Alkylation of Amines. A General Exhaustive Alkylation Method for the Synthesis of Quaternary Ammonium Compounds

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A method, whereby primary and secondary amines are exhaustively alkylated to their quaternary stage in a one-step procedure, has been extended to a broad spectrum of amines. The study synthetically utilizes the fact that protonation of sterically hindered amines is affected only slightly by steric hindrance, whereas nucleophilicity as measured by the rate of alkylation is considerably decreased. A sterically hindered organic base of greater base strength than the reactant amines is employed to bind the acid that is generated in alkylation reactions. Selection of an appropriate organic base as the proton acceptor enables complete alkylation of primary and secondary aromatic amines with pK_a values as low as 2.36 and alicyclic and strong aliphatic amines with pK_a values as high as 11.1. The mild and homogeneous reaction conditions result in good yields with minimal laboratory manipulations and effort. The method is of particular importance for reactions in which the amines and the alkylating agents possess labile functions.

In a previous study[1] a new quaternization method was developed, whereby primary or secondary aromatic amines are exhaustively alkylated to their quaternary stage in a one-step procedure.

In the conventional methods[2-4] for direct alkylation of primary or secondary amines to their quaternary salts, strong inorganic bases, such as sodium hydroxide or sodium carbonate, are used to bind the acid generated as the reaction proceeds. The free amines are thus liberated from their hydrohalide salts, and the equilibria are shifted toward complete alkylation. However, the harsh reaction conditions that require prolonged heating of strongly basic and generally heterogeneous reaction mixtures give rise to undesirable side reactions and consequently low yields. These methods, therefore, are of value only in those instances where both the amines and the alkylating agents are thermally stable and are insensitive to strong inorganic bases.

In the new method, an organic base that is readily protonated, yet is a relatively poor nucleophile, serves as the proton acceptor in direct alkylation reactions of primary and secondary amines to their quaternary stage. The base should fulfill the following requirements. (1) The organic base should have solubilities similar to those of the starting amines and the alkylating agents, in order to attain homogeneous reaction conditions. (2) It must be stronger in base strength (larger pK_a) than the reacting amines, in order to combine preferentially with the acid released during the reaction. (3) It must undergo alkylation at a significantly lower rate than the amines to be quaternized. (4) The acid salt of the organic base and the quaternary ammonium product should be separable on the basis of their solubilities in common solvents.

The seemingly contradictory requirements, that the organic base has a larger pK_a yet react with the alkylating agent at a slower rate than the amines to be alkylated, led to a close examination of the relationship between basicity and nucleophilicity.[5-17] Even though a direct relationship between basicity and nucleophilicity has been shown in most studies, sterically hindered amines do not react with alkylating agents at the rates expected on the basis of their pK_a values.[7,11,13,14]

It was concluded that the interaction between a proton and a hindered amine and the interaction of the same amine with an alkylating agent must be substantially different. The proton, due to its small size and electron deficiency, appears to be able to approach the nitrogen of an amine and form a chemical bond in spite of steric hindrance. On the other hand, a sterically hindered nucleophile is hampered or even completely blocked in its attack on the alkylating agent. Whereas electron-donating groups favor the protonation of the amine, the inherent bulk of these groups retards alkylation. Severely hindered amines, therefore, exhibit an inverse relationship between basicity and nucleophilicity.

Sommer and Jackson[1] selected the complete alkylation of aniline and substituted aniline derivatives with methyl iodide in the presence of the hindered base, 2,6-lutidine, to test the validity and practical implementation of the above concepts. Primary and secondary aromatic amines with pK_a values ranging from 3.8 to 5.3 were successfully quaternized in good yields in a one-step procedure.

The present study synthetically applies the new quaternization method to a broad spectrum of amines, extending the method to include weak aromatic amines as well as alicyclic and strong aliphatic amines.

The synthetic utility of the new alkylation reaction lies in the ease by which high yields of quaternary products can be obtained directly from the generally more accessible primary amines at ambient temperature and under mildly basic reaction conditions. Quaternary compounds possessing labile functions that either cannot be prepared at all or are prepared with considerable

(1) H. Z. Sommer and L. L. Jackson, *J. Org. Chem.*, **35**, 1558 (1970).
(2) P. Karrer, "Organic Chemistry," 4th ed, Elsevier, Amsterdam, 1950, p 128.
(3) J. Goerdeler in Houben-Weyl, "Methoden Der Organishen Chemie, Stickstoffverbingdungen," Eugen Muller, Ed., Vol. XI/2, Georg Thieme Verlag, Stuttgart, Germany, 1958, pp 587–640.
(4) 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.
(5) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).
(6) (a) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **78**, 2570 (1956); (b) *ibid.*, **79**, 5441 (1957).
(7) K. Clarke and K. Rothwell, *J. Chem. Soc.*, 1885 (1960).
(8) D. P. Evans, H. B. Watson, and R. Williams, *ibid.*, 1345 (1939).
(9) A. I. Biggs and R. A. Robinson, *ibid.*, 388 (1961).
(10) E. Folkers and O. Runquist, *J. Org. Chem.*, **29**, 830 (1964).
(11) H. C. Brown and X. R. Mihm, *J. Amer. Chem. Soc.*, **77**, 1723 (1955).
(12) H. C. Brown and R. H. Holmes, *ibid.*, **77**, 1727 (1955).
(13) H. C. Brown and A. Cahn, *ibid.*, **77**, 1715 (1955).
(14) H. C. Brown, D. Gintis, and H. Podall, *ibid.*, **78**, 5375 (1956).
(15) (a) G. W. Aska and E. Grunwald, *ibid.*, **89**, 1371 (1967); (b) *ibid.*, **89**, 1377 (1967).
(16) M. M. Fickling, A. Fischer, B. R. Mann, J. Packer, and J. Vaughan, *ibid.*, **81**, 4226 (1959).
(17) (a) A. Fischer, W. J. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3591 (1964); (b) *ibid.*, 3596 (1964).

difficulties by the conventional exhaustive alkylation methods can now be synthesized in a one-step procedure without much effort from primarily amines or even directly from their acid salts.

The general procedure simply involves dissolving the amine, an appropriate sterically hindered organic base, and the alkylating agent, such as methyl iodide, in a suitable solvent and allowing the reaction mixture to stand at room temperature for a number of hours. A stoichiometric amount of the base is important. Although a sufficient amount of proton acceptor must be present to bind the acid released, an excess should be avoided to prevent formation of the methiodide of the acceptor base. Methyl iodide is normally taken in excess. The choice of the proton acceptor and the selection of the appropriate solvent are the two most important factors governing the reaction path. In principle, any organic base that is stronger in base strength and weaker in nucleophilicity than the specific amine to be alkylated can be employed to compel the reaction toward complete alkylation. Whereas only slightly greater base strength suffices, substantially lower nucleophilicities than those of the reacting amines are preferential. Additionally, the yields are greatly dependent on the differences in solubilities between the protonated base and the quaternary product in common solvents. Preferably, a combination of base and reaction solvent is selected to effect precipitation of either the desired product or the hydrohalide salt of the base. The following few guidelines facilitate the choice of the proper organic base and a convenient solvent scheme.

Quaternary ammonium compounds are generally more ionic in character than acid salts of amines and, hence, are less soluble in organic solvents. In both instances, the more aliphatic groups present in the molecule and the greater their size, the greater the solubility in organic solvents. The reactivities of the alkyl halides are in the order of iodides > bromides > chlorides. In the same order, both the quaternary and the amine salts are in most cases more soluble in organic solvent media.

The choice of the reaction solvent for alkylation reactions is dictated by the reactants used. For less reactive nucleophiles, such as amines with relatively low pK_a's, or those that are somewhat sterically hindered, solvents of higher dielectric constants are advantageous. A rough measure of relative rates for a variety of common organic solvents is provided in Table I.

If an anion other than the ion resulting from the reaction mixture is preferred the quaternary ammonium halide is easily exchanged by conventional ion exchange procedure.[18]

Several hindered organic bases were studied and are listed with their pK_a values in Table II. The first base investigated was 2,6-lutidine which has been successfully applied[1] to aromatic amines in the pK_a range from 3.86 to 5.34. In this study, trifluoromethylaniline has been quaternized in 84% yield using 2,6-lutidine as the proton acceptor.

In an attempt to extend the applicability of the method to amines with pK_a values lower than 3.86, di-*n*-propylaniline has been found to be of value. This base appears to be slightly more sterically hindered and approximately one order of magnitude weaker in base strength than 2,6-lutidine. Di-*n*-propylaniline enabled the quaternization of *m*-nitroaniline (pK_a = 2.6)[19] in nearly quantitative yield and *p*-aminobenzoic acid (pK_a = 2.36)[19] in 84% yield. However, attempts to quaternize *p*-nitroaniline (pK_a = 1)[20] were unsuccessful.

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

TABLE I

RELATIVE QUATERNIZATION RATES IN VARIOUS SOLVENTS[a]

Solvent	Approximate relative rate	Solvent	Approximate relative rate
Hexane	1	Ethanol	200
Diethyl ether	4	Methanol	285
Benzene	38	Acetone	340
1-Butanol	70	Acetonitrile	375
Chloroform	100	Nitromethane	500
Ethyl acetate	125	Dimethylformamide	900
Methyl ethyl ketone	150		

[a] F. F. Blicke and R. H. Cox, "Medicinal Chemistry," Vol. III, Wiley, New York, N. Y., 1956, p 51.

TABLE II

STERICALLY HINDERED AMINES USED AS PROTON ACCEPTORS

Base	pK_a
Di-*n*-propylaniline	5.63[a]
N,*N*-Diethylaniline	6.52[a]
2,6-Lutidine	6.77[b]
Dicyclohexylmethylamine	
Tri-*n*-butylamine	10.89[c]
1,2,2,6,6-Pentamethylpiperidine (PMP)	11.25[d]

[a] See ref 10. [b] See ref 7. [c] See ref 21. [d] See ref 22.

The scope of this exhaustive alkylation method has been extensively broadened with the introduction of strong sterically hindered organic bases. Thus, benzylamine (pK_a = 9.3)[19] underwent complete methylation in 85% yield, using *N*,*N*-dicyclohexyl-*N*-methylamine as the basic reagent. Tributylamine served as a good reagent for more basic amines, such as cyclohexylamine (pK_a = 10.6) and *n*-butylamine (pK_a = 10.6).[21] The quaternary products were obtained in 73 and 92% yields, respectively. The readily available tri-*n*-butylamine is advantageous in that its hydrohalide salts are soluble in less polar solvents, such as ethyl acetate, thereby affording in many instances effortless isolation of the desired products.

In the search for an "all purpose" reagent applicable to a wide spectrum of amines, 1,2,2,6,6-pentamethylpiperidine (PMP) appeared to be the base, possessing the required chemical and physical properties, by which this objective could be achieved. The five methyl groups surrounding the ring nitrogen, it was surmised, produce severe steric hindrance, whereas the inductive effects of the methyl groups increase basicity to make PMP one of the strongest organic bases known. As shown in Tables III and IV, PMP has been successfully applied over a pK_a range of 2.5 to 11, and excellent yields of quaternary products have been obtained. The apparent disadvantage that the PMP halo acid salts frequently precipitate from the reaction mixture together with the quaternary compounds can easily be overcome by simple extraction of the PMP halo acids with ace-

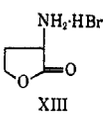
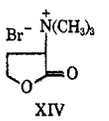
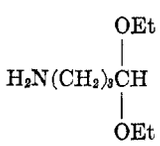
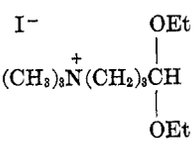
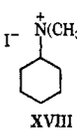
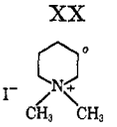
(19) Dictionary of Organic Compounds, Oxford University Press, New York, N. Y., 1965.

(20) H. H. Stroh and G. Westphal, *Ber.*, **96**, 184 (1963).

(21) H. K. Hall, Jr., *J. Phys. Chem.*, **60**, 63 (1956).

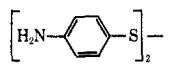
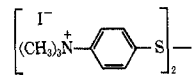
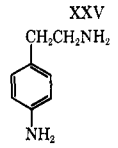
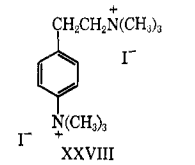
TABLE III

MONOAMINES QUATERNIZED WITH METHYL IODIDE IN THE PRESENCE OF VARIOUS STERICALLY HINDERED ORGANIC BASES

Amine	pK_a	Solvent	Base	Quaternary	Yield, %
p-COOHPhNH$_2$	2.36[a] (amine)	DMF[b]	PhN(*n*-Pr)$_2$	*p*-COOHPh$\overset{+}{N}$(Me)$_3$I$^-$[c]	84
I				II	
m-NO$_2$PhNH$_2$	2.6[a]	DMF	PhN(*n*-Pr)$_2$	*m*-NO$_2$Ph$\overset{+}{N}$(Me)$_3$I$^-$[e]	98
		DMF	PMP[d]		86
III		DMF	(*n*-Bu)$_3$N	IV	65
p-CF$_3$PhNH$_2$		DMF	PhN(*n*-Pr)$_2$	*p*-CF$_3$Ph$\overset{+}{N}$(Me)$_3$I$^-$	67
V				VI	
m-CF$_3$PhNH$_2$		DMF	PhN(*n*-Pr)$_2$	*m*-CF$_3$Ph$\overset{+}{N}$(Me)$_3$ I$^-$	84
		DMF	2,6-Lutidine		84
VII				VIII	
PhNH$_2$	4.65[f]	DMF	PhN(Et)$_2$	Ph$\overset{+}{N}$(Me)$_3$ I$^-$[g]	57
IX				X	
PhCH$_2$NH$_2$	9.30[a]	DMF	Dicyclohexyl-methylamine	PhCH$_2\overset{+}{N}$(Me)$_3$ I$^-$[h]	85
XI		DMF	(*n*-Bu)$_3$N	XII	64
 XIII		DMF	(*n*-Bu)$_3$N	 XIV	43[i]
		CH_3CN	(*n*-Bu)$_3$N		43
		EtOAC	(*n*-Bu)$_3$N		44
 XV		EtOAC	PMP	 XVI	90
Cyclohexylamine	10.6[j]	DMF	(*n*-Bu)$_3$N	 XVIII	73
XVII					
n-BuNH$_2$	10.61[l]	DMF	(*n*-Bu)$_3$N	(*n*-Bu)$\overset{+}{N}$(CH$_3$)$_3$I$^-$[m]	92
XIX				XX	
Piperidine	11.05[n]	DMF	PMP	 XXII	78
XXI					
NH(Et)$_2$	11.11[l]	Acetone	PMP	$\overset{+}{N}$(Et)$_2$(Me)$_2$ I$^-$[n]	90
XXIII				XXIV	

[a] See ref 19. [b] DMF = *N*,*N*-dimethylformamide. [c] A. Zaku and W. Tachoc, *J. Chem. Soc.*, 562 (1941). [d] PMP = 1,2,2,6,6-pentamethylpiperidine. [e] A. Zaku, *J. Chem. Soc.*, 1078 (1930). [f] See ref 10. [g] See ref 16. [h] G. M. Coppinger, *J. Amer. Chem. Soc.*, **76**, 1372 (1954). [i] The I$^-$ was exchanged to the Br$^-$ by means of ion exchange resin. [j] C. W. Bird and R. C. Cookson, *J. Chem. Soc.*, 2343 (1960). [k] Z. J. Vejdelek, M. Rajsner, and M. Protwa, *Collect. Czech. Chem. Commun.*, **25**, 245 (1960); *Chem. Abstr.*, **54**, 6580 (1960). [l] See ref 21. [m] V. Brann, *Justus Liebigs Ann. Chem.*, **382**, 16 (1911). [n] See ref 22. [o] R. O. Clinton and S. C. Laskowski, *J. Amer. Chem. Soc.*, **74**, 2226 (1952).

TABLE IV
DIAMINES QUATERNIZED WITH METHYL IODIDE IN THE PRESENCE OF STERICALLY HINDERED ORGANIC BASES

Diamine	pK_a	Solvent	Base	Bisquaternary	Yield, %
 XXV		DMF	PMP	 XXVI	93
 XXVII		DMF	PMP	 XXVIII	97
$H_2N(CH_2)_nNH_2$				$I^-_+ \quad +\ I^-$ $(CH_3)_3N(CH_2)_nN(CH_3)_3$	
XXIX, n = 3	10.54[a]	DMF	$(n\text{-Bu})_3N$	XXX, n = 3[b]	51
		DMF	PMP		57
XXXI, n = 4	10.71[a]	DMF	$(n\text{-Bu})_3N$	XXXII, n = 4[b]	40
		DMF	PMP		80
XXXIII, n = 10		DMF	$(n\text{-Bu})_3N$	XXXIV, n = 10[c]	52
		CH_3CN	$(n\text{-Bu})_3N$		42
		DMF	PMP		82

[a] See ref 19. [b] E. J. Zaimis, *Brit. J. Pharmacol.*, **5**, 424 (1950). [c] F. Calvert and N. Fernandez, *An. Real Soc. Espan. Fis. Quim., Ser. B*, **47**, 728 (1951); *Chem. Abstr.*, **46**, 10103 (1952).

tone, in which most quaternary ammonium salts are insoluble. In those instances where the quaternary products are soluble in relatively nonpolar solvents, exemplified by the methiodide of γ-aminobutyraldehyde diethyl acetal (XV), ethyl acetate is a suitable reaction solvent from which the PMP hydriodide precipitates out, as the reaction proceeds, while the methiodide remains in solution. After removal of the precipitate, mere evaporation of the solvent produced the analytically pure desired compound in 90% yield. The reaction with *p*-nitroaniline (pK_a = 1) resulted in appreciable amounts of quaternized PMP solely. Hence, the lower limit of the usefulness of PMP appears to be for amines with pK_a's in the vicinity of 2. The upper limit is determined by the basicity of PMP, *i.e.*, pK_a of 11.25.

As examples for direct quaternization of amines containing labile functions, the methiodides of an acetal, γ-trimethylammoniumbutyraldehyde iodide diethyl acetal (XV), a lactone, α-dimethylamino-γ-butyrolactone methobromide (XIII), and a bisquaternary disulfide, bis(4-dimethylaminophenyl) disulfide dimethiodide (XXV), were synthesized in good yields from the corresponding primary amines.

Table IV lists the bisquaternary ammonium compounds that were prepared directly from primary diamines in a one-step procedure. Here, a reaction solvent has to be selected in which the various monoquaternary intermediates that are formed during the reaction are soluble to ensure subsequent alkylation. The monoquaternary compounds still remaining as impurities can be easily removed from the bisquaternary products utilizing solubility differences. Of the cases cited in Table IV, the monoquaternary intermediates are soluble in hot acetone, in which the bisquaternary materials are insoluble.

In conclusion, it is noteworthy to cite an example that emphatically illustrates the underlying principle upon which the new exhaustive alkylation method is based. *m*-Nitroaniline (pK_a = 2.6)[19] was preferentially and completely methylated in 86% yield in the presence of 1,2,2,6,6-pentamethylpiperidine (pK_a = 11.25)[22] which is about 10^9 times greater in base strength than *m*-nitroaniline, whereas no quaternized product of 1,2,2,6,6-pentamethylpiperidine was detected.

Experimental Section

Materials.—All solvents and reagents were the best commercial grade available and were used as received, with the exception of bis(4-aminophenyl) disulfide (XXV) which was purified by recrystallization from benzene with activated carbon treatment. The material thus purified melted at 68–68.5°. All melting points are uncorrected.

1,2,2,6,6-Pentamethylpiperidine (PMP).—A solution of 20.0 g (0.14 mol) of 2,2,6,6-tetramethylpiperidine and 40.0 g (0.28 mol) of methyl iodide in 20 ml of methyl alcohol was kept at ambient temperature overnight. The crystals that formed were removed by filtration, washed with a 1:1 acetone–ether solution and then with ether, and dried under vacuum to give 28.0 g of 1,2,2,6,6-pentamethylpiperidine hydriodide. An additional 7.0 g was obtained by the addition of ether to the mother liquid, mp 279–280° (71% yield). *Anal.* Calcd for $C_{10}H_{22}IN$: C, 42.5; H, 7.8; I, 44.8; N, 4.7. Found: C, 42.2; H, 7.6; I, 45.0; N, 4.9. The hydriodide was converted to the free amine by stirring with 175 ml of 5% sodium hydroxide solution. The amine was extracted with ether, and the ether extract was dried with sodium sulfate and evaporated to give 17.1 g (92% yield) of 1,2,2,6,6-pentamethylpiperidine (PMP) as a colorless liquid.

General Procedure.—Methyl iodide (excess) is added to a solution of the amine or amine salt and the acceptor base in stoichiometric amounts in an appropriate solvent (see Tables III and IV). The amount of excess of methyl iodide taken is not critical, and amounts from 25 to 100% excess produce satisfactory results. The reactions are normally complete in a few hours at room temperature, although for convenience the reaction mixture is allowed to stand overnight. In many cases the quaternary ammonium compound precipitates directly from the reaction mixture. Mere washing of the precipitate with solvents such as

(22) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5444 (1957).

TABLE V
ANALYTICAL DATA OF NEW METHIODIDES

Compd	Formula	Temp, °C	Calcd, % C	H	I	N	X	Found, % C	H	I	N	X
VI	$C_{10}H_{13}INF_3$	195–196	36.2	4.0	38.4	4.2	17.2 (F)	36.2	3.9	38.5	4.0	17.2 (F)
VIII	$C_{10}H_{13}INF_3$	242–243	36.2	4.0	38.4	4.2	17.2 (F)	36.5	3.9	38.1	4.0	16.9 (F)
XVI	$C_{11}H_{26}INO_2$	71–72	40.0	7.9	38.5	4.2		39.9	7.9	38.5	4.5	
XIV	$C_7H_{14}BrNO_2$	210–211	37.2	6.7	35.6 (Br)	6.2		37.6	6.6	35.6 (Br)	6.4	
XXVIII	$C_{14}H_{26}I_2N_2$	260–261	35.3	5.5	53.3	5.9		35.0	5.8	53.0	5.7	
XXVI	$C_{18}H_{26}I_2N_2S_2$	145–146	36.7	4.4	43.2	4.8	10.9 (S)	37.0	4.6		4.7	10.6 (S)

acetone, ethyl acetate, or ether results in generally analytically pure products.

For those instances in which little or no precipitate is formed, a relatively nonpolar solvent, such as acetone, ethyl acetate, or ether, is employed to precipitate the product together with various amounts of acceptor base hydriodide. The latter is then removed by extraction with acetone or 6% *N*,*N*-dimethylformamide in acetone. The remaining quaternary salt is dried to give pure product.

When 1,2,2,6,6-pentamethylpiperidine is used as the sterically hindered base, the precipitate that forms as the reaction proceeds is treated with either acetone at reflux temperature or with 6% *N*,*N*-dimethylformamide in acetone at room or slightly elevated temperatures to dissolve coprecipitated pentamethylpiperidine hydriodide.

It should be noted that, in the exhaustive methylation reaction of the diamines, the precipitates that are obtained directly from the reaction mixture, or by the addition of a nonpolar solvent, should be heated and stirred with acetone at reflux temperature to remove any of the various monoquaternary intermediates that might be present as impurities. These are generally soluble in hot acetone, whereas the bisquaternary compounds are insoluble. Because the reactions are exothermic, slow addition of the alkylating agent is advisable.

Representative examples of the general procedure along with exceptions are described below. The known quaternary products were identified by their melting points, elemental analyses, and nmr spectra. Analytical and physical data of compounds not found in the literature are given in Table V.

***N*,*N*-Dimethyl-3-(trifluoromethyl)aniline Methiodide (VIII).**—A solution of 3.0 g (18.6 mmol) of *m*-(trifluoromethyl)aniline, 6.6 g (37.2 mmol) of di-*n*-propylaniline, and 14.2 g (0.1 mol) of methyl iodide in 15 ml of *N*,*N*-dimethylformamide was kept at room temperature overnight. The precipitated product was then collected on a filter, washed with acetone and then with ether, and dried to give 5.2 g (84% yield) of VIII as colorless crystals, mp 242–243°. *Anal.* Calcd for $C_{10}H_{13}F_3IN$: C, 36.2; H, 4.0; F, 17.2; I, 38.4; N, 4.2. Found: C, 36.5; H, 3.9; F, 16.9; I, 38.1; N, 4.0.

Trimethylbutylammonium Iodide (XX).—To a solution of 0.73 g (0.01 mol) of *n*-butylamine and 3.7 g (0.02 mol) of tri-*n*-butylamine in 5 ml of *N*,*N*-dimethylformamide, 5.68 g (0.04 mol) of methyl iodide was added gradually. After standing overnight, the addition of ether precipitated white solid crystals. The precipitate was removed by filtration, recrystallized from ethanol, washed with ether, and dried to give 2.25 g (92% yield) of XX, mp 223–225°. *Anal.* Calcd for $C_7H_{18}IN$: C, 34.6; H, 7.4; N, 5.8. Found: C, 34.7; H, 7.6; N, 5.9.

***N*,*N*-Dimethyl-3-nitroaniline Methiodide (IV).**—A solution of 500 mg (3.6 mmol) of *m*-nitroaniline, 1.12 g (7.2 mmol) of 1,2,2,6,6-pentamethylpiperidine, and 3.1 g (21.6 mmol) of methyl iodide in 5.0 ml of *N*,*N*-dimethylformamide was kept overnight at room temperature. The solid that formed was removed by filtration and washed with hot acetone to give 0.95 g (86%) of IV as pale yellow crystals, mp 198–199°. *Anal.* Calcd for $C_9H_{13}IN_2O_2$: C, 35.2; H, 4.2; I, 41.1; N, 9.1; O, 10.4. Found: C, 35.4; H, 4.2; I, 41.5; N, 9.3; O, 10.2.

4-Dimethylaminobutyraldehyde Diethyl Acetal Methiodide (XVI).—A solution of 500 mg (3.1 mmol) of γ-aminobutyraldehyde diethyl acetal and 960 mg (6.2 mmol) of 1,2,2,6,6-pentamethylpiperidine in 10.0 ml of ethyl acetate was treated with 14.2 g (0.1 mol) of methyl iodide. The tenfold excess of methyl iodide aided in keeping all the quaternary product in solution. The reaction mixture was allowed to stand overnight at room temperature. The pentamethylpiperidine hydriodide that precipitated was removed by filtration, and the filtrate evaporated under reduced pressure at ambient temperature to give a white solid which was washed with ether and dried to give 940 mg (90% yield) of XVI, mp 71–72°. *Anal.* Calcd for $C_{11}H_{26}INO_2$: C, 40.0; H, 7.9; I, 38.5; N, 4.2. Found: C, 39.9; H, 7.9; I, 38.5; N, 4.5.

α-Dimethylamino-γ-butyrolactone Methobromide (XIV).—A solution of 500 mg (2.7 mmol) of α-amino-γ-butyrolactone hydrobromide and 1.5 g (8.1 mmol) of tri-*n*-butylamine in 10.0 ml of ethyl acetate was treated at ambient temperature with 2.5 g (16.2 mmol) of methyl iodide. A precipitate formed almost immediately. After 3 hr, the solid was removed by filtration and washed with ethyl acetate and then ether.

The product thus obtained was dissolved in methanol and passed through a Bio-Rad analytical anion exchange resin column (AG1-X8) saturated with bromide ions. The eluent was concentrated to 15 ml and upon addition of ether a solid precipitated. The solid material was collected on a filter and vacuum dried at ambient temperature to give 320 mg (44% yield) of XIV, mp 210–211°. *Anal.* Calcd for $C_7H_{15}BrNO_2$: C, 37.2; H, 6.7; Br, 35.6; N, 6.2. Found: C, 37.6; H, 6.6; Br, 35.6; N, 6.4.

1-Dimethylamino-2-(4-dimethylaminophenyl)ethane Dimethiodide (XXVIII).—1-Amino-2-(4-aminophenyl)ethane (1.0 g, 7.3 mmol), 4.53 g (29.2 mmol) of 1,2,2,6,6-pentamethylpiperidine, and 11.5 g (88 mmol) of methyl iodide were dissolved in 10.0 ml *N*,*N*-dimethylformamide. Heat evolved immediately, and a precipitate formed. After the mixture was kept at room temperature overnight, 250 ml of a 6% *N*,*N*-dimethylformamide in acetone solution were added and stirred for 20 min under reflux conditions. The remaining solid was collected on a filter and redissolved in methanol. Addition of ethyl acetate, filtration, and drying produced 3.4 g (97% yield) of XXVIII as white crystals, mp 260–261°. *Anal.* Calcd for $C_{14}H_{26}I_2N_2$: C, 35.3; H, 5.5; I, 53.3; N, 5.9. Found: C, 35.0; H, 5.8; I, 53.0; N, 5.7.

Registry No.—II, 880-00-2; IV, 27389-55-5; VI, 27389-56-6; VIII, 27389-57-7; X, 98-04-4; XII, 4525-46-6; XIV, 27389-60-2; XVI, 1116-78-5; XVIII, 3237-34-1; XX, 7722-19-2; XXII, 3333-08-2; XXIV, 4325-24-0; XXVI, 21787-24-6; XXVIII, 27389-67-9; XXX, 27389-68-0; XXXII, 23045-52-5; XXXIV, 1420-40-2; PMP, 79-55-0.

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