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A NOVEL METHYLATION OF TERTIARY AMINES WITH METHYL SALICYLATE

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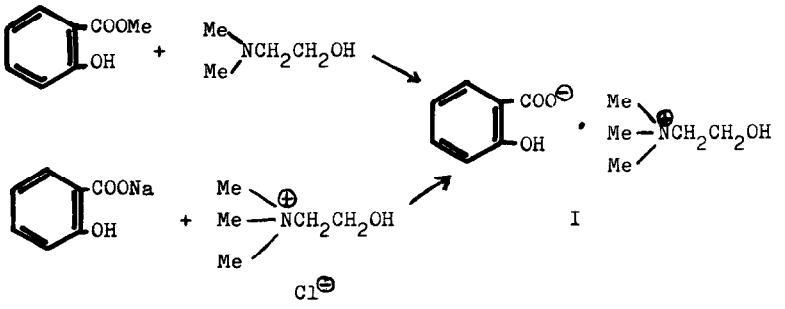
The choline salicylate, (2-hydroxyethyl)trimethylammonium salicylate (I), which is prepared from sodium salicylate and choline halide (1,2,3), is well known as an analgesic agent.

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 methyl 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 crystallized from acetone-ether as hygroscopic colourless 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 which was recrystallized from ethanol to

give yellow needles, m.p. 243 - 244°, identical (infrared spectrum) and undepressed on admixture with the choline picrate of the above authentic sample (1). Acidification of an aqueous solution of (I) with 10% hydrochloric acid gave quantitatively salicylic acid as colourless needles, m.p. 158 - 159°.

This reaction proceeded smoothly with an excellent yield by 15 hours' refluxing in toluene, 10 hours' refluxing in xylene, and 10 hours' refluxing in butanol.



I

A similar reaction occurred between several tertiary amines and methyl salicylate, yielding the expected quarternary ammonium salicylate (II - V) as is shown in Table I.

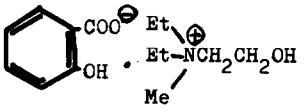
These ammonium salts were characterized as the O-picrate and the methiodide.

TABLE I. The Reaction of Several Amines with Methyl Salicylate

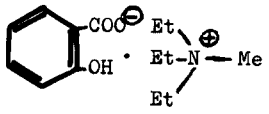
Compound	Amine	Methyl salicylate	Time (hr.)	Temperature (°C)	Yield	Character(Appearance and m.p.) of ammonium salt	
						Salicylate	Picrate
I	$Me_2NCH_2CH_2OH$ (8.9 g.)	15.2 g.	12	95 - 100°	16.8g.	colourless needles m.p. 50-52°	Yellow needles m.p.243 - 244°(4)
II	$Et_2NCH_2CH_2OH$	1.5 g.	10	100°	2.0g.	colourless plates m.p.194-196°	Yellow needles*1(5) m.p. 240°
III	Et_3N (1.0 g.)	1.5 g.	15	100°	1.1g.	brown oil	Yellow needles (6) m.p. 266-269°
IV	Pyridine (1.6 g.)	3.0 g.	5	120 -130°	3.5g.	brown oil	Yellow needles (7) m.p. 113-115°
V	Isoquinoline (3.3 g.)	3.8 g.	4	160°	4.8g.	brown syrup	Yellow needles*2(8) m.p. 164-166°

*1 Found: C, 43.06; H, 5.38; N, 15.83. $C_7H_{18}NO \cdot C_6H_2N_3O_7$ requires C, 43.33; H, 5.60; N, 15.55%.

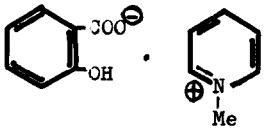
*2 Found: C, 51.39; H, 3.54; N, 15.04. $C_9H_{12}N_4O_7 \cdot C_6H_2N_3O_7$ requires C, 51.62; H, 3.25; N, 15.05%.



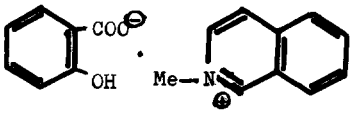
II



III

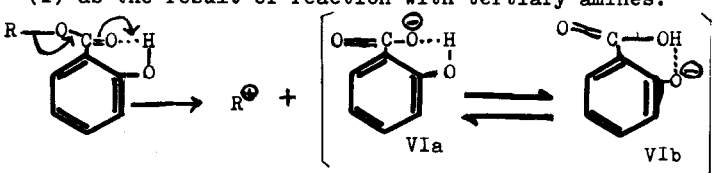


IV

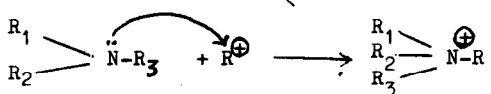


V

Perhaps the simplest mechanism to explain the formation of (I) would initiary involve strong chelation between ester carbonyl and hydroxyl radical and formation of (VI ⟷ VIb) and methyl carbonium cation R^+. We suggest that the alkyl carbonium cation which formed due to the presence of the hydroxyl radical adjacent to the methoxycarbonyl group led to the formation of (I) as the result of reaction with tertiary amines.



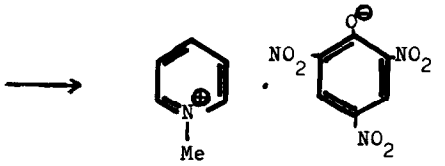
VIa VIb



In the case of methyl benzoate this reaction did not take place, but the reaction between pyridine and methyl cyanoacetate gave 1-methylpyridinium salt (VII), whose picrate (VIII) was characterized as yellow needles, m.p. 113 - 115°.

These facts reveal that the acid-strength of the carboxylic acid used as reagent is one of the important factors and that the similar reaction between the ester of carboxylic acid having a strong acidity and tertiary amines would occur.

VII



VIII

On the other hand, methylation of the tertiary amines having a strong basicity proceeded at a comparatively lower temperature, but the reaction between methyl salicylate and amines with a weak basicity needed a higher temperature.

Alkylation of tertiary amines with ethyl, isopropyl, tert-butyl and benzyl salicylate is under investigation.

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