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75. Tetsuji Kametani,*3 Kazuo Kigasawa,*3 Hiroshi Sugahara,*4 Mineharu Hiiragi,*4 Tetsutaro Hayasaka,*4 Takehiko Iwata,*4 and Haruhide Ishimaru*4 : Novel Methylation.*1 Methylation of Tertiary Amines with Alkyl Salicylate.*2

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The choline salicylate (I) was obtained by the reaction of 2-dimethylaminoethanol with methyl salicylate. Furthermore, a novel methylation of tertiary amines with alkyl salicylate was also established.

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The choline salicylate, namely (2-hydroxyethyl)trimethyl-ammonium salicylate (I), which is prepared from sodium salicylate and choline halide,[1~3] is well known as an analygesic agent.

The present paper describes an alternative synthesis by which the above compound (I) is obtained in better yield. A study of the methylation of various tertiary amines with alkyl salicylate was also investigated.

A mixture of 2-dimethylaminoethanol and methyl salicylate was heated at 95~100° for 12 hr.; addition of an excess of ether to the reaction mixture dissolved in a small amount of acetone afforded a resinous substance which was recrystallized from acetone-ether to give hygroscopic colorless needles (I), m.p. 50~52°, undepressed on admixture with an authentic sample prepared from sodium salicylate and choline chloride.[1] Both infrared spectra were also identical. The compound (I) formed a choline picrate. Recrystallization from ethanol gave yellow needles, m.p. 243~244°, which was also identical in IR spectrum and showed no depression on admixture with the choline picrate of the above authentic sample.[1] Acidification of the aqueous solution of I with

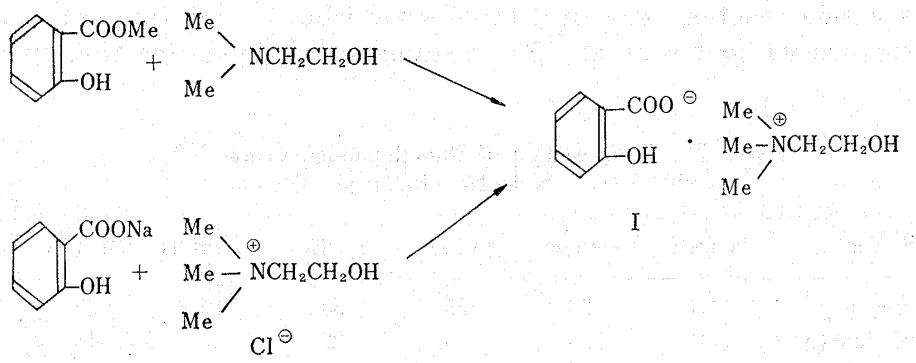

Chart 1.

*1 Short communication of this paper was reported in Tetrahedron Letters, No. 23, 1817 (1965).

*2 This forms Part CLXXIX of "Studies on the Syntheses of Heterocyclic Compounds," by T. Kametani. Part CLXXVIII. This Bulletin, **15**, 608 (1967).

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1) R. H. Bron-Kahn, E. T. Sasmor : U. S. Pat., 3,069,321 (1962); Japan Pat., 300,040 (1961); Brit. Pat., 869,553 (1961).

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3) "Veride" and Societa Italiano Medicinal Scandicci, Belg. Pat., 611,312 (1961).

10% hydrochloric acid solution gave quantitatively salicylic acid as colorless needles, m.p. 158~159°.

In the above case if a mixture of 2-dimethylaminoethanol and methyl salicylate was heated at 95~100° for 20 hr., the choline salicylate (I) was obtained in an excellent yield (ca. 90%), and therefore the reaction time seems to be one of the important factors. A similar reaction occurred between several tertiary amines and methyl salicylate, yielding the expected quarternary ammonium salicylate as is shown in Table I. These ammonium salts were characterized as its O-picrate.

Table I. The Reaction of Tertiary Amines with Methyl Salicylate

Compound	Amine	Methyl salicylate (g.)	Time (hr.)	Temperature (°C)	Yield (g.)	Appearance and m.p.	
						Salicylate	Picrate
I	$Me_2NCH_2CH_2OH$ 8.9 g.	15.2	12	95~100	16.8	colorless needles m.p. 50~52°	yellow needles m.p. 243~244°
		15.2	20	95~100	21.8		
II	$Et_2NCH_2CH_2OH$ 1.1 g.	1.5	10	100	2.0	colorless plates m.p. 194~196°	〃 m.p. 240°
III	Et_3N 1.0 g.	1.5	15	100	1.1	brown oil	〃 m.p. 266~269°
IV	Pyridine 1.6 g.	3.0	5	120~130	3.5	〃	〃 m.p. 113~115°
V	Isoquinoline 3.3 g.	3.8	4	160	4.8	brown syrup	〃 m.p. 164~166°

Methylation of the tertiary amines having a strong basicity generally proceeded at a comparatively lower temperature, but the reaction between methyl salicylate and amines having a weak basicity needed a higher temperature.

Furthermore, this reaction also proceeded in an excellent yield by 30 hours' refluxing in benzene, 15 hours' refluxing in toluene, 8 hours' refluxing in xylene, and 13 hours' refluxing in *n*-butanol as is shown in Table II. The reaction generally proceeded at a higher temperature for a short time, but *trans*-esterification was recognized as a side reaction only in a large scale when a mixture was heated at a higher temperature without solvent. For instance, dimethylaminoethyl salicylate was obtained.

Table II. The Reaction of Dimethylaminoethanol (8.9 g.) with Methyl Salicylate (15.2 g.) in Solvent

Solvent	benzene	toluene	xylene	EtOH	iso-PrOH	*n*-PrOH	*n*-BuOH
Volume (ml.)	25	25	25	50	25	25	25
Reflux time (hr.)	30	15	8	22	13	13	13
Yield of (I) (%)	80	80	80	27	70	79	85

In the second place alkylation of tertiary amines with ethyl, *n*-propyl, *n*-butyl, *iso*-propyl, and benzyl salicylate was examined, giving some results as is shown in Table III. In this case only the reaction of isoquinoline with ethyl, *n*-propyl and *n*-butyl salicylate proceeded successfully, but the reaction of the other amines with alkyl salicylate resulted in failure. Nevertheless, the reaction of various tertiary amines with benzyl salicylate proceeded smoothly in better yield, as is shown in Tabel IV. Furthermore, the reaction of tertiary amines, for instance, triethylamine and pyridine,

with ethyl salicylate in a sealed tube under a higher pressure proceeded successfully, as is shown in Table V.

Table Ⅲ. The Reaction of Isoquinoline with Alkyl Salicylate

Compound	Ester used	Isoquinoline used (g.)	Time (hr.)	Temperature (°C)	Yield (g.)	Appearance and m.p.	
						Salicylate	Picrate
Ⅵ	Ethyl salicylate 3.2 g.	2.5	5	165～170	1.75	brown syrup	yellow cubes m.p. 181～182°
Ⅶ	*n*-propyl salicylate 4.2 g.	1.6	10.5	165～170	0.9	〃	yellow prisms m.p. 167～168°
Ⅷ	*n*-butyl salicylate 3.9 g.	2.6	11	165～170	0.35	〃	yellow plates m.p. 178～179°

Table Ⅳ. The Reaction of Tertiary Amines with Benzyl Salicylate

Compound	Benzyl salicylate (g.)	Tertiary amine (g.)	Reaction temp. (°C)	Reaction time (hr.)	Yield (g.)	Appearance and m.p.	
						Salicylate	Picrate
Ⅸ	22	$Me_2NCH_2CH_2OH$ 0.9	100	13	1.75	colorless syrup	yellow prisms m.p. 98～100°
Ⅹ	2.2	Et_3N 1.0	reflux	21	0.15	brown syrup	yellow needles m.p. 124°
Ⅺ	4.6	Pyridine 1.6	〃	10	3.2	reddish-brown oil	〃 m.p. 118°
Ⅻ	3.4	Isoquinoline 1.9	150～170	0.5	1.8	brown oil	yellow cubes m.p. 175～176°

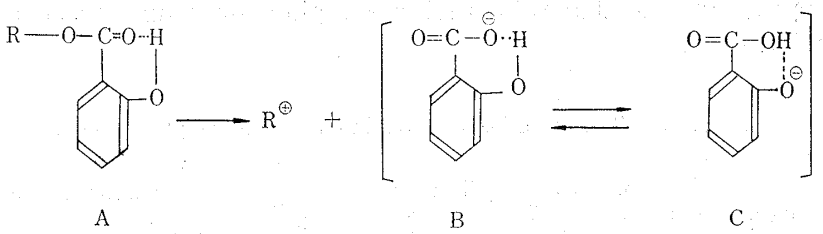
Table Ⅴ. The Reaction of Tertiary Amines with Ethyl Salicylate in a Sealed Tube

Compound	Ethyl salicylate (g.)	Tertiary amine (g.)	Reaction temp. (°C)	Reaction time (hr.)	Yield (g.)	Appearance and m.p.	
						Salicylate	Picrate
XIII	0.5	Et_3N 0.5	165～175	12	0.05	brown syrup	yellow needles m.p. 254°
XIV	1.0	Pyridine 0.7	150～165	15	0.75	〃	yellow leaflets m.p. 91°

Perhaps the simplest mechanism to explain the formations of (D) would initially involve strong chelation between ester carbonyl and hydroxyl radical of the compound (A) and formation of (B $\rightleftharpoons$ C) and alkyl carbonium cation R^+. We suggest that the alkyl carbonium cation which formed due to the presence of the hydroxyl radical adjacent to the alkoxycarbonyl group led to the formation of (D) as the result of reaction with tertiary amines.

These facts reveal that the acid-strength of the carboxylic acid used as reagent is one of the important factors and that the reaction of carboxylic acid ester having a strong acidity and tertiary amines would afford our objective ammonium salts. For instance, the reaction between pyridine and methyl cyanoacetate gave 1-methylpyridinium salt, whose picrate was characterized as yellow needles, m.p. 113～115°.

The novel methylation of tertiary amines with the other ester is under examination.



A B C

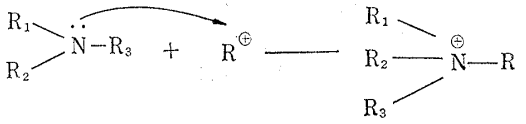


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Chart 2.

Experimental*5

N-(2-Hydroxyethyl)-N-trimethylammonium Salicylate (I)——a) After a mixture of 8.9 g. of 2-dimethylaminoethanol and 15.2 g. of methyl salicylate had been heated at 95~100° for 20 hr., the resultant mixture was fully washed with ether. Recrystallization of the residue from Me_2CO-ether gave 21.8 g. of the salicylate (I) as hygroscopic colorless needles, m.p. and mixed m.p. 50~52° (lit.,[1] m.p. 50~52°), whose IR spectrum was superimposable on that of an authentic sample. Salicylic acid (105 mg.; 92%) was recovered by acidification of 200 mg. of the above salicylate with 10% HCl aq. solution.

To a solution of the above salicylate (I) in EtOH was added a solution of picric acid in EtOH, giving the O-picrate as yellow needles, m.p. 243~244° (from EtOH), which showed no depression of melting point on admixture with an authentic sample.[4]

Removal of the solvent from the reaction mixture which was obtained under the conditions in Table II gave the dark brown residue, whose treatment as usual and recrystallization from Me_2CO-ether afforded the same salicylate (I) as above.

b) A mixture of 11.6 kg. of 2-dimethylaminoethanol and 19.9 kg. of methyl salicylate was heated in an oil-bath at 100~128° for 12 hr. After the reaction, the reaction mixture was poured into 66 kg. of water and extracted with 31 kg. of $CHCl_3$. After the organic solvent layer had been separated, an aqueous solution was evaporated to dryness *in vacuo*. Recrystallization of the resultant residue from Me_2CO-ether gave 24.4 kg. of the above salicylate (I) as colorless needles, m.p. 50~52°. The above $CHCl_3$ extract was treated with 10% HCl aq. solution, whose acidic solution separated was basified with saturated $NaHCO_3$ aq. solution and extracted with benzene. The benzene extract was washed with water, dried on K_2CO_3 and distilled *in vacuo* to give 5 g. of dimethylaminoethyl salicylate as a colorless oil, b.p. 125~127°/5 mm. (lit.,[5] b.p. 110°/1.5 mm.), whose HCl salt was recrystallized from EtOH to yield colorless needles, m.p. 155~157°. *Anal.* Calcd. for $C_{11}H_{15}O_3N \cdot HCl$: C, 53.76; H, 6.51; N, 5.70. Found: C, 53.82; H, 6.56; N, 5.53.

N-Diethyl-N-(2-hydroxyethyl)-N-methylammonium Salicylate (II)——A mixture of 1.1 g. of 2-diethylaminoethanol and 1.5 g. of methyl salicylate was heated at 100° for 10 hr., and the resultant mixture was washed with an excess of ether. Recrystallization of the residue from Me_2CO-ether gave 2.0 g. (76.9%) of the salicylate (II) as colorless needles, m.p. 194~196°. Recrystallization of the picrate from EtOH gave yellow needles, m.p. 240°, whose melting point agreed with that of an authentic sample (lit.,[6] m.p. 239.9~240.5°). *Anal.* Calcd. for $C_7H_{18}ON \cdot C_6H_2O_7N_3$: C, 43.33; H, 5.60; N, 15.55. Found: C, 43.06; H, 5.38; N, 15.83.

N-Triethyl-N-methylammonium Salicylate (III)——A mixture of 1.0 g. of triethylamine and 1.5 g. of methyl salicylate was heated under reflux for 15 hr., and then washed with 160 ml. of ether, to give 1.1 g. (44%) of III as a brown syrup. A solution of 200 mg. of the above salicylate in 1 ml. of conc. HCl aq. solution was washed with ether. The above acidic solution was evaporated to dryness. To a solution of

*5 All m.p.s. were not corrected.

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the preceding residue in EtOH was added a solution of an excess of KI in EtOH, KCl separated being removed by filtration. Removal of the solvent from the filtrate and recrystallization of the residue from EtOH–ether gave 60 mg. (31.2%) of this iodide as pale yellow needles, m.p. >260°, whose IR spectrum was identical with that of an authentic sample.[7] Recrystallization of the picrate from EtOH gave yellow needles, m.p. and mixed m.p. 266~269 (lit.,[8] m.p. 268~268.5°).

To one-half (80 ml.) of the above ethereal washing was added a solution of picric acid in ether, 0.85 g. of triethylammonium picrate being recovered. Recrystallization from EtOH gave yellow needles, m.p. 172~173°, which was identical with an authentic sample.

Furthermore, the remaining (80 ml.) of the above ethereal solution was washed with 10% HCl aq. solution and water, dried on Na_2SO_4, and distilled off, to give 0.4 g. of methyl salicylate whose IR spectrum was superimposable on that of an authentic sample.

N-Methylpyridinium Salicylate (IV)——A mixture of 1.6 g. of pyridine and 3.0 g. of methyl salicylate was heated under reflux for 5 hr., and then washed with ether, giving 3.5 g. (76.0%) of the salicylate (Ⅳ) as a brown syrup. After a solution of 200 mg. of the above salicylate (Ⅳ) in 1 ml. of conc. HCl aq. solution had been washed with ether, an acidic solution separated was evaporated to dryness and the residue was dissolved in EtOH, to which solution was added a solution of KI in EtOH. KCl separated was removed by filtration and the resultant ethanolic filtrate was condensed, 30 mg. (15.7%) of iodide being precipitated on cooling. Recrystallization from MeOH gave colorless needles, m.p. 116°, which was identical with an authentic sample[9] from mixed m.p. and IR spectrum. Recrystallization of the picrate from EtOH gave the same yellow needles as the literature,[10] m.p. 113~115°.

The former ethereal washing was extracted with 10% HCl aq. solution and the resultant acidic solution was evaporated *in vacuo* to give the solid, to which solution in EtOH was added a solution of sodium picrate in EtOH. Recrystallization of 1.1 g. of the recovered pyridinium picrate from EtOH gave yellow needles, m.p.165~166°, which was identical with an authentic sample. On the other hand an ethereal layer as above was separated and dried on Na_2SO_4. Removal of the solvent gave 0.7 g. of methyl salicylate.

N-Methylisoquinolinium Salicylate (V)——A mixture of 3.3 g. of isoquinoline and 3.8 g. of methyl salicylate was heated at 160° for 4 hr., and then washed with ether, giving 4.8 g. (67.6%) of the salicylate (Ⅴ) as a brown syrup. To a solution of the above salicylate (Ⅴ) in EtOH was added a solution of picric acid in EtOH. Recrystallization of the picrate from MeOH gave yellow needles, m.p. 163~166°, which was identical with an authentic sample.[11,12] *Anal.* Calcd. for $C_{10}H_{10}N\cdot C_6H_2O_7N_3$: C, 51.62; H, 3.25; N, 15.05. Found: C, 51.39; H, 3.54; N, 15.04.

The preceding ethereal washing was extracted with 10% HCl aq. solution and the acidic layer was separated from ether (A), basified with 10% NaOH aq. solution and extracted with ether. The extract was dried on Na_2SO_4 and removal of the solvent recovered isoquinoline (1.0 g.). On the other hand removal of the above ethereal extract (A) gave 1.2 g. of methyl salicylate.

N-Ethylisoquinolinium Salicylate (VI)——A mixture of 2.5 g. of isoquinoline and 3.2 g. of ethyl salicylate was heated at 165~170° for 5 hr., and the reaction mixture was, after cooling, washed with ether, a brown syrup (1.75 g.; 30.7%) being remained as a residue. Recrystallization of the picrate from water and then from MeOH gave yellow cubes, m.p. 179~180°, which was identical with an authentic sample[13] from mixed m.p. and IR spectrum. *Anal.* Calcd. for $C_{11}H_{12}N\cdot C_6H_2O_7N_3$: C, 52.85; H, 3.65; N, 14.50. Found: C, 53.05; H, 3.27; N, 14.34.

N-*n*-Proylisoquinolinium Salicylate (VII)——A mixture of 10.5 g. of isoquinoline and 2.4 g. of *n*-propyl salicylate was heated at 165~170° for 10.5 hr., and then washed with ether, 0.4 g. (22.5%) of the salicylate (Ⅶ) being obtained as a brown syrup. Recrystallization of the picrate from water and then from MeOH gave yellowish-orange prisms, m.p. 167~168°, which was identical with an authentic sample[14] by mixed m.p. and IR spectrum. *Anal.* Calcd. for $C_{12}H_4N\cdot C_6H_2O_7N_3$: C, 54.00; H, 4.03; N, 14.00. Found: C, 53.76; H, 4.28; N, 13.78.

N-*n*-Butylisoquinolinium Salicylate (VIII)——A mixture of 2.6 g. of isoquinoline and 3.9 g. of *n*-butyl salicylate was heated at 165~170° for 11 hr., and then washed with ether, to give 0.55 g. (5.3%) of the salicylate (Ⅷ) as a brown syrup. Recrystallization of the picrate from water and then from MeOH gave yellow plates, m.p. 178~179°, which was identical with the picrate obtained from N-*n*-butylisoquinolinium iodide[15] as usual. *Anal.* Calcd. for $C_{13}H_{16}N\cdot C_6H_2O_7N_3$: C, 55.07; H, 4.38; N, 13.52. Found: C, 54.87; H, 4.24; N, 13.70.

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N-Benzyl-N-(2-hydroxyethyl)-N-dimethylammonium Salicylate (IX)——A mixture of 0.9 g. of 2-dimethylaminoethanol and 2.2 g. of benzyl salicylate was heated at 100° for 13 hr. and washed with ether, to give 1.75 g. (54.7%) of the salicylate (IX) as a colorless syrup. Recrystallization of the picrate from EtOH gave yellow prisms, m.p. 98~100°, which was identical with the sample obtained from N-benzyl-N-(2-hydroxyethyl)-N-dimethylammonium iodide[16] as usual. *Anal.* Calcd. for $C_{11}H_{18}ON \cdot C_6H_2O_7N_3$: C, 50.00; H, 4.94; N, 13.72. Found: C, 50.10; H, 5.03; N, 13.75.

N-Benzyl-N-triethylammonium Salicylate (X)——A mixture of 1.0 g. of triethylamine and 2.2 g. of benzyl salicylate was heated under reflux for 21 hr. and washed with ether, yielding 0.15 g. (4.6%) of the salicylate (X) as a brown syrup. Recrystallization of the picrate from EtOH-benzene (1:3) gave yellow needles, m.p. 124°, which was identical with an authentic sample[17] by mixed m.p. and IR spectrum.

N-Benzylpyridinium Salicylate (XI)——A mixture of 1.6 g. of pyridine and 4.6 g. of benzyl salicylate was heated under reflux for 10 hr. and then washed with ether, giving 3.2 g. (51.6%) of the salicylate (XI) as a reddish-brown oil. Recrystallization of the picrate from EtOH gave yellow prisms, m.p. 118°, which was identical with an authentic sample[18] by mixed m.p. and IR spectrum.

N-Benzylisoquinolinium Salicylate (XII)——A mixture of 1.9 g. of isoquinoline and 3.4 g. of benzyl salicylate was heated under reflux at 150~170° for 0.5 hr., and then washed with ether, giving 1.8 g. (33.9%) of the salicylate (XII) as a brown oil, to which was added 100 ml. of 10% HCl aq. solution. After salicylic acid separated had been extracted with ether, 2.5 g. of KI was added to the preceding acidic solution. The iodide separated was collected by filtration. Recrystallization from EtOH gave 1.4 g. (79.1%) of N-benzylisoquinolinium iodide as yellow cubes, m.p. 175~176°, which was identical with an authentic sample[19] by mixed m.p. and IR spectrum.

Tetramethylammonium Salicylate (XIII)——A mixture of 0.5 g. of triethylamine and 0.5 g. of ethyl salicylate was heated at 165~175° for 12 hr. in a sealed tube, and the reaction mixture was washed with ether, giving 0.05 g. (6.3%) of the salicylate (XIII) as a brown syrup. Recrystallization of the picrate from water gave yellow needles, m.p. 254°, which was identical with an authentic sample.[20]

N-Ethylpyridinium Salicylate (XIV)——A mixture of 0.7 g. of pyridine and 1.0 g. of ethyl salicylate was heated at 150~165° for 15 hr. in a sealed tube and washed with ether after the reaction. The salicylate (XIV) (0.75 g.) was obtained as a brown syrup with a yield of 44.5%. Recrystallization of the picrate from EtOH gave yellow leaflets, m.p. 91~92°, which was identical with an authentic sample[13] by mixed m.p. and IR spectrum.

N-Methylpyridinium Cyanoacetate——A mixture of 1.52 g. of pyridine and 1.98 g. of methyl cyanoacetate was refluxed for 10 hr. After the reaction mixture had been washed with ether, 1.8 g. (51.4%) of N-methylpyridinium cyanoacetate was obtained as a reddish brown oil. Recrystallization of the picrate from EtOH gave yellow needles, m.p. 116~117°.[13]

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