

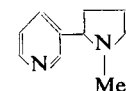
NICOTINE MONOMETHIODIDE

By R. B. BARLOW and N. A. DOBSON

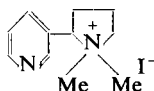
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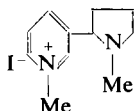
NICOTINE (I) is a di-tertiary base. It can, therefore, form two monomethiodides (II and III) and a dimethiodide (IV).



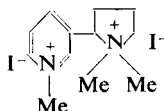
Nicotine (I)



Nicotine monomethiodide (II)



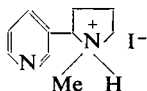
Nicotine *iso*-methiodide (III)



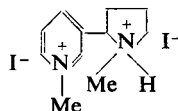
Nicotine dimethiodide (IV)

Nicotine dimethiodide, which is obtained by treating nicotine with an excess of methyl iodide, was studied by Crum Brown and Fraser¹. They showed that it produced a "curare-like" paralysis of a frog nerve-muscle preparation, but that it was very much less toxic than nicotine itself.

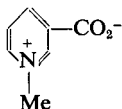
The nicotine monomethiodide (III), in which the pyridine nitrogen atom is quaternised, was prepared by Pictet and Genequand² and named nicotine *isomethiodide*. Nicotine was converted into the di-hydrogen iodide, which was then refluxed in ethanol with 1 mol. of nicotine. This solution contains nicotine mono-hydrogen iodide (V), in which the proton is attached to the more basic pyrrolidine nitrogen atom. It was treated with an excess of methyl iodide and so converted to the hydrogen iodide (VI) of nicotine *isomethiodide*. From this, nicotine *isomethiodide* itself (III) was easily obtained. This substance melted at 164° C.; the platinichloride of the corresponding nicotine *isomethochloride*, C₁₀H₁₄N₂, MeCl, HCl, PtCl₄, a yellow material, decomposed without melting at



Nicotine mono-hydrogen iodide (V)



Nicotine *isomethiodide* hydrogen iodide (VI)



Trigonelline (VII)

235° to 240° C. The structure of this material was established beyond all doubt, because Pictet and Genequand succeeded in isolating trigonelline (VII) from the products of oxidation with alkaline permanganate.

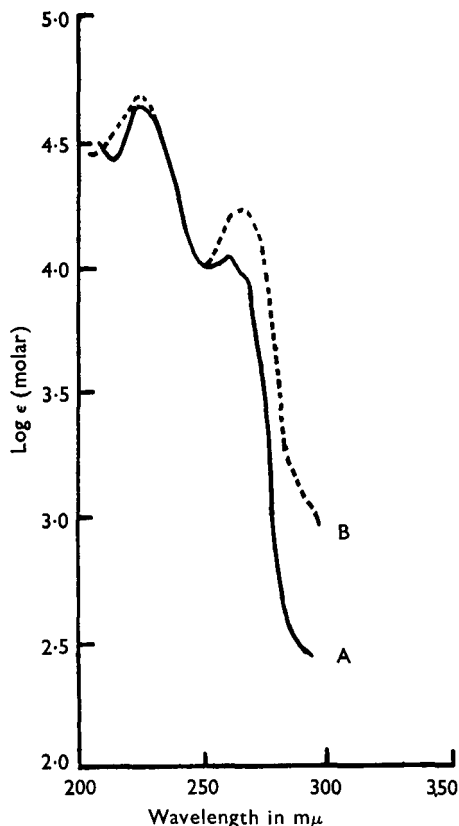


FIG. 1. Ultra-violet absorption spectra in water:—

- A ——— Nicotine monomethiodide,
B - - - Nicotine isomethiodide.

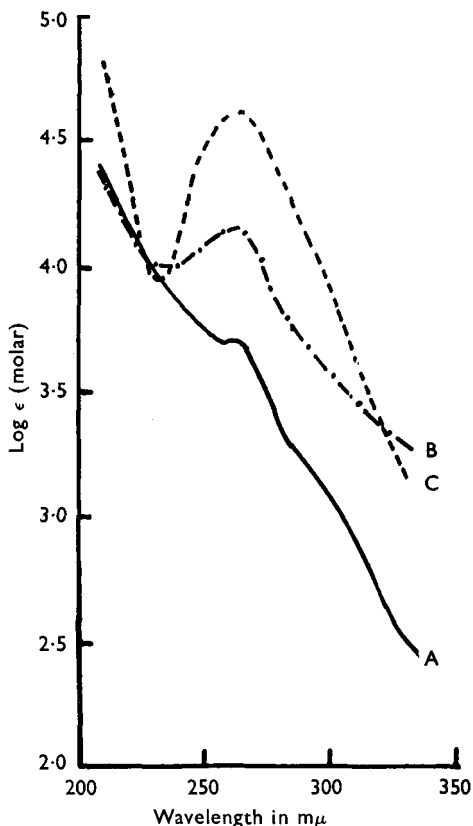


FIG. 2. Ultra-violet absorption spectra in water:—

- A ——— Platinichloride from nicotine monomethochloride,
B - · - · Platinichloride from nicotine isomethochloride,
C - - - Chloroplatinic acid ($H_2PtCl_6 \cdot 6H_2O$).

Pictet and Genequand tried to obtain nicotine monomethiodide (II), by treating nicotine, dissolved in methanol, with 1 mol. of methyl iodide. The reaction mixture was concentrated but nothing could be induced to crystallise from the residue. An orange platinichloride of the corresponding methochloride was, however, obtained. This melted with decomposition at 266° C., a fact which suggested that the reaction had yielded a monomethiodide different from nicotine isomethiodide.

Most highly active nicotine-like compounds (i.e., substances which stimulate synapses in ganglia and at voluntary nerve-endings) contain a

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quaternary ammonium, or other onium, group (see review by Ing³). Nicotine itself, however, is a notable exception. The properties of nicotine mono- and *isomethiodides* are therefore of great interest.

CHEMICAL RESULTS

We found that, when nicotine was dissolved in ether and refluxed with 0.75 mol. of methyl iodide, it was possible to isolate—after removal of nicotine dimethiodide—a crystalline product, which sintered at 149° C. and melted at 161° C. The analysis of this material corresponded with that of nicotine monomethiodide. This substance was tested in Professor Burn's laboratories at Oxford and did not appear to have a nicotine-like action on the cat's blood-pressure and frog rectus preparation. The closeness of the melting point to that of nicotine *isomethiodide* suggested that it might be that compound. A sample of nicotine *isomethiodide* was prepared by the method of Pictet and Genequand. This material sintered at 149° to 150° C. and a mixture of the 2 specimens sintered at 147° to 150° C. The ultra-violet absorption spectra of the 2 substances in water were found to be identical. They are shown in Figure 1 (curve B) and agree well with those obtained by Lowry and Lloyd⁴. We concluded, therefore, that one of the products of the reaction was nicotine *isomethiodide*.

We repeated the experiment and submitted the product, after removal of nicotine dimethiodide, to fractional crystallisation from mixtures of ethanol and ether. Material obtained from the most soluble fraction sintered at 137° to 142° C., and from the least soluble fraction at 142° to 148° C. The ultra-violet absorption spectra of these compounds in water were again identical with that of nicotine *isomethiodide*. We concluded that nicotine *isomethiodide* was the only monomethiodide formed in this reaction.

This lead us to suspect that the gummy product obtained by Pictet and Genequand and designated nicotine monomethiodide might, in fact, be the *isomethiodide*, or a mixture of mono- and *isomethiodides*. It seemed very necessary to establish that the two platinichlorides of the methochlorides were not actually identical.

We repeated the experiments of Pictet and Genequand and found that the platinichloride of the methochloride obtained from nicotine monomethiodide decomposed at 266° to 268° C.; that obtained from nicotine *isomethiodide* decomposed at 248° to 250° C. The platinichloride derived from the product obtained by treating nicotine with 0.75 mol. of methyl iodide in ether decomposed at 246° C. to 247° C. The ultra-violet absorption spectrum of the first compound in water (Fig. 2, curve A) was quite different from the spectra of the second and third compounds, which were identical (Fig. 2, curve B). The absorption spectrum of the gummy solid in water was therefore examined and found to be different from that of nicotine *isomethiodide*. The differences were in accord with the idea that the former was the monomethiodide, in which the onium group is quite separate from the conjugated system in the pyridine ring. We have obtained

chemical evidence in support of this by isolating nicotinic acid from the products of oxidising the gummy material with alkaline permanganate.

Since this work was completed the gum itself (after several months) has turned crystalline. The substance is extremely hygroscopic and analysis indicates that it contains one molecule of water of crystallisation.

EXPERIMENTAL

Analyses are by Mr. J. M. L. Cameron and Miss M. W. Christie; melting points are uncorrected; absorption spectra were determined in water; ether was dried with sodium and filtered before use.

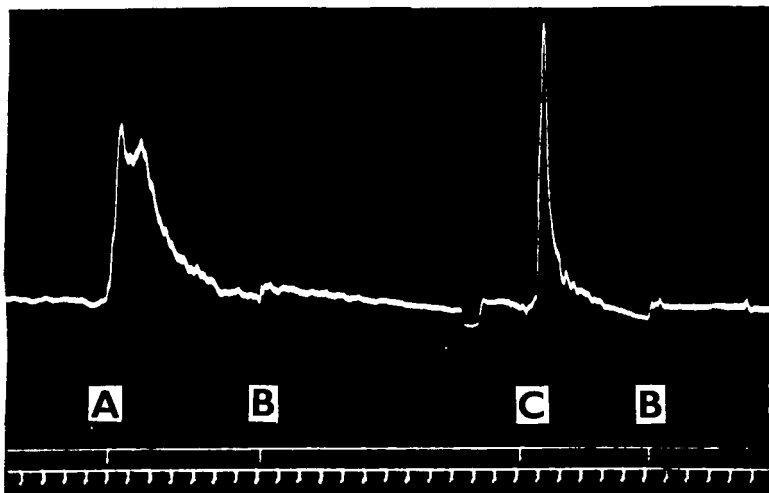


FIG. 3. Spinal cat: upper record, blood-pressure; middle record, signal; lower record, time (1-minute intervals).

A—0.4 mg. Nicotine hydrogen tartrate + 2 ml. saline;

B—2 ml. saline;

C—0.4 mg. Nicotine monomethiodide monohydrate + 2 ml. saline.

Methylation of nicotine in ether: Methyl iodide (10 g., 0.07 mol.) dissolved in ether (25 ml.) was added to nicotine (15 g., 0.09 mol.) dissolved in ether (50 ml.) and the mixture refluxed for 2 hours. The ether was decanted off and the residue taken up in ethanol. Ether was added and a solid was precipitated, which was filtered off. This was a mixture of nicotine mono- and dimethiodides, free from unchanged nicotine; it was extracted with hot ethanol. The extract was filtered from undissolved nicotine dimethiodide and ether was added. A solid was precipitated, which was very soluble in ethanol. It was recrystallised from a mixture of ethanol and ether and melted at 145° to 149° C. It was recrystallised twice more from a mixture of ethanol, methyl ethyl ketone, and ether, and dried *in vacuo* over calcium chloride. It sintered at 140° C. and melted at 161° C. A mixture of this substance and nicotine *iso*-methiodide, prepared by the method of Pictet and Genequand, sintered at

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147° to 150° C. Found: C, 43.3; H, 5.77; N, 9.42: Calculated for $C_{11}H_{17}N_2I$: C, 43.4; H, 5.59; N, 9.21 per cent. Ultra-violet absorption spectrum (Fig. 1, curve B); λ_{max} , 226 and 264 $m\mu$ ($\log\epsilon$, 4.20 and 3.72 respectively). Lowry and Lloyd observed one peak in the absorption of nicotine isomethiodide, λ_{max} , 266 $m\mu$ ($\log\epsilon$, 3.74).

A portion of the methiodide was dissolved in water and poured down a basic ion exchange column (Amberlite resin IRA 400). The solution of the quaternary hydroxide was neutralised with dilute hydrochloric acid and an aqueous solution of chloroplatinic acid was added. An orange precipitate was formed which was recrystallised from water. This material decomposed at 246° to 247° C. Ultra-violet absorption spectrum (Fig. 2, Curve B); λ_{max} , 263 $m\mu$ ($\log\epsilon$, 4.17).

Fractionation of the products of the reaction in ether: The reaction was repeated, the ether decanted off, the product dissolved in ethanol and the nicotine dimethiodide filtered off as before. Ether was added to the filtrate and a solid was precipitated. This was filtered off—the filtrate was retained for further use (see below)—and recrystallised 4 times from mixtures of ethanol and ether. It was dried *in vacuo* over calcium chloride and melted at 145° to 148° C. Ultra-violet absorption spectrum; λ_{max} , 224 and 264 $m\mu$ ($\log\epsilon$, 4.11 and 3.70 respectively).

The filtrate (see above) was left for some time, during which further solid crystallised out. This was filtered off and dissolved in a mixture of ethanol and ether. More ether was added until crystallisation commenced. The solid formed was filtered off and discarded. Further material was obtained by adding more ether to the filtrate. This second crop was dried *in vacuo* over calcium chloride and melted at 137° to 142° C. Ultra-violet absorption spectrum; λ_{max} , 224 and 264 $m\mu$ ($\log\epsilon$, 4, 11 and 3.61 respectively).

Nicotine isomethiodide: This was prepared by the method of Pictet and Genequand. It was dried *in vacuo* over calcium chloride and sintered at 149° to 150° C. Ultra-violet absorption spectrum; (Fig. 1, curve B); λ_{max} , 226 and 264 $m\mu$ ($\log\epsilon$, 4.18 and 3.73 respectively).

The platinichloride of the methochloride decomposed at 248° to 250° C. Found: Pt, 33.3; Calculated for $C_{11}H_{18}Cl_6N_2Pt$: Pt, 33.3 per cent. Ultra-violet absorption spectrum (Fig. 2, curve B); λ_{max} , 262 $m\mu$ ($\log\epsilon$, 4.15).

Nicotine monomethiodide: The procedure of Pictet and Genequand was followed exactly. It is interesting that no nicotine dimethiodide appeared to be formed during the reaction. The product was concentrated to a gum, which was extremely hygroscopic and was stored *in vacuo* over calcium chloride. Ultra-violet absorption spectrum (Fig. 1, curve A); λ_{max} , 225 and 260 $m\mu$ ($\log\epsilon$, 4.41 and 3.55 respectively). The platinichloride of the methochloride, a yellow substance, decomposed at 266° to 268° C. Ultra-violet absorption spectrum (Fig. 2, curve A); λ_{max} , 260 $m\mu$ ($\log\epsilon$, 3.39).

Oxidation: A quantity of the gummy monomethiodide was dissolved in water and passed down a basic ion exchange column (Amberlite resin IRA 400) and the quaternary hydroxide was treated, drop by drop, with a cold alkaline solution of potassium permanganate, until the colour persisted. Ethanol was added and the manganese dioxide filtered off. The

filtrate was concentrated under reduced pressure on a steam bath. The residue consisted of crystalline material and an oil. The crystalline material was inorganic and was filtered off. The residual oil was made just acid with dilute hydrochloride acid and taken up in hot ethanol. The solution was left to cool and seeded with a crystal of nicotinic acid. White needles at once crystallised; they were filtered off and dried on a steam bath. The melting point, which was 233°C ., was not depressed by mixing the crystals with pure nicotine acid. McElvain⁵ recorded the melting point of nicotine acid as 230° to 232°C .

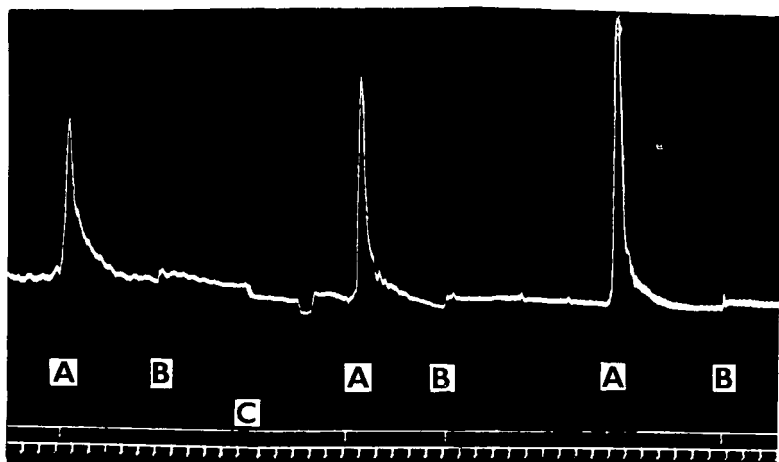


FIG. 4. Spinal cat: upper record, blood-pressure; middle record, signal; lower record, time (1-minute intervals).

- A—0.4 mg. Nicotine monomethiodide monohydrate + 2 ml. saline;
 B—2 ml. saline;
 C—This represents an interval of 35 minutes, during which nicotine hydrogen tartrate (one dose of 0.3 mg., one of 0.4 mg.) was given.

Crystallisation: The gummy monomethiodide eventually turned crystalline. It was suspended in ether, filtered off, and dried *in vacuo* over calcium chloride. It sintered at 73°C . and melted at 89°C . It is extremely hygroscopic, too much so for an accurate determination of carbon and hydrogen or nitrogen, but the iodide content indicates that it is a monohydrate: Found: I^+ , 39.2; calculated for $\text{C}_{11}\text{H}_{17}\text{N}_2\text{I}$: I^+ , 41.7; calculated for $\text{C}_{11}\text{H}_{17}\text{N}_2\text{I}, 1\text{H}_2\text{O}$: I^+ , 39.4 per cent.

PHARMACOLOGICAL RESULTS

Professor Burn tested nicotine dimethiodide and the material, obtained by methylation of nicotine with 0.75 mol. of methyl iodide in ether, subsequently shown to be nicotine *isomethiodide*. Doses of 5 mg. of these substances were without effect on the blood-pressure of spinal cats, whereas a dose of 0.4 mg. of nicotine acid tartrate produced a large rise in

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pressure. We have confirmed this result in two further experiments and it is clear that, on this preparation, nicotine di- and *iso*-methiodides cannot be more than—and are probably much less than—10 per cent. as active as nicotine hydrogen tartrate.

On the same preparation the activity of nicotine monomethiodide was found to be of the same order as that of nicotine hydrogen tartrate. The first estimate of the activity was 40 per cent. of that of nicotine hydrogen tartrate, but, in two subsequent experiments, the monomethiodide was found to be at least as active as, if not more active than, nicotine hydrogen tartrate (Fig. 3). The shape of the blood-pressure response to the monomethiodide was consistently different from that to nicotine. It was difficult to obtain an accurate comparison of the activities of the two substances, because the preparation appeared to become sensitised to the monomethiodide (Fig. 4). An attempt was made to produce a block of the sympathetic ganglia with the monomethiodide but, even after administration of 140 mg. of the compound (in doses of 10 mg. over a period of 1 hour), the block was incomplete. The effect of 1 mg. of nicotine hydrogen tartrate was considerably reduced, however, after the preparation had been treated in this way (Fig. 5). The effects of 0.6 mg. of the monomethiodide, and those of 0.6 mg. of nicotine hydrogen tartrate, were almost abolished by prior injection of 0.25 mg. of hexamethonium.

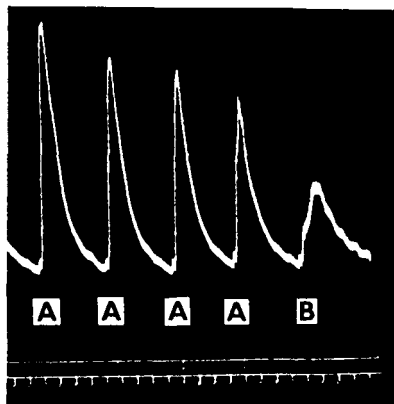


FIG. 5. Spinal cat: upper record, blood-pressures; middle record, signal; lower record, time (1-minute intervals).

A—10 mg. Nicotine monomethiodide monohydrate + 2 ml. saline;

B—1.0 mg. Nicotine hydrogen tartrate + 2 ml. saline. The preparation had already been treated with 100 mg. of the monomethiodide (in doses of 10 mg.) during the preceding hour.

SUMMARY

1. When nicotine, dissolved in methanol, is treated with 1 mol. of methyl iodide, the product is nicotine monomethiodide, in which the pyrrolidine nitrogen atom is quaternised. We have obtained this in a crystalline state, as a monohydrate.

2. When nicotine, dissolved in ether, is treated with 0.75 mol. of methyl iodide, the product, along with nicotine dimethiodide, is nicotine *iso*-methiodide, in which the pyridine nitrogen atom is quaternised.

3. Nicotine *iso*- and dimethiodides have only feeble—if any—pressor activity on spinal cats.

4. Nicotine monomethiodide produces effects in spinal cats comparable with those of nicotine hydrogen tartrate. The actions of the two compounds may, however, be slightly different.

5. These results warrant further investigation of nicotine monomethiodide. This is being undertaken by Mr. J. J. Lewis, of the Department of Materia Medica, of this University.

We wish to thank Professor J. H. Burn for testing nicotine *iso*- and *di*-methiodides, Mr. J. J. Lewis for assistance with the other pharmacological experiments, which were performed in Professor S. Alstead's laboratory, Mr. D. Morrison, for some of the ultra-violet absorption spectra, and Professor J. W. Cook for his interest in this work, which was done during the tenure by one of us (R. B. B.) of an I.C.I. Fellowship.

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