CCCCXI.—4-*Nitro*-5-(3-*pyridyl*)*pyrazole, a New Oxidation Product of Nicotine. Part I.*

By GEORGE ALECK CROCKER GOUGH and HAROLD KING.

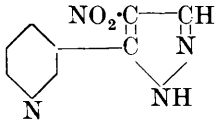
DURING the preparation of nicotinic acid by the oxidation of nicotine with nitric acid by the method of McElvain and Adams (*J. Amer. Chem. Soc.*, 1923, **45**, 2743; "Organic Syntheses," 1925, **4**, 49), it was observed that the nicotinic acid liberated from the crude nitrate contains a sparingly soluble substance which gives a yellow colour with alkalis. This substance proves to be only weakly acidic, and by making use of this property and its sparing solubility in water it has been found that it is produced in approximately 5% yield from all specimens of commercial nicotine, whether medicinal or commercial 98% grade. To eliminate the possibility of its origin from an unknown alkaloid in nicotine, pure nicotine, $[\alpha]_{5461}$ — 205° (Gifford and Lowry, *Proc. Roy. Soc.*, 1927, *A*, **114**, 592, give — 205°; Lowry and Lloyd, J., 1929, 1771, give — 204°), was prepared by fractional crystallisation of the sparingly soluble picrate, by fractional crystallisation of the zincichloride (Ratz, *Monatsh.*, 1905, **26**, 1241), and by fractional distillation of nicotine base. All these products give the new substance in approximately 5% yield. Finally, nicotine prepared by ourselves from Empire-grown tobacco also gives rise to the same substance on oxidation.

The new substance has the formula $C_8H_6O_2N_4$ and a molecular weight in agreement therewith. It is optically inactive, forms a *monohydrochloride*, a sodium salt, and a *monosilver* salt. It is insoluble in sodium hydrogen carbonate solution, does not contain an *N*-methyl group, and is stable to boiling aqueous potassium permanganate. When the silver salt is treated with methyl iodide the acidic character is lost. On reduction with tin and hydrochloric acid a di-acid base, $C_8H_8N_4$, is obtained which yields a *dihydrochloride* and a *dipicrate*. This base contains an amino-group of aromatic character, as is shown by its diazotisation and coupling with sodium β-naphthoxide solution; and on oxidation with permanganate it gives nicotinic acid.

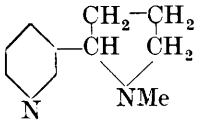
On the basis of these properties it is possible to formulate the new oxidation product with a considerable degree of certainty. During the reduction with tin and acid, the nitro-compound, $C_8H_6O_2N_4$, passes into the base $C_8H_8N_4$ through reduction of a nitro-group. The parent base has therefore the formula $C_8H_7N_3$. In the oxidation of nicotine by various oxidising agents the pyridine nucleus usually remains intact; and since, as we have shown, it is so in the present instance, the formula may be written C_5H_4N–$C_3H_3N_2$. The stability

of the nitro-compound to nitric acid and to permanganate and the markedly low hydrogen content of the second half of the molecule suggest an aromatic structure, and this is confirmed by the observation that the diazotisable amino-group is not in the pyridine nucleus.

The most probable structure for the nitro-compound is that of 4-nitro-5-(3-pyridyl)pyrazole (I) in which three carbon atoms and



(I.)



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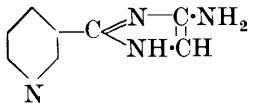
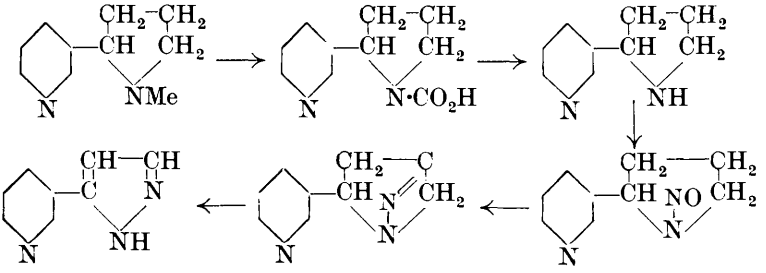


(III.)

one nitrogen atom of the original pyrrole nucleus of nicotine (II) remain intact. The position of the nitro-group follows from the known behaviour of pyrazole and its derivatives on nitration. The diacid character of the base obtained on reduction agrees with this structure, since the two nitrogen atoms of pyrazoles are negligibly basic. It also excludes the possibility, improbable on other grounds also, of its being an aminopyridylglyoxaline (III), which would form a trihydrochloride, since Fargher (J., 1920, **117**, 669) has shown that an analogously constituted base, 4-amino-5-methylglyoxaline, forms a dihydrochloride.

There only remains for discussion the question of the mode of formation of the pyrazole nucleus from nicotine. It is clear that a potential pyrazole structure must be formed prior to extrusion of the α-methylene carbon atom of the tetrahydropyrrole nucleus, since rupture of the cyclic structure would inevitably lead to degradation to nicotinic acid. We therefore suggest that the new compound has arisen by the following stages :



Although numerous workers have prepared nicotinic acid by the oxidation of nicotine by nitric acid, we have only been able to find one reference to the formation of a by-product, which may or may not be identical with ours. Wintersfein and Weinhagen (*Z. physiol.*

Chem., 1917, **100**, 170) state that a crystalline by-product, which was not further examined, is formed by the action of nitric acid on nicotine.

We are indebted to Mr. J. H. Gaddum, M.A., of these laboratories for a physiological examination of 4-amino-5-(3-pyridyl)pyrazole. When tested on a cat's denervated gastrocnemius in a dose of 1 mg., it was not possible to detect any nicotine-like action on the tension of the muscle, whereas a dose of 0·005 mg. of nicotine tartrate produced a definite effect. We should also like to express our thanks to Messrs. Whiffen & Sons of Fulham for the gift of ample supplies of nicotine, both medicinal and commercial 98% grade.

EXPERIMENTAL.

Oxidation of Nicotine by Nitric Acid. Isolation of a Base $C_8H_6O_2N_4$. —Commercial 98% nicotine was oxidised by nitric acid as described in " Organic Syntheses," 1925, **4**, 49. The crude nicotinic acid nitrate (from 156 c.c. of nicotine) obtained by evaporation of the nitric acid under reduced pressure was dissolved in water (1000 c.c.), and the reaction made slightly alkaline to litmus by addition of 40% sodium hydroxide solution. On removal of the alkalinity by passage of carbon dioxide or by careful addition of acetic acid a light yellow-brown crystalline powder separated (7·5 g.). This was crystallised from boiling glacial acetic acid (63 c.c.), from which it separated in compact facetted tablets (6·2 g.), m. p. 272—274°. It was dissolved in hot water (75 c.c.) by addition of 15 c.c. of concentrated hydrochloric acid, treated with charcoal, and filtered; one portion was neutralised to liberate the base, and another treated with excess of concentrated hydrochloric acid. The *hydrochloride*, m. p. 300°, separated in fine, light yellow needles (Found : Cl, 15·5, 15·7, 15·8. $C_8H_6O_2N_4$,HCl requires Cl, 15·7%). The liberated base was once more crystallised from glacial acetic acid before analysis (Found : C, 50·6, 50·7; H, 3·4, 3·5; N, 29·4. $C_8H_6O_2N_4$ requires C, 50·5; H, 3·1; N, 29·5%). The molecular weight determined by Rast's method in camphor gave values between 176 and 189 (calc., 190). When treated with dilute sodium hydroxide solution, the base dissolved, forming a primrose-yellow solution, but with 2*N*-sodium hydroxide a sodium salt crystallising in yellow needles was obtained. When ammonia was added to a suspension of the base (1 g.) in boiling water (115 c.c.) until solution was effected, and an excess of silver nitrate solution added, a *silver* salt separated (1·5 g.) as a yellow powder (Found : Ag, 36·7. $C_8H_5O_2N_4Ag$ requires Ag, 36·3%). This salt decomposes somewhat explosively on heating. When treated with methyl alcohol and methyl iodide, it gives a substance no longer soluble in sodium hydroxide solution.

Reduction of the Base $C_8H_6O_2N_4$ *to a Base* $C_8H_8N_4$.—The nitro-compound (20 g.) was reduced by warming on the water-bath with 16% hydrochloric acid (150 c.c.) and 30 g. of tin. After removal of the tin as sulphide the mother-liquor on concentration gave a *dihydrochloride* (18·75 g.), crystallising in needles or elongated plates, m. p. 300—302° (Found: C, 41·0; H, 4·6; N, 24·1: Cl, 30·2. $C_8H_8N_4,2HCl$ requires C, 41·2; H, 4·4; N, 24·4; Cl, 30·4%). It gave with Mayer's reagent a precipitate soluble in excess of acids. The free base, an oil, cannot be extracted by means of ether from a solution made alkaline with sodium hydroxide, but it can be when ammonia is employed. The *dipicrate* crystallises from water in two forms, fine needles and bold orange prisms, both of which melt at 219—220° (Found: picric acid by nitron, 74·6. $C_8H_8N_4.2C_6H_3O_7N_3$ requires picric acid, 74·1%).

Oxidation of the Base $C_8H_8N_4$ *to Nicotinic Acid.*—A solution of the dihydrochloride (2·33 g.) in water (500 c.c.) was treated with a slight excess of silver sulphate and filtered from silver chloride and the excess of silver was removed by hydrogen sulphide. After removal of hydrogen sulphide by boiling the solution, aqueous $2\frac{1}{2}$% potassium permanganate was slowly added to the boiling solution until a permanent pink colour was obtained, 300 c.c. being required. The decolorised solution after filtration was made neutral to Congo-paper and evaporated to dryness and the residue was extracted with boiling absolute alcohol. This extract was again evaporated to dryness, and the residue extracted with boiling absolute alcohol. On addition of water (10 c.c.) and evaporation under reduced pressure to a small volume, nicotinic acid was obtained in two crops, (*a*) 0·35 g., m. p. 228°, (*b*) 0·1 g., m. p. 225°. Neither showed any depression of m. p. in admixture with pure nicotinic acid, the observed m. p.'s being 231° and 228° respectively: the m. p. of pure nicotinic acid, taken simultaneously, was 235°. The first crop was converted into the nitrate by treatment with 3*N*-nitric acid (yield, 0·3 g.). It melted at 188°, whereas pure nicotinic acid nitrate melted at 190° and a mixture of the two at 188°. The acid set free from the nitrate melted at 233° and in admixture with pure nicotinic acid at 233°. A portion of the second crop was converted into the hydrochloride by treatment with concentrated hydrochloric acid. This melted at 271°, whilst pure nicotinic acid hydrochloride melted simultaneously at 275° and a mixture of the two at 273°.

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