STUDIES ON ANÆSTHETICS AND LOCAL ANÆSTHETICS

N-Substituted Amides and Esters of Nicotinic, Picolinic, and *Iso*-Nicotinic Acids

Of the three isomeric pyridine monocarboxylic acids, the β-variety, *viz.*, nicotinic acid has, in recent years, assumed great importance as an accessory food factor belonging to the vitamin B complex[1] with great therapeutic possibilities. Further its diethylamide, familiarly known as 'Coramine', is a reputed cardio-respiratory stimulant.[2] A further point of interest in this acid is that its N-substitued ethanolamine and homologous esters have been shown to possess local anæsthetic activity.[3]

The present work, therefore, involves the preparation of the three isomeric acids from β- and γ-picolines isolated from the middle oil fraction of Indian coal-tar, and the α-acid from a sample of α-picoline. The β-acid was also prepared by the decarboxylation of quinolinic acid obtained by the oxidation of qinoline (*i*) isolated from Indian coal-tar, and (*ii*) synthesised by Scraup's method.

Though there is considerable literature on the oxidation of the picolines and quinoline, the available information was found to be very inadequate, and the detailed conditions for their convenient preparation had to be worked out using $KMnO_4$ solution at temperatures below 100° C., and isolation of the acids through the copper salts. Results of our experiments are given below:—

Raw material used	Acid obtained	Yield (% on theory)	M.P.	Equivalent
1. α-Picoline B.P. 124–29°	Picolinic acid	25	135–136°	123·4
2. Mixture of β & γ-picoline B.P. 140–47°	* Nicotinic acid	11	225–226°	125·5
	* Isonicotinic acid	12·5	305–306°	122·1
3. Quinoline B.P. 230–35°	Quinolinic acid	33	180° (decomp.	83·9
4. Quinolinic acid	Nicotinic acid	80	232°	125·2

* Separated from the oxidation product by repeated crystallisation from absolute alcohol.

Coramine (b.p. 172-173°/19 mm.) has been prepared (yield, 68·8 per cent.) from nicotinic acid, *via.* its acid chloride, by the action of diethylamine also prepared in this laboratory.

From the acid chloride of the above pure mono acids, the following *new* N-substituted amides, which are likely to possess anæsthetic action, have been prepared.

(1) Picolinic acid *p*-anisidide, m.p. 88°;
(2) Picolinic acid *o*-anisidide, m.p. 110°;
(3) Nicotinic acid *p*-anisidide, m.p. 141°;
(4) Isonicotinic acid *p*-anisidide, m.p. 153°;
(5) Picolinic acid benzyl amide (semi-solid).

β-Chlorethyl picolinate, $C_5H_4N\text{-}CO_2\text{-}CH_2.CH_2.Cl$ (b.p. 136-138°/5-7 mm.) and β-chlorethyl nicotinate (b.p. 167-69°/45 mm.), have been prepared from the corresponding acid chlorides by the action of ethylene chlorhydrin. *p*-Methoxyphenylaminoethyl picolinate, $C_5H_4N\text{-}COO.CH_2.CH_2.NHC_6H_4.OCH_3$, was prepared from the chlorethyl ester by the action of *p*-anisidine; acetyl derivative, m.p. 170°. Further work on the preparation of some typical esters and amides of this series is in progress. The compounds prepared await pharmacological examination.

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1. *Indian Med. Gaz.*, 1942, **77**, 98. 2. *J. Amer. Pharm. Assoc.*, 1944, **33**, 72. 3. *J. Amer. Chem. Soc.* 1942, **64**, 1721.