composition 2 *p*:1 *o*. Our earlier conclusion was probably in error because of failure to obtain equilibrium owing to the extreme viscosity of the cresols and their outstanding tendency to remain undercooled. The possibility that there exist both a 2:1 compound and a 1:1 is, of course, not excluded, but we have been unable to repeat the results showing the existence of the latter.

The eutectic between *o*-cresol and compound at 0° and the transition point of the compound to *p*-cresol at 8.1° were obtained by extrapolation; they are, respectively, 0.6 and 1.2° lower than found by Dawson and Mountford. The curves for the two components are in reasonable agreement with those of the same investigators.

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[CONTRIBUTION FROM THE FURMAN CHEMICAL LABORATORY OF VANDERBILT UNIVERSITY]

# ESTERS OF THE PROCAINE TYPE DERIVED FROM NICOTINIC ACID

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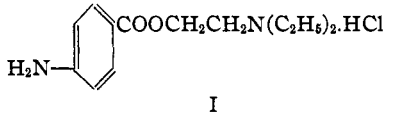
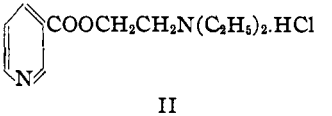
The work reported in this paper was undertaken with a view to determine to what extent, if any, the local anesthetic properties of procaine (I) and its homologs would be retained in compounds of the same type derived from the pyridine-carboxylic acids. For this purpose the esters of nicotinic acid with β-diethylamino-ethyl alcohol (II) and with γ-diethylamino-propyl alcohol have been prepared and tested.




I




II

Of the pyridine-carboxylic acids, nicotinic acid is apparently the most closely related in structure to *p*-aminobenzoic acid, and was chosen for this reason.

Although several derivatives of partially hydrogenated nicotinic acid, notably arecoline,[1] are included among the potent alkaloids, few other derivatives of nicotinic acid have been studied as to their physiological behavior. Nicotinic acid itself is stated to be slightly poisonous and is detoxicated in dogs by conversion in part to the corresponding methyl-betaine (trigonelline) and in part to nicotinyl glycine.[2] The diethyl- and dipropylamides and the piperidide have been patented as drugs.[3] While

[1] S. Frankel, "Die Arzneimittel Synthese," J. Springer, Berlin, **1921**, pp. 41 and 311.

[2] Ackermann, *Z. Biol.*, **59**, 17 (1912).

[3] U. S. pat. 1,403,117 (1922).

the simple alkyl esters of nicotinic acid appear not to have been tested, the methyl ester methochloride (Cesol) is the representative of several analogs that have been patented as therapeutic agents.[4] No esters with amino alcohols have previously been described.

Previous studies on the relation of molecular structure to local anesthetic action in esters of the procaine type have shown, in general, that when the β-diethylamino-ethyl group is replaced by related groups, or when the *p*-aminobenzoyl group is replaced by other aromatic acyl groups, the resulting esters have at least some anesthetic activity. On the other hand, when the acyl groups are of the saturated aliphatic or mixed types, the resulting esters are but rarely anesthetics.[5] In fact, the existence of anesthetic action in compounds of this type, extending, as it does, to the esters of the thiophene-, furane- and pyrrole-carboxylic acids, has been proposed as a possible test for the "aromatic" nature of the acyl group involved.[5]

In view of the above considerations it was rather surprising to find, as the result of careful tests, that both of the esters prepared were entirely lacking in anesthetic properties. Also, no mydriatic action and only a slight toxicity were observed. Whether the absence of anesthetic action in these esters should be ascribed to an essentially non-aromatic character of the pyridine ring or to some other property peculiar to this ring cannot be decided at present. It is suggested that an examination of the esters derived from the isomeric pyridine-carboxylic acids would be interesting in this connection.

## Discussion of the Syntheses

The esters, as monohydrochlorides, were prepared by the action of β-diethylamino-ethyl alcohol and γ-diethylaminopropyl alcohol, respectively, upon pure nicotinyl chloride in suspension in dry benzene or acetone. The nicotinyl chloride was prepared by heating nicotinic acid in a closed flask with a small excess of thionyl chloride dissolved in dry benzene. Meyer[6] has given general directions for preparing the chlorides of the pyridine-carboxylic acids by heating these in a sealed tube with a large excess of thionyl chloride as solvent. Attempts to apply his method to nicotinic acid invariably gave so large a proportion of the corresponding acid chloride-hydrochloride as to make this method unsatisfactory for our purpose. The modified method gives a product melting nearly 20° higher than Meyer's preparation and appears to be more economical of time and materials.

[4] Ger. pat. 340,874 (1921); 343,054 (1922).

[5] Gilman and Pickens [THIS JOURNAL, **47**, 245 (1925)] present a recent summary of the theory.

[6] Meyer, *Monatsh.*, **22**, 109 (1901).

## Experimental Part

**Nicotinyl Chloride.** (a) ATTEMPTED PREPARATION BY MEYER'S METHOD.—Fifteen g. of well-dried nicotinic acid and 45.0 g. of thionyl chloride were placed in a small flask into which was wired a rubber stopper bearing a sealed capillary tube. The mixture was heated in a steam-bath for two hours. The capillary was then broken and the clear solution allowed to cool. The greater part of the substance in solution separated as white needles. After being washed with benzene and dried, these melted sharply at 148° (uncorr.). The substance absorbed moisture readily and dissolved with decomposition in cold water and in alcohol. It was moderately soluble in boiling benzene. From its properties and analysis it was the hydrochloride of nicotinyl chloride which has been imperfectly described by Laiblin[7] and by Meyer.[6]

*Anal.* Subs., 0.2355, 0.2497: AgCl, 0.3692, 0.3921. Calcd. for $C_6H_5ONCl_2$: Cl, 39.84. Found: 38.78, 38.85.

The reaction described above was repeated under various conditions with essentially the same results. When, however, the excess of thionyl chloride was distilled before crystallization occurred and the residue was extracted repeatedly with boiling benzene, the product then gave the properties and analysis of rather impure nicotinyl chloride. This process was not satisfactory for preparing the quantities desired, nor could pure esters be obtained from the product.

(b) THE MODIFIED METHOD.—Preliminary experiments showed that the acid chloride, mixed with only small amounts of its hydrochloride, was formed when the acid was heated with a small excess of thionyl chloride in dry benzene. After a number of trials the following procedure was adopted.

Ten g. (0.082 mole) of nicotinic acid was suspended in 75 cc. of benzene (dried over sodium) in a small flask and 14.5 g. (0.123 mole) of thionyl chloride was added. The flask was closed as described in (a) above and heated during frequent shaking in a steam-bath for two hours. The benzene was decanted while still warm and the residue of nicotinyl chloride was extracted thrice with 30cc. portions of boiling benzene to remove the hydrochloride. The product was kept over calcium chloride and paraffin wax. In four runs the yield was 88–91% of a white, semi-crystalline solid that always melted at 264–265° (uncorr.). Meyer gave 245° as the melting point of his preparation, which probably was somewhat impure.[8]

*Anal.* Subs., 0.2216: AgCl, 0.2166. Calcd. for $C_6H_4ONCl$: Cl, 25.06. Found: 24.18.

**β-Diethylamino-ethyl Nicotinate (Hydrochloride).**—Preliminary experiments showed that this compound could be formed by the reaction of equivalent quantities of nicotinyl chloride and β-diethylamino-ethyl alcohol in benzene solution and subsequent crystallization of the pasty product from pure acetone. The purity was somewhat higher, however, when the reaction was run in acetone solution and the product crystallized by cooling the solvent. The following procedure is typical.

Eight g. of finely powdered nicotinyl chloride was suspended in 40 cc. of acetone in a small flask. An equal volume of acetone containing 6.83 g. of the amino alcohol

[7] Laiblin, *Ann.*, **196**, 167 (1879).

[8] Compare Wolffenstein and Hartwich, *Ber.*, **48**, 2043 (1915).

was gradually added during cooling and the mixture was warmed and shaken for an hour. The acetone solution was then filtered while hot from a small amount of solid and cooled to crystallization. A second crop of crystals obtained by concentrating the filtrate was united with the first and these were recrystallized from fresh solvent. From three preparations the average yield was 41% of white needles that melted gradually between 140° and 160° when slowly heated, but rather abruptly in contact with a bath previously heated to 169–170°. The substance is hygroscopic and dissolves readily in cold water and the lower alcohols, from which it cannot be crystallized.

*Anal.* Subs., 0.3741, 0.2655: AgCl, 0.2110, 0.1505. Calcd. for $C_{12}H_{19}O_2N_2Cl$: Cl, 13.71. Found: 13.95, 14.02.

**γ-Diethylaminopropyl Nicotinate (Hydrochloride).**—Four g. of nicotinyl chloride was suspended in 30 cc. of dry benzene, and 3.67 g. of γ-diethylaminopropyl alcohol in an equal volume of benzene was gradually added. Upon refluxing for an hour the nicotinyl chloride was slowly replaced by a pasty layer that collected upon the bottom of the flask. Upon triturating with fresh portions of hot benzene and cooling, the paste changed to a powdery white solid. It was brought to constant weight in a desiccator over calcium chloride and paraffin wax; yield, 90%. The substance is very hygroscopic and is readily soluble in water and the lower alcohols, but could not be crystallized from any common solvent. It melted at 172–173° in a previously heated bath.

*Anal.* Subs., 0.2982, 0.3158: AgCl, 0.1587, 0.1682. Calcd. for $C_{13}H_{21}O_2N_2Cl$: Cl, 13.06. Found: 13.16, 13.18.

Attempts to carry out the reaction in acetone solution appeared to give the same substance, but it could be obtained only as a semi-crystalline mass which rapidly absorbed moisture.

## Pharmacological Tests

The authors are indebted to Professor P. D. Lamson of the Vanderbilt University Medical School for tests on the two compounds described above. These were applied in dilute and in concentrated solution, under a variety of conditions, to the exposed vagus nerves of anesthetized dogs, to the eyes of rabbits, and to the nerve endings of the operator's tongue. In no case was there any certain evidence of local anesthesia or of mydriatic action, and no marked irritation of the mucous membrane. The intravenous injection of as much as 150 mg. of the substances produced only a slight depression of the blood pressure and no appreciable effect on the respiration. No definite difference could be detected in the action of the two compounds, both of which are remarkably inert.

## Summary

The β-diethylamino-ethyl and γ-diethylaminopropyl esters of nicotinic acid have been prepared and found to be devoid of local anesthetic properties. The preparation of nicotinyl chloride has been improved.

NASHVILLE, TENNESSEE