Relative Reactivities of Enamines in Alkylation Reactions

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Competitions of enamines with varied amine and olefinic moieties in the reactions with methyl acrylate, acrylonitrile, benzyl bromide, methyl iodide, and ethyl iodide gave relative reactivities for substitution on carbon. A correlation with the nmr chemical shift of the enamine β proton was shown for the first three. The C to N alkylation ratios of these enamines with methyl iodide, ethyl iodide, *sec*-butyl bromide, and benzyl bromide (before and after possible rearrangement) were determined.

The use of enamines for electrophilic α substitution of ketones and aldehydes has resulted in a formidable collection of examples.[1] Yet little quantitative information has been advanced, which would help in choosing the optimum enamine system for a desired reaction. It has been suggested that morpholine enamines are preferable for acylation reactions[2] but pyrrolidine and hexamethylene imine enamines for alkylations.[3] In reactions of cyclohexanone derived enamines with cyanogen chloride[4] highest yields were obtained with the pyrrolidine enamine in the presence of triethylamine but the piperidine enamine was better in absence of triethylamine and the morpholine enamine poor in either case. While arylations with reactive nitro aryl halides require pyrrolidine or piperidine enamines[5] one obtained higher yields with morpholine enamines in reactions with nitro olefins.[6] In alkylations of enamines derived from aldehydes, branched secondary amines have shown an advantage in preventing the otherwise prevalent nitrogen alkylation[7,8] also found in the ethylation of pyrrolidine enamines of 7-(53%), 8-(95%) and 9-(88%) membered ring ketones.[9] The relative facility for rearrangement of N to C protonated enamines[10] and the relative yields of alkylidene derivatives obtained by condensing aldehydes with enamines[11,12] are other examples which have been used as analogs in planning synthetic reactions.

In the present study we have determined the relative reactivities of a variety of enamines with several electrophiles in enamine alkylation reactions. Competitions between enamines in Michael additions to acrylonitrile and methyl acrylate established reactivities with dependence on structure and basicity of the cyclic amine and the olefinic portions of the enamine. In these reactions N alkylation, if present, is expected to be readily reversible[3] and should thus not affect the relative rates of competing carbon alkylations, unless large and different concentrations of intermediate zwitterionic N alkylation products arise from competing pairs of enamines. A parallel reactivity series was found on alkylation of the enamines with benzyl bromide in refluxing dioxane. Under these conditions rearrangement[13] of N to C benzylation products could be demonstrated (Table I) and final amounts of N alkylation were found to be small (2–8% for eight cyclic enamines).

With a notation for the enamines of amine ring size/olefin ring size, with h representing the 4-substituted 3-heptene moiety and m for morpholine, *one finds reactivity orders of 5/5 > 5/6 > 5/7 + 5/h and 5/6 > 7/6 > 6/6 > m/6 in both Michael addition reactions and on benzylation.* While the relative reactivity orders are the same in these reactions, individual reactivity differences between enamines were not the same in the three series. In general they were smaller in the reactions of benzyl bromide than in the Michael addition reactions.

Electrophilic attack of an enamine at carbon leads to an imonium salt through a transition state which could, in principle, look like the starting enamine or the product. Thus, in either case, one would expect a correlation of reactivity with the amount of charge delocalization in the enamine (negative charge density on carbon or ease of obtaining imonium structure). If steric hindrance to attack of the enamine is present, however, a relative decrease in reactivity is expected and the correlation may then not be possible.

A measure of the amount of charge delocalization in enamines can be obtained from the nmr chemical shift of a β-vinyl proton, which becomes more shielded by increasing electron density on the β carbon.[14] Thus a correlation of enamine reactivity and the chemical shift of the β proton is expected if steric factors are held constant and spatial direct shielding effects from nitrogen to β proton are negligible or constant.

In the series of eight cyclic enamines studied, this correlation was found, with inversions observed only where the chemical shifts of the enamine β protons came close to each other (about 1-cps difference). *Thus nmr shielding of the β proton decreased in the order of 5/5 > 5/6 > 7/6 > 6/5 > m/5 > 5/7 > m/6 > 6/6 and the relative reactivities decreased as 5/5 > 5/6 > 6/5 > 7/6 > m/5, 5/7 > 6/6 > m/6.* The inverted reactivities of the 7/6 and 6/5 systems are in line with the more favorable C to N benzylation ratio of the latter and may thus be due to relative steric shielding at carbon. Inversion of the m/6 and 6/6 systems, however, requires a different explanation and could be due to decreased relative nucleophilicity of the morpholine system, thus demonstrating the fallibility of equating negative charge density on carbon with reactivity, even

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TABLE I

RELATIVE REACTIVITIES OF COMPOUNDS LISTED HORIZONTALLY WITH RESPECT TO COMPOUNDS LISTED VERTICALLY

	5/5	5/6	7/6	6/5	5/h	m/5	5/7	m/6	6/6
5/5	1.0[a]	0.37[a]	0.20[a]		0.14[a]		*a*	0.018[a]	0.076[a]
	1.0[b]	0.42[b]	0.20[b]		*b*		0.12[b]	0.066[b]	0.077[b]
	1.0[c]	0.83[c]	0.67[c]		0.27[c]		0.63[c]	0.10[c]	0.15[c]
6/5		1.3[a]	0.26[a]	1.0[a]	0.32[a]		0.43[a]	<0.067[a]	0.11[a]
		1.1[b]	0.77[b]	1.0[b]	*b*		*b*	0.11[b]	0.30[b]
		1.4[c]	0.95[c]	1.0[c]	0.77[c]		*c*	0.32[c]	0.83[c]
m/5		2.9[a]	1.5[a]		0.90[a]	1.0[a]	1.0[a]	0.13[a]	0.30[a]
		3.5[b]	1.1[b]		*b*	1.0[b]	*b*	0.11[b]	0.22[b]
		1.5[c]	1.1[c]		1.2[c]	1.0[c]	*c*	0.29[c]	0.67[c]
5/7	*a*	*a*	*a*	2.3[a]	*a*	1.0[a]	1.0[a]	*a*	*a*
	8.1[b]	2.5[b]	*b*	*b*	*b*	*b*	1.0[b]	*b*	*b*
	1.6[c]	*c*	*c*	*c*	*c*	*c*	1.0[c]	*c*	*c*
5/h	6.9[a]	3.6[a]	*a*	3.1[a]	1.0[a]	1.1[a]	*a*	0.72[a]	0.75[a]
			b	*b*	1.0[b]	*b*	*b*	*b*	*b*
	3.7[c]	*c*	*c*	1.3[c]	1.0[c]	0.83[c]	*c*	*c*	0.45[c]

[a] With methyl acrylate. [b] With acrylonitrile. [c] With benzylbromide.

with constant steric hindrance to electrophilic attack. In this connection it should be noted that we found the rates of quaternization of corresponding simple tertiary amines with methyl iodide to decrease in the order of N-methylpyrrolidine > N-methylpiperidine > N-methylmorpholine. An alternative interpretation is that the close nmr chemical shifts of the m/6 and 6/6 systems are inverted relative to charge densities on carbon, by a small difference in spatial proton–nitrogen interaction. This receives support from the expected 6/5 > m/5 ratios of reactivity and shielding.[15]

The acyclic 5/h enamine showed a more shielded β proton than any of the cyclic enamines. However, its reactivity in Michael addition reactions and on benzylation fell near the bottom of the sequence between the m/5 and 6/6 systems. The decreased reactivity is due to increased steric shielding of the enamine β carbon by the rotating alkyl chains. This is also reflected by the relatively low C to N benzylation ratio, which decreases even further on branching of the alkyl chains, in the pyrrolidine enamine of di-*sec*-butyl ketone, even though the vinyl proton is still more shielded here.

Methylations and ethylations of the same cyclic enamines led to a different sequence of reactivity at carbon: $7/6 > 5/6 \simeq 5/7 \simeq 5/5 > 6/5 > m/5 > 6/6 \simeq m/6$. Here, a more difficult reversal of alkylation on nitrogen was expected to alter the order of competitive C alkylation found with the previous three reactions. The most remarkable change occurred by interchanging the 5/5 and 7/6 compounds from the top and middle of the series, even though these compounds still showed high and similar carbon to nitrogen alkylation ratios. These results suggest the synthetic advantage of using hexamethylene imine in enamine methylations of cyclohexanones.

While relatively high reactivity on carbon is desirable for an enamine substitution reaction, selection of a favorable C to N alkylation ratio may be more significant. Examination of the ratios listed in Table II shows no correlation of data for alkylations of nine enamines with methyl iodide, ethyl iodide, *sec*-butyl bromide, or benzyl bromide, nor any correlation of the C to N alkylation ratios with the electron density at the β carbon, as estimated from nmr spectra. Since no predictive rules can be established here, the data should be especially helpful in selection of optimum enamine systems for desired alkylation systems.

The methylation reactions of the nine enamines shown in Table II were found to be 95–100% completed at room temperature after 24 hr. A small excess of enamine was used in these reactions. When the reaction mixtures were then heated to 100° for 18 hr, the C to N alkylation ratio was found to increase drastically. This increase was followed in the 7/6 methylation by comparison of the relative intensities of the N-methyl amonium singlet at δ 3.12 with the C-methyl imonium doublet at δ 1.08. It was also found that the absolute intensity of the methyl doublet of 2-methylcyclohexanone, obtained from these mixtures by hydrolysis, increases correspondingly when compared with a known absolute standard (0.33 equiv of added *t*-butyl alcohol). These increases of C methylation products seen by nmr also compared quantitatively with the titration values given in Table II.

The increased ratio of C to N methylation products found on heating the alkylation reactions, which contained excess enamine, should be due to intermolecular N to C methyl transfer. However, with an excess of alkylating agent in reaction mixtures stored at room temperature for ten days, one did not observe values equal to or lower than those obtained with excess enamine at room temperature in 24 hr in all cases. Heating of one such reaction mixture still showed an increase of the C to N alkylation ratio. The facility of the N alkylated enamines to act as carbon methylating agents was also found to vary with the structure of the heterocyclic and olefinic moieties of the enamines. On this basis morpholine enamines are particularly poor and the hexamethylene imine enamine system best for the methylation reaction.

Experimental Section

Preparation of Enamines.—The following enamines were prepared by reported procedures: pyrrolidine enamine of cyclopentanone,[3] cyclohexanone,[3] cycloheptanone;[4] piperidine enamine of cyclopentanone,[16] cyclohexanone;[2] morpholine enamine of cyclopentanone,[3] cyclohexanone;[2] hexamethylene imine enamine

(15) After submission of this manuscript, K. Nagarajan and S. Rajappa, *Tetrahedron Lett.*, 2293 (1969), reported similar nmr data for these enamines. Their measurements in carbon tetrachloride showed equivalence of the 7/6 and 6/5 systems and 6/6 > m/6 by 2 cps.

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TABLE II
C TO N ALKYLATION RATIOS
(EQUIVALENTS ON C PER EQUIVALENT ON N)[a]

Code	Benzyl bromide Rt	Benzyl bromide 100°	Methyl iodide[b] Rt	Methyl iodide[b] 100°	Ethyl iodide 100°	sec-Butyl bromide 100°
5/5	13	53	4.3	20	6.6	5.7
5/6	3.8	78	2.6	3.2	1.9	11
6/5	3.9	80	1.8	17	2.3	8.4
6/6	0.67	12	0.45 (0.33)	1.5	1.3	20
7/6	4.2	28	2.9 (4.9)	26	5.6	8.7
m/5	15	20	2.4 (3.0)	4.6	12	7.4
m/6	6.6	28	1.7 (0.63)	5.5 (2.0)	11	12
5/h	16	16	4.3	5.9	3.9	6.8
5/n	2.9	5.4	1.2	4.1		

[a] Reaction conditions: 24 hr at room temperature, 18 hr at 100°, with excess enamine. [b] Values in parentheses: 10 days at room temperature, 24 hr at 100°, with 2 equiv of methyl iodide.

of cyclohexanone.[2] The pyrrolidine enamine of 2,6-dimethyl-4-heptanone was prepared by refluxing a solution of 42 g (0.29 mol) of the ketone, 25 g (0.35 mol) of pyrrolidine, and a crystal of *p*-toluenesulfonic acid in 100 ml of benzene for 30 hr, under nitrogen, passing the condensate through a Soxhlet extractor filled with Linde, type 4A Molecular Sieve. Distillation gave 9.8 g (17% yield) of the enamine, bp 112–115° (12 mm). The pyrrolidine enamine of 4-heptanone was prepared by the same procedure in 40% yield and distilled at 97–100° (13 mm). These enamines showed the usual ir enamine absorptions[1] and nmr spectra with the expected proton integration ratios.

Nmr Chemical Shifts of β Protons.—All measurements were made with a Varian A-60 instrument on samples dissolved in deuteriochloroform with internal TMS standard. The listed downfield shifts from TMS are average values of three measurements. The enamines are listed as amine ring size/olefin ring size, with m for morpholine, h for 4-substituted 3-heptene, and n for 2,6-dimethyl-4-substituted-3-heptene: 5/n (238.0 cps), 5/h (239.5 cps), 5/5 (241.7 cps), 5/6 (256.8 cps), 7/6 (261.0 cps), 6/5 (262.3 cps), m/5 (265.9 cps), 5/7 (269.5 cps), m/6 (278.7 cps), 6/6 (279.7 cps).

Competition Reactions.—One equivalent (0.01 mol) each of two different enamines was added to 25 ml of dry dioxane. One equivalent of the alkylating agent was added and the mixture refluxed for about 15 hr under nitrogen. After cooling, 5 ml of water was added, the mixture refluxed for 1 hr, cooled and concentrated under vacuum to about 10 ml. The concentrate was extracted with 75 ml of ether, the extract dried over magnesium sulfate and filtered, and the volume reduced to about 5 ml under vacuum. Ratios of ketone products were measured with an Aerograph A-90-P thermal conductivity gas chromatograph. Conditions for separations, with retention times in parentheses, were as follows: a, 2-methylcyclopentanone (12 min) and 2-methylcyclohexanone (38 min), 20 psi, column 9-ft 10% Apiezon L, 80°, injector 150°, detector 190°; b, 2-ethylcyclopentanone (30 min) and 2-ethylcyclohexanone (63 min), 20 psi, column 9 ft 10% Apiezon L, 90°, injector 170°, detector 180°; c, 2-benzylcyclopentanone (25 min) and 2-benzylcyclohexanone (45 min), 35 psi, column 9 ft 10% Apiezon L, 170°, injector 210°, detector 195°; d, 2-(2-cyanoethyl)cyclopentanone (11 min) and 2-(2-cyanoethyl)cyclohexanone (16 min), 60 psi, column 5 ft 20% Apiezon L, 175°, injector 200°, detector 247°; e, 2-(2-carbomethoxyethyl)cyclopentanone (12 min) and 2-(2-carbomethoxyethyl)cyclohexanone (19 min), 30 psi, column 9 ft 10% Apiezon L, 180°, injector 200°, detector 200°; f, cyclohexanone (9 min) and 2-(2-butyl)cyclohexanone (21 min), 20 psi, column 9 ft 10% Apiezon L, 120°, injector 180°, detector 200°; g, 2-benzylcyclopentanone (28 min) and 3-benzyl-4-heptanone (22 min), 60 psi, column 30 ft 20% Apiezon L, 224°, injector 270°, detector 290°; i, 2-(2-carbomethoxyethyl)cyclopentanone (14 min) and 2-(2-carbomethoxyethyl)-4-heptanone (9 min), 20 psi, column 6 ft 10% ethylene glycol adipate, 133°, injector 240°, detector 254°; j, 2-benzylcyclohexanone (28 min) and 3-benzyl-4-heptanone (15 min), 60 psi, column 9 ft 10% Apiezon L, 170°, injector 200°, detector 200°; k, 2-(2-carbomethoxyethyl)cyclohexanone (22 min) and 2-(2-carbomethoxyethyl)-4-heptanone (13 min), 30 psi, column 9 ft 10% Apiezon L, 170°, injector 200°, detector 200°.

Using the 5/5 enamine as standard competitor with C alkylation 1.0, other enamines showed the following competitive relative C alkylations: with methyl acrylate, 5/6 (0.37), 6/6 (0.076), m/6 (0.018), 7/6 (0.20); with acrylonitrile, 5/6 (0.42), 6/6 (0.077), m/6 (0.066), 7/6 (0.20); with benzyl bromide, 5/6 (0.83), 6/6 (0.15), m/6 (0.10), 7/6 (0.67); with ethyl iodide, 5/6 (1.1), 6/6 (0.22), m/6 (0.24); with methyl iodide, 5/6 (1.1), 6/6 (0.25), m/6 (0.12), 7/6 (6.7).

Using the 6/5 enamine as standard competitor with C alkylation 1.0, other enamines showed the following competitive relative C alkylations: with methyl acrylate, 5/6 (1.3), 6/6 (0.11), m/6 (less than 0.067), 7/6 (0.26); with acrylonitrile, 5/6 (1.1), 6/6 (0.30), m/6 (0.11), 7/6 (0.77); with benzyl bromide, 5/6 (1.4), 6/6 (0.83), m/6 (0.32), 7/6 (0.95); with ethyl iodide, 5/6 (1.2), 6/6 (0.17), m/6 (0.11), 7/6 (2.1), with methyl iodide, 5/6 (3.2), 6/6 (0.26), m/6 (0.38), 7/6 (8.2).

Using the m/5 enamine as standard competitor with C alkylation 1.0, other enamines showed the following competitive relative C alkylations: with methyl acrylate, 5/6 (2.9), 6/6 (0.30), m/6 (0.13), 7/6 (1.5); with acrylonitrile, 5/6 (3.5), 6/6 (0.22), m/6 (0.11), 7/6 (1.1); with benzyl bromide, 5/6 (1.5), 6/6 (0.67), m/6 (0.29), 7/6 (1.1); with ethyl iodide, 5/6 (1.4), 6/6 (0.38), m/6 (0.10), 7/6 (2.0); with methyl iodide, 5/6 (1.6), 6/6 (0.53), m/6 (0.53), 7/6 (7.0).

Using the 5/7 enamine as standard competitor with C alkylation 1.0, other enamines showed the following competitive relative C alkylations: with methyl acrylate, 6/5 (2.3), m/5 (1.0); with acrylonitrile, 5/5 (8.1), 5/6 (2.5); with benzyl bromide, 5/5 (1.6); with methyl iodide m/5 (0.53).

Using the 5/h enamine as standard competitor with C alkylation 1.0, other enamines showed the following competitive relative C alkylations: with methyl acrylate, 5/6 (3.6), 6/6 (0.75), m/6 (0.72), m/5 (1.1), 6/5 (3.1), 5/5 (6.9); with benzyl bromide 6/6 (0.45), m/5 (0.83), 6/5 (1.3), 5/5 (3.7).

Quaternization of Tertiary Amines.—To 50 ml of 50% aqueous dioxane was added 0.02 ml of N-methylpyrrolidine or N-methylpiperidine, or N-methylmorpholine. The solution was stirred and the pH measured with a Fisher Accumet pH meter equipped with a Beckman glass electrode and a calomel reference electrode. Methyl iodide, 5.0 g (0.035 mol), was added and the pH mea-

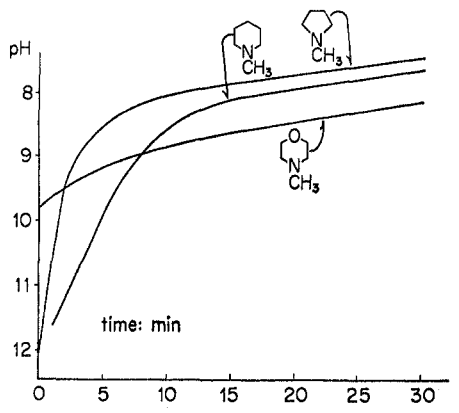

Figure 1.—Quarternization of tertiary amines with methyl iodide.

sured at 1-min intervals for 15 min and after 20, 25, and 30 min. A plot of the data is shown in Figure 1.

C to N Alkylation Ratios.—An enamine (6–7 ml) from Table I was added to about 80 ml of dry dioxane. From this mixture three 25-ml samples were drawn. One sample was diluted with 50 ml of dioxane and enough water to increase the volume to 100 ml. From this 10-ml aliquots were drawn, diluted with water, and titrated with standard hydrochloric acid to determine the total enamine per 25-ml sample. Each of the other 25-ml samples was refluxed for 18 hr, or cooled in ice, and then stored for 24 hr at 25° with <1 equiv of a different alkylating agent, under nitrogen. After cooling, 5 ml of water was added and the mixture refluxed for 1 hr. The cooled reaction mixtures were diluted with 50 ml of dioxane in volumetric flasks and diluted with water to 100 ml. The amount of unreacted enamine was determined by titrating 10-ml aliquots, dissolved in water, with standard hydrochloric acid. The amount of amine acid salt, which equals the amount of C alkylated products, was determined by titrating 10-ml aliquots, dissolved in 50 ml of alcohol, with standard sodium hydroxide. Amount of N alkylated product = total enamine − unreacted enamine − C alkylated product. Titrations were carried out with the pH meter described above and end points determined[17,18] from the following equation: endpoint volume = maximum volume + $0.05\Delta(\Delta pH/\Delta V)_{max}/[\Delta(\Delta pH/\Delta V)_{max-1} + \Delta(\Delta pH/\Delta V)_{max+1}]$. The results are listed in Table I.

Registry No.—5/5, 7148-07-4; 5/6, 1125-99-1; 5/7, 14092-11-6; 5/h, 23516-90-7; 5/n, 3494-04-0; 6/5, 1614-92-2; 6/6, 2981-10-4; 7/6, 23430-63-9; m/5, 936-52-7; m/6, 670-80-4; methyl acrylate, 96-33-3; acrylonitrile, 107-13-1; benzyl bromide, 100-39-0; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; *sec*-butyl bromide, 78-76-2.

(17) D. A. Skoog and D. M. West, "Fundamentals of Analytical Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1963, p 556.

(18) J. J. Lingane, "Electroanalytical Chemistry," 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1958, p 93.

Alkylation of Amines. A New Method for the Synthesis of Quaternary Ammonium Compounds from Primary and Secondary Amines

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Primary and secondary amines have been exhaustively alkylated to their quaternary stage in a one-step procedure. The observation that protonation of sterically hindered amines is only slightly affected by steric hindrance, whereas nucleophilicity as measured by the rate of alkylation is considerably decreased, has been synthetically utilized. An organic base of greater base strength than the reactant amines has been employed to bind the acid generated in alkylation reactions. Aniline and aniline derivatives with pK_a values of 3.86–5.34 have been completely methylated in the presence of the stronger, but sterically hindered base, 2,6-lutidine (pK_a = 6.77). The mild and homogeneous reaction conditions resulted in good yields with minimal laboratory manipulations and effort. As an example of the applicability of the method to amines that possess labile functions, the bisquaternary carbamate, 5-(dimethylcarbamoyloxy)-1,3-phenylenebis(trimethylammonium iodide), has been prepared from 3,5-diaminophenyl dimethylcarbamate in a one-step procedure.

Quaternary ammonium compounds are prepared in most cases from tertiary amines, primary or secondary amines being used only occasionally as the starting materials.[1–3] The methods previously available for direct alkylation of primary and secondary amines to the quaternary stage require relatively harsh reaction conditions and give rise to undesirable side reactions, and, hence, are limited to stable amines and alkylating agents. These methods were developed by A. W. Hofmann in the nineteenth century and are still employed without significant changes. The reaction of a primary or secondary amine with an alkylating agent, such as an alkyl halide, involves the liberation of a hydrohalic acid which combines with the reactant amines to form a mixture of amine hydrohalide salts. Consequently, very low concentrations of free amines remain for subsequent alkylation. To increase the concentration of the free amines, inorganic bases are utilized as the proton acceptors.

The general procedure for the direct alkylation of primary or secondary amines to their quaternary ammonium salts is to reflux a mixture of the amine, an excess of the alkyl halide, and sodium carbonate or sodium hydroxide in water or alcohol. Under these heterogenous reaction conditions prolonged heating is needed leading to numerous side reactions and low yields. Consequently, this method is of value only in those instances where both the amines and the alkylating agents are thermally stable and are insensitive to strong inorganic bases. Further complications arise from the fact that the physical properties of quaternary ammonium salts closely resemble those of inorganic salts. Thus, the purification of quaternary compounds in the presence of inorganic salts can be very laborius, since their solubilities in most common solvents are very similar. In view of the above difficulties and in spite of the addi-

(1) For a review, see J. Goerdeler in "Methoden Der Organishen Chemie, Stickestoffverbindugen" (Houben-Weyl), Eugen Muller, Ed., Vol. XI/2, Georg Thieme Verlag, Stuttgart, Germany, 1958, pp 587–640.

(2) W. Krucker, "Synthese de Sels d'Ammonium quaternaires derives d'Aminophenols et Etude de leur Action sur la Transmission neuromusculaire," J. Peyronnet, Paris, 1951, pp 11–60.

(3) M. M. Markowitz, *J. Org. Chem.*, **22**, 983 (1957).