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Novel Methylation. III (1a). Methylation of Tertiary Amines such as Pyridine and Isoquinoline with Alkyl Carboxylates (1b).

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The alkylation of tertiary amines, namely, 2-dimethylaminoethanol, triethylamine, pyridine and isoquinoline with various alkyl carboxylates was investigated. This reaction afforded the corresponding quarternary ammonium salts, *e.g.*, methylation of 2-dimethylaminoethanol with methyl salicylate.

Choline salicylate (Ia) (2) was obtained by the reaction of 2-dimethylaminoethanol with methyl salicylate (3). Furthermore, the novel methylation of tertiary amines with alkyl salicylates was reported in previous papers (1a, 3).

The present paper describes the alkylation of the tertiary amines, 2-dimethylaminoethanol, triethylamine, pyridine, and isoquinoline with various alkyl carboxylates. A mixture of the tertiary amine and methyl aliphatic or aromatic carboxylate was heated under reflux or at 80-165°. The addition of an excess of ether to the reaction mixture gave a syrup from which the product was characterized as the *O*-picrate or chloroplatinate.

Esters of strongly acidic monobasic or dibasic carboxylic acids were used as the methylation agents. The reaction proceeded by heating the amines mentioned above with the ester. The reaction of the tertiary amines with methyl aliphatic carboxylates is shown in Table I, the reaction with dimethyl aliphatic dicarboxylates is shown in Table II and the reaction with methyl aromatic carboxylates is shown in Table III.

These experimental results reveal that the yields of the reaction between 2-dimethylaminoethanol and methyl *o*-nitrobenzoate is better than that of the reaction with methyl *p*-nitrobenzoate and, furthermore, the yield in case of the latter ester exceeds that of the reaction with methyl *o*-methoxybenzoate. This information suggests that the acid-strength of the carboxylic acid corresponding to the ester used as the reagent is an important factor in this reaction and that the reaction of an ester of a strongly acidic carboxylic acid with tertiary amines would afford the required salts.

Likewise, alkylation of tertiary amines with ethyl, *n*-propyl, *n*-butyl, and benzyl carboxylates was investigated. The results with aliphatic carboxylic acid esters are recorded in Table IV and with aromatic carboxylic acid esters in Table V. Although the esters of a strongly acidic carboxylic acids appeared more suitable as reagents, the reaction of tertiary amines with diethyl, di-*n*-propyl, di-*n*-butyl, and dibenzyl malonate failed even though the mixture was heated under reflux in the cases of triethylamine and pyridine, and 140-150° in the case of isoquinoline. This observation suggests that steric hinderance of the reagent inhibits alkylation in the case of the diesters. The reactions using methyl and benzyl esters of monobasic acids generally proceeded in much better yields than with *n*-propyl and *n*-butyl esters.

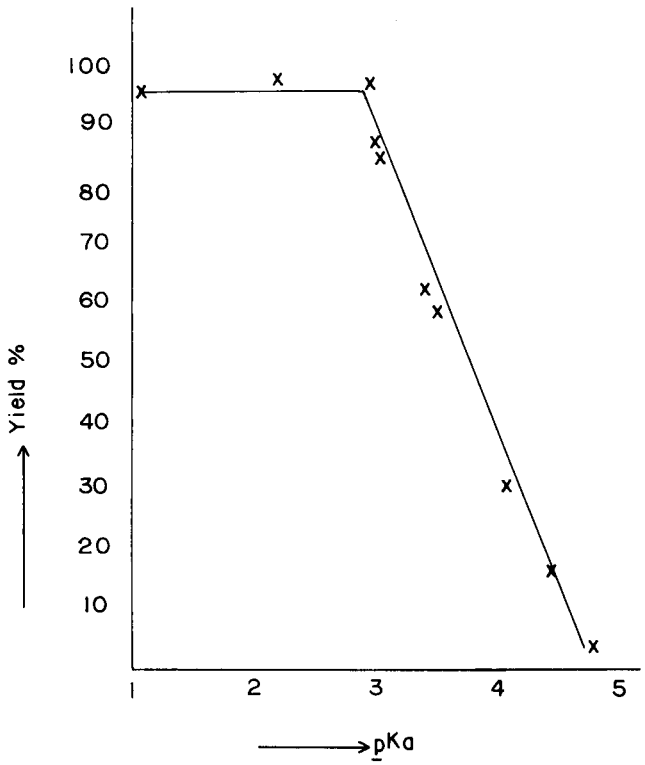
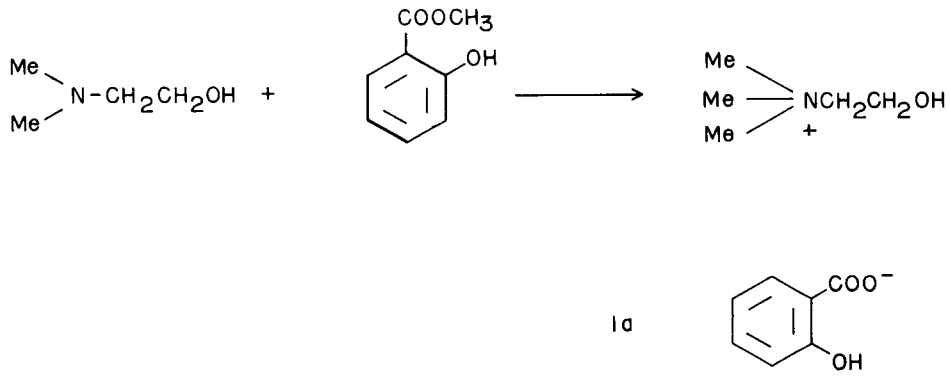


Fig. 1. The Relationship Between *p*Ka of the Carboxylic Acid and Yield of the Quarternary Ammonium Salts.

CHART 1



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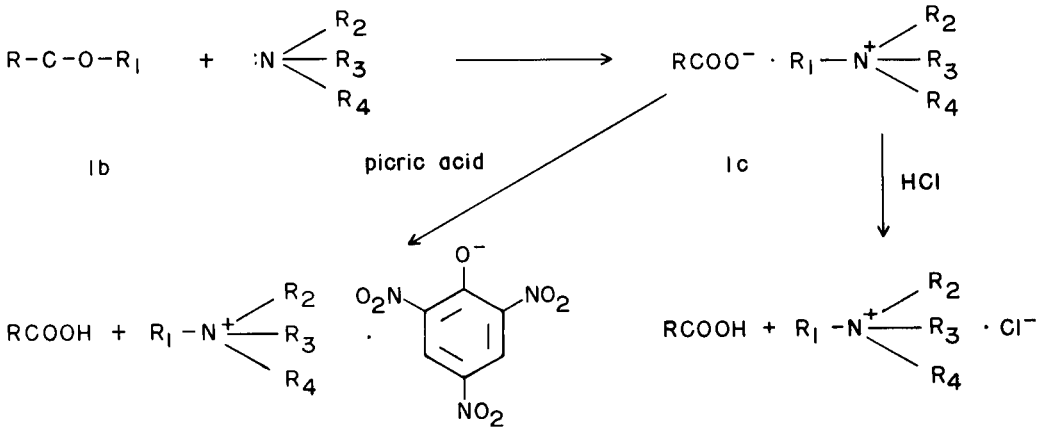


TABLE I

The Reaction of Tertiary Amines with the Methyl Esters of Aliphatic Carboxylic Acids

Compound No.	Ester used (g.)	Tertiary amine used (g.)	Reaction time (hr.)	Reaction temp. (°C)	Yield (g.;%)	Reference of picrate
I	$CNCH_2CO_2Me$ (1.98)	$Me_2NCH_2CH_2OH$ (1.78)	8	100	1.0 (26)	4
II	$CNCH_2CO_2Me$ (1.98)	Et_3N (2.02)	15	reflux	1.2 (30)	5
III	$CNCH_2CO_2Me$ (1.98)	pyridine (1.52)	10	reflux	1.8 (51)	6
IV	HCO_2Me (1.98)	$Me_2NCH_2CH_2OH$ (1.35)	17	120-130 (a)	1.8 (82)	6
V	$CH_3\underset{\displaystyle OH}{\underset{\vert}{C}}HCO_2Me$ (2.08)	$Me_2NCH_2CH_2OH$ (1.78)	13	100-110	3.2 (82)	4
VI	CH_3CO_2Me (1.48)	$Me_2NCH_2CH_2OH$ (1.78)	12	100 (a)	0.1 (4.4)	4
VII	$CH_3CH_2CO_2Me$ (1.76)	$Me_2NCH_2CH_2OH$ (1.78)	17	120-130 (a)	0.3 (8.4)	4

(a) This reaction was carried out in a sealed tube.

TABLE II

The Reaction of Tertiary Amines with Methyl Esters of Aliphatic Dicarboxylic Acids

Compound No.	Ester used	(g.)	Tertiary amine used (g.)	Reaction time (hr.)	Reaction temp. (°C)	Yield (g.;%)	Reference of picrate
VIII		(2.36)	$Me_2NCH_2CH_2OH$ (1.78)	16	100	4.0 (96)	4
IX	CO_2Me | CO_2Me	(2.36)	Et_3N (2.02)	6	reflux	2.8 (63)	5
X		(2.36)	pyridine (1.58)	6	100	1.8 (45)	6
XI		(2.58)	isoquinoline (2.36)	16	100	0.5 (10)	7
XII		(2.88)	$Me_2NCH_2CH_2OH$ (1.78)	8	100	2.66 (57)	4
XIII	$CHCO_2Me$ ‖ $CHCO_2Me$	(2.88)	Et_3N (2.02)	15	reflux	0.2 (4.0)	5
XIV		(2.88)	pyridine (1.58)	12	reflux	0.2 (4.4)	6
XV		(1.5)	isoquinoline (1.3)	4.5	135	0.1 (3.5)	7
XVI	CH_2 < CO_2Me / CO_2Me	(2.64)	$Me_2NCH_2CH_2OH$ (1.78)	13	80-100	1.1 (24)	4
XVII		(2.64)	Et_3N (2.02)	15	reflux	0.3 (6.4)	5
XVIII		(2.64)	pyridine (1.58)	8.5	110	trace	6
XIX		(2.88)	$Me_2NCH_2CH_2OH$ (1.78)	12	100	4.0 (85)	4
XX	MeO_2CCH ‖ $CHCO_2Me$	(2.88)	Et_3N (2.02)	15	reflux	0.3 (6.1)	5
		(2.88)	pyridine (1.58)	10	110	0	
XXI		(2.92)	$Me_2NCH_2CH_2OH$ (1.78)	15	100	0.9 (19)	5
	CH_2CO_2Me | CH_2CO_2Me	(2.92)	Et_3N (2.02)	15	reflux	0	
		(2.92)	pyridine (1.58)	10	110	0	

TABLE III

The Reaction of Tertiary Amines with Methyl Esters of Aromatic Carboxylic Acids

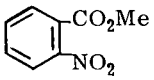
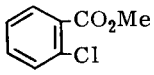
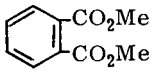
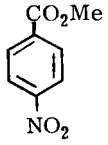
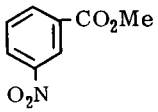
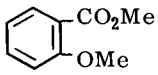
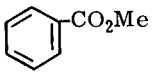
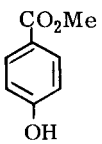
Compound No.	Ester used	(g.)	Tertiary amine used (g.)	Reaction time (hr.)	Reaction temp. (°C)	Yield (g.;%)	Reference of picrate
XXII		(3.62)	$Me_2NCH_2CH_2OH$ (1.78)	16	100	5.3 (98)	4
XXIII		(4.3)	Et_3N (2.5)	9	reflux	0.7	5
XXIV		(3.62)	pyridine (1.58)	8.5	100	0.55 (10)	6
XXV		(1.8)	isoquinoline (1.3)	4	120-130	0.9 (29)	7
XXVI		(3.41)	$Me_2NCH_2CH_2OH$ (1.78)	14	100-110	5.0 (96)	4
XXVII		(3.41)	Et_3N (2.02)	15	reflux	0.2 (3.6)	5
XXVIII		(3.41)	pyridine (1.58)	12	reflux	0.1 (2.0)	6
XXIX		(1.7)	isoquinoline (1.3)	18.5	140-150	0.05 (1.6)	7
XXX		(3.88)	$Me_2NCH_2CH_2OH$ (1.78)	14	100	5.0 (88)	4
XXXI		(8.5)	Et_3N (5.0)	4	reflux	1.9 (14)	5
XXXII		(3.88)	pyridine (1.58)	10	110	0.1 (1.8)	6
XXXIII		(3.62)	$Me_2NCH_2CH_2OH$ (1.78)	16	100	3.5 (64)	4
XXXIV		(3.62)	Et_3N (2.02)	15	reflux	0.3 (5.3)	5
		(3.62)	pyridine (1.58)	6	reflux	0	
XXV		(3.62)	$Me_2NCH_2CH_2OH$ (1.78)	16	100	3.2 (59)	4
XXXVI		(3.62)	Et_3N (2.02)	15	reflux	1.2 (21)	5
XXXVII		(3.62)	pyridine (1.58)	8.5	100	0.08 (1.5)	6
XXXVIII		(3.32)	$Me_2NCH_2CH_2OH$ (1.78)	14	100-110	1.6 (31)	4
		(3.32)	Et_3N (2.02)	15	reflux	0	
		(3.32)	pyridine (1.58)	8	reflux	0	
XXXIX		(2.72)	$Me_2NCH_2CH_2OH$ (1.78)	9	100-110	1.5 (33)	4
		(2.72)	pyridine (1.58)	20	reflux	0	
XL		(3.04)	$Me_2NCH_2CH_2OH$ (1.78)	15	100 110	0.74 (15.4)	4
XLI		(3.04)	pyridine (1.58)	10	reflux	2.0 (43)	6

TABLE IV

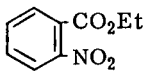
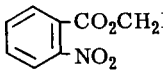
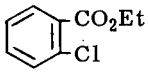
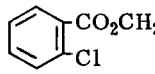
The Reaction of Tertiary Amines with Dialkyl Esters of Aliphatic Dicarboxylic Acids

Compound No.	Ester used	(g.)	Tertiary amine used (g.)	Reaction time (hr.)	Reaction temp. (°C)	Yield (g.;%)	Reference of picrate
	CO_2Et	(3.0)	Et_3N (2.0)	20	reflux	0	
XLII	CO_2Et	(2.9)	pyridine (1.6)	9	reflux	1.1 (24)	6
XLIII		(3.0)	isoquinoline (2.6)	10	120-130	0.8 (14)	6
	CO_2n-Pr	(3.5)	Et_3N (2.0)	20	reflux	0	
XLIV	CO_2n-Pr	(3.5)	pyridine (1.6)	32.5	reflux	0.5 (9.8)	6
XLV		(7.0)	isoquinoline (5.2)	11	130-140	2.5 (20)	1a
	CO_2n-Bu	(4.0)	Et_3N (2.0)	20	reflux	0	
XLVI	CO_2n-Bu	(4.0)	pyridine (1.6)	35	reflux	0.35 (6.2)	8(a)
XLVII		(4.0)	isoquinoline (2.0)	11	130-140	1.0 (37)	1a
XLVIII		(1.0)	Et_3N (0.37)	5.5	reflux	0.52 (37)	9
XLIX	CO_2CH_2Ph	(0.5)	pyridine (0.15)	2.5	reflux	0.16 (24)	6
L	CO_2CH_2Ph	(0.5)	isoquinoline (1.24)	1	145-150	0.64 (86)	10

(a) This compound was characterized as the chloroplatinate.

TABLE V

The Reaction of Tertiary Amines with Dialkyl Esters of Aromatic Dicarboxylic Acids

Compound No.	Ester used	(g.)	Tertiary amine used (g.)	Reaction time (hr.)	Reaction temp. (°C)	Yield (g.;%)	Reference of picrate
		(1.0)	Et_3N (0.5)	15	reflux	0	
LI		(1.0)	pyridine (0.4)	16	reflux	0.07 (5.0)	6
LII		(1.0)	isoquinoline (0.7)	16	120-140	0.1 (5.8)	6
LIII		(1.29)	Et_3N (0.5)	8.5	reflux	0.24 (13)	9
LIV		(1.29)	pyridine (0.4)	6	reflux	0.22 (13)	6
LV		(1.29)	isoquinoline (0.65)	5	130	0.43 (22)	10
		(1.9)	Et_3N (1.0)	15	reflux	0	
		(1.9)	pyridine (0.8)	15	reflux	0	
		(1.9)	isoquinoline (1.3)	15	150-160	0	
		(1.0)	Et_3N (0.4)	15	reflux	0	
		(1.0)	pyridine (0.3)	20	reflux	0	
LVI (a)		(1.0)	isoquinoline (0.5)	7	165	0.05 (3.3)	10

(a) This compound was prepared by the reaction of *o*-chlorobenzoic acid with benzyl chloride in the presence of potassium carbonate. *Anal.* Calcd. for $C_{14}H_{11}O_2Cl$: C, 68.18; H, 4.49. Found: C, 67.79; H, 4.58. Colorless oil, b.p. 230°/16 mm.

TABLE VI

The Formation of Methyl Half-esters of Dicarboxylic Acids

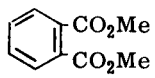
	Tertiary amine used (g.)	Reaction time (hr.)	Reaction temp. (°C)	Yield of ammonium salt (g.;%)	Yield of half-ester (g.;%)	Character (m.p. or b.p.) (°C)
CO_2Me | CO_2Me (5.6)	Et_3N (5.1)	12	reflux	8.9 (83.2)	3.4 (82.9)	colorless oil (11) b.p. 102-104/10mm.
dimethyl fumarate (2.8)	$Me_2NCH_2CH_2OH$ (1.8)	12	100	4.0 (86.9)	1.8 (81.7)	colorless prisms (12) (EtOH) m.p. 142-144
CH_2CO_2Me | CH_2CO_2Me (2.9)	$Me_2NCH_2CH_2OH$ (1.8)	15	100	0.9 (19.1)	0.36 (13.8)	colorless needles (13) (EtOH) b.p. 121-123/4mm. m.p. 56-55
 (7.8)	$Me_2NCH_2CH_2OH$ (3.6)	10	100	10.4 (91.3)	2.0 (30.8)	colorless plates (14) (benzene-petroleum ether) m.p. 82-83

TABLE VII

The Relationship between *p*Ka and the Yield of Ammonium Salt formed by the Reaction with 2-Dimethylaminoethanol with Methyl Carboxylates

Compound No.	Carboxylic acid	*p*Ka	Reaction time (hr.)	Reaction temp. (°C)	Yield of ammonium salt (%)
VIII	oxalic acid	1.22	16	100	96
XXII	*o*-nitrobenzoic acid	2.17	16	100	98
XXVI	*o*-chlorobenzoic acid	2.92	14	100-110	96
XXX	phthalic acid	3.00	14	100	88
XIX	fumaric acid	3.02	12	100	85
XXXIII	*p*-nitrobenzoic acid	3.42	16	100	64
XXXV	*m*-nitrobenzoic acid	3.49	16	100	59
XXXVIII	*o*-methoxybenzoic acid	4.09	14	100	31
XL	*p*-hydroxybenzoic acid	4.48	15	100-110	15.4
VI	acetic acid	4.81	12	100 (in a sealed tube)	4.4

The reaction conditions shown in Tables I-V were selected in order to determine whether or not the desired ammonium salts would be formed. An additional study of reaction time and temperature appears indicated if one wishes to improve the yields. For instance, from the reaction between isoquinoline and benzyl *o*-chlorobenzoate at 130° for 13 hours both starting materials were recovered, however, when both reactants were heated at 165° for 7 hours, the product (LVI) was obtained. Therefore, it appears certain that these reactions would proceed in better yields under more carefully controlled conditions.

Perhaps the simplest mechanism to explain the formation of quarternary ammonium salt (Ic) would initially involve the formation of an alkyl carbonium cation R_1^+ due to strong chelation in the case of the salicylate (3) or due to the presence of a strongly electro-negative group adjacent to the alkoxycarbonyl group. We suggest that formation of Ic results from reaction of the generated carbonium ion with the tertiary amine.

Furthermore, the half-ester of the dicarboxylic acids was obtained in case of alkylation with dialkyl dicarboxylates as shown in Table VI. Therefore this reaction may be a useful procedure for preparing half-esters.

The relationship between the *p*Ka of a carboxylic acid and the yield of the quarternary ammonium salt obtained by the reaction of 2-dimethylaminoethanol with methyl carboxylate is shown in Table VII and Fig. 1. These results indicate that the methyl carboxylates of acids having a *p*Ka of less than 3 gave almost the same yield under the same conditions and the yield with carboxylates whose corresponding acids have a *p*Ka greater than 3 decreases as a straight line function (Fig. 1).

EXPERIMENTAL

General Preparation of Quarternary Ammonium Salts (15).

A 1:1 molar mixture of tertiary amine and ester was heated and the reaction mixture was repeatedly washed with an excess of ether to remove the unreacted starting materials, giving quarternary ammonium salts, which were characterized as the picrates (or chloroplatinates). These salts were identical with an authentic sample by mixed melting point determination and by IR spectrum. The starting materials were recovered from the ethereal solutions.

General Synthetic Method for the Formation of Monoalkyl Hydrogen Carboxylates.

The quarternary ammonium salts which were obtained by the reaction under the conditions indicated in Table VI were dissolved in 10% hydrochloric acid solution and extracted with ether. The solvent layer was separated, washed with water, and dried over sodium sulfate. Removal of the solvent gave half-esters as oils or crystals, which were identical with authentic samples by mixed melting point determination and by infrared spectrum.

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(15) All the quarternary ammonium salts shown in Tables I-V were characterized as their picrates, but only the representative examples which were reported in the literature are described in the experimental data.

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