate indicates the existence of a thermodynamic state of some stability with respect to the over-all reaction profile, *i.e.*, a definite species. The carbanionic character in the α-alkylation process, however, is based on a kinetic relationship. Thus the transition state rather than any intermediate species is under consideration. Certain simple analogs may help us to construct a model for this state.

The transition states for the related reactions, metalation, halogen–metal interchange, and Wurtz coupling aided in the construction of a model for α alkylation. Streitwieser in his extensive studies of reaction kinetics for hydrocarbon acidities has found a four-membered-ring transition state,[21,22] where M is cesium or lithium and R is cyclohexylamide, to be in best agreement with the kinetic data.

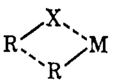
Similar states represent the halogen–metal interchange and Wurtz coupling. In terms of the simpler four-membered ring, these are



metalation



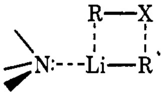
interchange

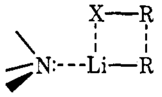


coupling

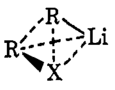
Rather than ionic species, these models seem to be reasonable transition states in such solvents as ethers or tertiary amines. However, the participation of additional RLi in any of the states may not be evident since the $(RLi)_2$-solvent complex may mask this secondary role as Screttas and Eastham[15] have pointed out in considering literature data on the Wurtz reaction.

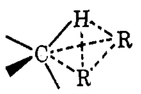
Both halogen–metal interchange and Wurtz coupling compete with α alkylation of tertiary amines. Our earlier studies[3,5] indicated that a complex between the base and amine was involved in the alkylation, and that the group forming the carbon–carbon bond came with equal ease from either the alkyl halide or organolithium reagent even when halogen–metal interchange was limited. A transition state in which halogen–metal interchange occurs on the amine complex is then a strong possibility. This intermediate can either undergo exchange and then dissociate, or be involved in alkylation. Alternatively the complex might participate in Wurtz coupling or α alkylation.





The close relationship between coupling and interchange suggests that a simpler model may relate to both. If the groups of interest occupy the corners of a tetrahedron, slight variations in the attractive forces could give either of these reactions or interchange followed by coupling. Now if we have the lithium atom associated with nitrogen of the amine in such a fashion that the α hydrogen and carbon form a second approximate tetrahedron having a common R---R edge with the first, a transition state allowing α alkylation is generated. The carbanionic character relationship to this model would indicate that the CH bond is considerably weakened in the configuration for reaction. Although such a model seems exceedingly complex, the use of Fisher–Taylor–Hirshfelder space filling models shows that, if reaction of the alkyl halide occurs on the amine complex, the α N-alkyl hydrogens are very near the alkyl groups from halide or lithium compound. This is particularly true in the tetrahedral conformation.





Much more information is needed on both α alkylation and competing reactions of the other partcipating reagents to justify this model. However, the model provides a fundamental basis for further understanding of these several reactions. The stereochemical implications represented by such a transition state may well furnish the means of clarifying this situation. While some of this stereochemistry may be

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[20] A. Streitwieser, Jr., D. E. Van Sickle, and W. S. Langeworthy, *J. Amer. Chem. Soc.*, **84**, 244 (1962).

[21] A. Streitwieser, Jr., and D. E. Van Sickle, *ibid.*, **84**, 249 (1962).

[22] A. Streitwieser, Jr., R. A. Caldwell, R. G. Lawler, and G. R. Ziegler, *ibid.*, **87**, 5399 (1965).

[23] A. Streitwieser, Jr., and W. R. Young, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, O 19.

in evidence in the current inter- and intramolecular competition results, a more extensive study including organometallic and halide structures is needed for a thorough analysis.

Experimental Section[24]

Physical Constants.—Proton magnetic resonance (pmr) spectra were measured on a Varian A-60 spectrometer as 20% v/v solutions in carbon tetrachloride with approximately 1% tetramethylsilane as an internal standard and are reported as δ values in parts per million. Infrared measurements were made on the pure liquids using a Perkin-Elmer Model 137 spectrophotometer. Wavelengths are given in microns; intensities relative to the most intense peak (*) as equivalent to 100% are s = strong 76–100%, m = medium 51–75%, w = weak 26–50%, and vw = very weak 10–25% (very weak bands are given only when quite sharp and characteristic). Refractive indices were measured with a Bausch and Lomb Abbé refractometer. Ethylbenzene was used as the standard in determining specific gravities with a Fisher-Davidson gravitometer.

Gas Chromatography.—Retention ratios, resolution, and product yields were determined using an internal standard method.[3,8] An F & M Model 500 gas chromatograph was used with 0.25 in. × 10 ft column of 20% GE-SF96 on 40–60 mesh Chromosorb W. The flow rate was maintained between 160 and 170 cc/min of helium for analyses at either 100 or 185°. Retention ratio reproducibility was ±0.2–1.0% of the reported values with the lower value applying at only very high retention ratios. Quantitative analyses were accomplished by adding 1.0 ml of the organic layer from a reaction mixture to a accurately weighed amount of the appropriate standard. The mixture was shaken well and a specific volume (usually 25–50 μl) was injected into the gas chromatograph. Areas of peaks, calculated from peak heights and peak widths at half-height, were used to determine the weight of product formed and its yield.[3]

Chemicals.—Methyl- and dimethylanilines, N-methyldiphenylamine, 1-iodobutane, 2-bromobutane, and 1-bromopentane were obtained from Eastman. Ethyl- and diethylanilines, N-methyl-N-ethylaniline, triethylamine, triethylenediamine, and 2-bromohexane were products of Matheson Coleman and Bell. N-(2-Butyl)aniline was from Chemicals Procurement Laboratories. Monofree dimethyl- and diethylanilines and triethylamine were dried over sodium wire before use. Commercial N-methyl-N-ethylaniline was purified using benzoyl chloride in the Schotten-Baumann reaction, dried over KOH, distilled, and stored over sodium wire; material treated in this fashion did not give an immediate precipitate formation with *n*-butyllithium. The active lithium content of *n*-butyllithium (Foote Mineral, 20% in hexane) was determined by the double titration method[25] before use. Benzhydryldimethylamine,[26] N,N-diethyl-2-hexylamine,[4] N-ethyl-N-(2-hexyl)aniline,[5] *o*-(diethylamino)biphenyl,[26] N-methyl-N-(1-pentyl)aniline,[5] and N-(1-pentyl)diphenylamine[26] were available from previous studies.

N-Methyl-N-(2-hexyl)aniline.—N-Methylaniline (5.4 ml, 50 mmol) was mixed with 5.9 ml (40 mmol) of 2-bromohexane and heated on a steam bath in a sealed flask for 2 days. The reaction mixture was treated with concentrated sodium hydroxide solution; the oil was separated; and the aqueous solution was extracted twice with ether. The oil and ether extracts were combined and washed several times with water. The ether solution, which showed gc peaks for starting amine and product, was evaporated to remove the solvent. The residue was shaken well with benzoyl chloride and aqueous sodium hydroxide. This mixture was poured into ice water and extracted with ether; the product was removed from the combined ether layers by repeatedly extraction with 2 *N* hydrochloric acid. The acid solution was cooled in ice and made strongly alkaline with sodium hydroxide. The separated oil and several ether extracts of this aqueous solution were dried over sodium sulfate and distilled. The pure product, 2.3 g, 30% yield, was collected at 73° (0.3 mm).

Anal. Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.07; N, 7.32. Found: C, 81.38; H, 11.21; N, 7.46.

The infrared spectrum had bands at 3.30 w, 3.39 s, 3.49 m, 6.25 s, 6.36 w, 6.67 s*, 6.88 w, 7.20 w, 7.41 w, 7.58 m, 8.00 vw, 8.17 w, 8.29 w, 8.38 w, 8.66 vw, 8.83 m, 9.20 vw, 9.34 vw, 9.65 w, 10.08 w, 10.79 vw, 11.60 vw, 13.32 s, 14.08 vw, and 14.48 m μ.

N-Ethyl-N-(1-pentyl)aniline.—N-Ethylaniline (12.6 ml, 0.1 mol) was mixed with 12.1 g (80 mmol) of 1-bromopentane and treated as in the preparation of N-methyl-N-(2-hexyl)aniline. Distillation gave 9.3 g (61% yield) of a chromatographically pure product: bp 74° (0.1 mm); $n^{21.5}{}_{\rm D}$ 1.5221, $d^{20}{}_4$ 0.911.

Anal. Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.07; N, 7.32. Found: C, 81.57; H, 11.06; N, 6.97.

Infrared analysis showed bands at 3.29 w, 3.40 s, 3.49 m, 6.27 s, 6.38 w, 6.67 s*, 6.82 w, 7.19 w, 7.30 m, 7.40 m, 7.70 vw, 7.89 m, 8.08 vw, 8.21 w, 8.41 m, 8.62 w, 9.08 w, 9.30 vw, 9.61 w, 10.04 w, 11.6 vw, 11.8 vw, 12.6 vw, 13.39 s, and 14.46 m μ.

N-Methyl-N-(2-butyl)aniline.[9]—Freshly distilled N-methylaniline (44 g, 0.41 mol) was mixed with 54 g (0.40 mol) of 2-bromobutane and heated at 120° for 36 hr. The mixture was made strongly alkaline with potassium hydroxide solution. The oil which separated and several ether extracts of the aqueous solution were combined and dried over sodium sulfate. The solvent was stripped off and the reaction product was refluxed with 25 ml of acetic anhydride for 2 hr. The mixture was poured into about 480 ml of ice cold 4 *N* hydrochloric acid. The acid layer was extracted with ether for several days in a continuous extractor. The acid layer was made alkaline with sodium hydroxide and repeatedly extracted with ether. The latter ether solution was washed with water, dried over sodium, and distilled. Gas chromatographically pure product, 20 g, 31% yield, distilled at 61–62° (0.1 mm) [lit. 121° (20 mm)[9]], $n^{21.5}{}_{\rm D}$ 1.5360, $d^{20}{}_4$ 0.934, and had a gc retention ratio of 0.475 *vs.* N-ethyl-N-(2-hexyl)aniline as a standard.

The infrared spectrum had bands at 3.30 vw, 3.37 m, 3.48 w, 3.58 vw, 6.27 s, 6.39 w, 6.67 s*, 6.89 w, 7.21 w, 7.42 w, 7.59 m, 7.78 w, 7.79 w, 8.27 w, 8.39 vw, 8.66 vw, 8.87 m, 8.95 w, 9.10 vw, 9.48 vw, 9.68 vw, 9.83 vw, 10.09 w, 10.44 vw, 10.91 vw, 11.5–11.6 vw, 13.33 s, 14.09 vw, and 14.48 m μ.

N-(2-Butyl)-N-(1-pentyl)aniline.—N-(2-Butyl)aniline (14.9 g, 0.1 mol) was mixed with 22.6 g (0.15 mol) of 1-bromopentane and heated at 100° in a sealed flask for 2 days. The reaction mixture was then cooled, treated with concentrated sodium hydroxide solution, and extracted with ether. Since gc analysis of this ether solution showed a small amount of starting amine, the ether was evaporated and the residue was shaken with benzoyl chloride and sodium hydroxide solution. The mixture was poured into ice water and extracted with ether; the combined ether layers were extracted with several portions of 6 *N* hydrochloric acid. This acid solution was washed once with ether and then made strongly alkaline with sodium hydroxide. The amine was picked up in ether, washed with water, and dried over anhydrous sodium sulfate. Pure N-(2-butyl)-N-(1-pentyl)aniline, 8.7 g, 40% yield, distilled at 90–93° (0.1 mm), $n^{21.5}{}_{\rm D}$ 1.5140, $d^{20}{}_4$ 0.898, and had a retention ratio of 1.376 relative to N-ethyl-N-(2-hexyl)aniline.

Anal. Calcd for $C_{15}H_{25}N$: C, 82.13; H, 11.48; N, 6.39. Found: C, 82.21; H, 11.55; N, 6.27.

Infrared analysis showed bands at 3.30 vw, 3.38 s, 3.49 m, 6.28 s, 6.38 vw, 6.67 s*, 6.88 w, 7.20 w, 7.28 w, 7.42 w, 7.76 w, 7.97 w, 8.09 vw, 8.23 vw, 8.49 w, 8.63 vw, 8.81 w, 9.10 vw, 9.61 w, 10.04 vw, 13.38 m, 13.8 vw, and 14.48 m μ.

General Procedure for Competitive α-Substitution Reactions.—Equimolar amounts (50 mmol) of dried monofree N,N-dimethylaniline and a second tertiary amine were mixed in a dry glass stoppered 100-ml round-bottomed flask containing a Teflon-coated stirring bar and cooled to −10° in an ice–salt bath. In the case of intramolecular competition reactions, no N,N-dimethylaniline was used but 0.1 mol of a tertiary amine with two different reactive alkyl sites was employed.

n-Butyllithium, 20 mmol of 1.6 *N* in hexane,[25] was added rapidly with stirring and cooling to the amine mixture. This solution was allowed to reach bath temperature, approximately 5 min, and 20 mmol of 1-iodobutane was added, either rapidly or over a 5-min period in the case of an immediate vigorous reaction. The reaction was continued by allowing slow melting of the cooling bath. After about 1 hr, the mixture had attained room temperature and the bath was removed. After 1.5 hr the temperature reached 32° and this temperature ±2° was maintained during the remainder of the reaction period; over-all reaction time was 2 hr.

The reaction was terminated by adding crushed ice with rapid

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[24] Analyses were performed by Crobaugh Laboratories, Cleveland, Ohio. Melting and boiling points are uncorrected.

[25] H. Gilman and A. Haubein, *J. Amer. Chem. Soc.*, **66**, 1515 (1944); H. Gilman and F. K. Cartledge, *J. Organometal. Chem.*, **2**, 447 (1964).

[26] A. R. Lepley, A. G. Giumanini, A. B. Giumanini, and W. A. Khan, *J. Org. Chem.*, **31**, 2051 (1966).

stirring. The reaction mixture was allowed to stand for 15 min and then 1.0-ml samples of the organic layer were withdrawn for qualitative and quantitative gc analysis. The products were isolated by preparative gc and characterized by their gc retention ratios and infrared and pmr spectra. Comparisons of these properties for the products were made with those of synthetic materials. In intermolecular competition reactions, N,N-dimethylaniline, *n*-butyllithium, and 1-iodobutane were common reagents.

Intermolecular Competition Reactions. A. Triethylenediamine.—N,N-Dimethylaniline (6.1 ml, 50 mmol) was mixed with 5.7 g (50 mmol) of triethylenediamine and the mixture was treated with 13 ml of 1.6 *N* (20 mmol) *n*-butyllithium. 1-Iodobutane (2.3 ml, 20 mmol) was added slowly to control the vigorous reaction which was accompanied by the immediate formation of a precipitate. The reaction was continued for 2 hr as described above and quenched with ice, and the organic phase was analyzed by gc at 100 and 185°; see Table III.

B. **Triethylamine.**—N,N-Dimethylaniline (6.1 ml, 50 mmol) was mixed with 7.0 ml (50 mmol) of dry triethylamine. *n*-Butyllithium (13 ml, 20 mmol) was added to the cooled mixture with stirring. 1-Iodobutane (2.3 ml, 20 mmol) was added slowly over a period of 5 min since the reaction was very vigorous on rapid addition. On slow addition, the reaction proceeded controllably and was completed as described in the general procedure. The organic products reported in Table III were determined by gc analysis at 100° using aniline as a standard and at 185° with a benzhydryldimethylamine reference.

C. **N,N-Diethylaniline.**—N,N-Dimethylaniline (6.1 ml, 50 mmol) was mixed with 8.0 ml (50 mmol) of anhydrous monofree N,N-diethylaniline and 13 ml (20 mmol) of *n*-butyllithium. 1-Iodobutane (2.3 ml, 20 mmol) was added rapidly and the reaction was carried out as in the general procedure. After 2 hr, the reaction was quenched and the organic phase was analyzed by quantitative gc at 185° using benzhydryldimethylamine as the internal standard. Two product peaks were observed, Table III.

D. **N-Methyl-N-ethylaniline.**—N,N-Dimethylaniline (6.1 ml, 50 mmol) was mixed with 7.3 ml (50 mmol) of purified anhydrous N-methyl-N-ethylaniline and 13 ml (20 mmol) of *n*-butyllithium. After stirring briefly, 2.3 ml (20 mmol) of 1-iodobutane was added. When the reaction mixture was worked up as described in the general procedure, two product peaks (Table III) were observed in the gc of the organic phase at 185° with retention ratios of 0.525 and 0.618 using benzhydryldimethylamine as a standard.

E. **N-Methyldiphenylamine.**—N,N-Dimethylaniline (6.1 ml, 50 mmol) was mixed with 9.0 ml (50 mmol) of N-methyldiphenylamine and 13 ml (20 mmol) of *n*-butyllithium. 1-Iodobutane (2.3 ml, 20 mmol) was added rapidly and the reaction was carried out following the general procedure. The reaction was quenched after 2 hr, and the organic phase was analyzed by gc at 185°. The two product peaks observed (Table III) were determined using *o*-(diethylamino)biphenyl as an internal standard.

Intramolecular Competition Reactions. A.—N-Methyl-N-ethylaniline (14.7 ml, 0.1 mol) was mixed with 13 ml of 1.6 *N* (20 mmol) *n*-butyllithium at −10°. 1-Iodobutane (2.3 ml, 20 mmol) was added rapidly and the reaction was carried out according to the general procedure. The reaction was quenched after 2 hr and the organic phase when examined by gc at 185° showed only one product peak with a retention ratio of 0.618 *vs.* benzhydryldimethylamine as an internal standard. This peak corresponded to a 19.0% yield of $C_{13}H_{21}N$ products. Preparative gc was used to collect this material for infrared and pmr analysis. The infrared spectrum corresponded to that of N-ethyl-N-(1-pentyl)aniline except for very weak bands at 7.58 and 8.83 μ which are characteristic of two medium-intensity bands in N-methyl-N-(2-hexyl)aniline. In the pmr spectrum, δ values of the NCH_3 singlet at 2.59 ppm and NCHRR′ multiplet centered at 3.78 ppm in N-methyl-N-(2-hexyl)aniline were adequately separated from the NCH_2R overlapping quartet ($J = 6.9 \pm 0.1$ cps) of ethyl and multiplet of *n*-pentyl (centered respectively at 3.28 and 3.18 ppm) in N-ethyl-N-(1-pentyl)aniline to allow quantitative determination of the two isomeric products. The absence of a NCH_3 singlet at 2.78 ppm showed the separated product to be free of starting N-methyl-N-ethylaniline. The ratios of products as determined from pmr integral ratios was 3.3:1.0 methyl to ethyl position reaction for yields of 14.6% N-ethyl-N-(1-pentyl)aniline and 4.4% N-methyl-N-(2-hexyl)-aniline.

B. **N-Methyl-N-(2-butyl)aniline.**—N-Methyl-N-(2-butyl)-aniline (12.2 ml, 75 mmol) combined with 10 ml of 1.6 *N* (15 mmol) *n*-butyllithium and 1.6 ml (14 mmol) of 1-iodobutane was rapidly added to the mixture at −10°. The reaction was carried out as before and quenched after 2 hr, and the organic phase was examined using N-ethyl-N-(2-hexyl)aniline as a gc standard at 185°. Only one product peak was observed with a retention ratio of 1.37 relative to this standard. The infrared spectrum of a preparative gc sample was comparable with that of N-(2-butyl)-N-(1-pentyl)aniline but the pmr spectrum had a very weak singlet at 2.65 ppm. The integral ratio of this singlet and the $NCHR_2$ multiplet centered at 3.71 ppm was used for quantitative analysis indicating a maximum of 1.2% N-methyl-N-(3-methyl-3-heptyl)aniline in the over-all yield of 23.4%. The bulk of the product, at least 22.2%, was N-(2-butyl)-N-(1-pentyl)aniline.

Synthesis and Reactions of N-*p*-Tolylsulfonyl-N′-cyclohexylcarbodiimide

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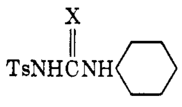
The synthesis of the title compound (**2a**) is described, and its reactions with several nucleophiles are described. Amino acid esters underwent addition–cyclization with **2a** giving imidazolidones, while cyclohexylamine and sodium azide afforded a guanidine and tetrazole, respectively. The condensation of N-carbobenzyloxyglycine with **2a** required a high temperature and gave only pyrolysis products.

Carbodiimides (**1**) are of considerable interest because of their use as agents in peptide synthesis[1] and more recently as oxidizing agents in dimethyl sulfoxide solution.[2] Our interest in sulfonylcarbodiimides (**2**) derived from the expectation that this highly polar diimide might have interesting uses in peptide chemistry. Ulrich[3] and coworkers have reported most completely on the synthesis of sulfonylcarbodiimides and some of their reactions. Using the Ulrich thiourea phosgenation procedure we have synthesized N-*p*-toluenesulfonyl-N′-cyclohexylcarbodiimide (TsCC) (**2a**) from the corresponding thiourea (**3a**) in 65% yield.

$RN{=}C{=}NR'$ **1**

$RSO_2N{=}C{=}NR'$ **2a**

$R = 4\text{-}CH_3C_6H_4$; R' = cyclohexyl



3a, X = S

b, X = O

$Ts = 4\text{-}CH_3C_6H_4SO_2$

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[1] F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, **67**, 107 (1967).

[2] K. E. Pfitzner and J. G. Moffat, *J. Amer. Chem. Soc.*, **85**, 3027 (1963); **87**, 5661, 5670 (1965).

[3] H. Ulrich, B. Tucker, and A. A. R. Sayigh, *Tetrahedron*, **22**, 1565 (1966).