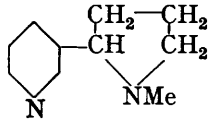
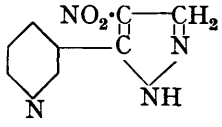
94. *4-Nitro-5-(3-pyridyl)pyrazole, a New Oxidation Product of Nicotine. Part III. Confirmatory Synthetical Experiments.*

By George A. C. Gough and Harold King.

In the oxidation of nicotine (I) to nicotinic acid by nitric acid a by-product was isolated to which the constitution of 4-nitro-5-(3-pyridyl)pyrazole (II) was assigned on the evidence of its properties (J., 1931, 2968) and of its methylation (J., 1932, 2768).


(I.)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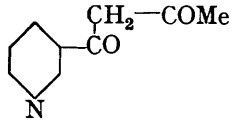
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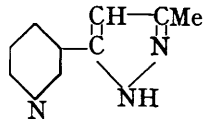
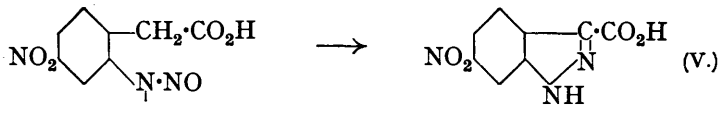

(IV.)

On reduction it gave the corresponding amino-derivative; this has now been deaminated to a liquid base, 5-(3-*pyridyl*)*pyrazole*, which does not give the Pauly reaction with diazotised sulphanilic acid and cannot therefore contain the glyoxaline nucleus, a possibility already dismissed by us (*loc. cit.*). The constitution of this base has been confirmed by synthesis from ethyl nicotinate, which by condensation with acetone in the presence of sodium gave pyridoylacetone (III). On treatment of this diketone with hydrazine a quantitative yield of 3-*methyl*-5-(3-*pyridyl*)*pyrazole* (IV) was obtained, which yielded 5-(3-*pyridyl*)*pyrazole*-3-*carboxylic acid* on oxidation with potassium permanganate. At 310° this acid lost carbon dioxide with the formation of 5-(3-pyridyl)pyrazole, which has been shown to be the same as the product obtained from nicotine. The *picrates*, *flavianates*, *methiodides*, and *methopicrates* of the two bases were identical in all respects and each pair showed no depression of m. p. in admixture.

The proof of the constitution now submitted lends support to the mechanism suggested in our first communication for the mode of origin of a pyrazole nucleus from a reduced pyrrole nucleus. In this connexion it is of interest and of significance that almost the exact counterpart has been found by Hahn and Just (*Ber.*, 1932, **65**, 717; cf. Jacobson and Huber, *ibid.*, 1908, **41**, 660) in the formation of a substituted benzpyrazole (indazole) ring, for *ON*-diacetylyohimbine on oxidation with dilute nitric acid gives 6-nitroindazole-3-carboxylic acid (V), which the authors suggest arises by the action of nitrous acid on an *o*-aminophenylacetic acid group.


(V.)

Experimental.

Deamination of 4-Amino-5-(3-pyridyl)pyrazole. Isolation of 5-(3-Pyridyl)pyrazole.—A suspension (4·66 g.) of the aminopyridylpyrazole dihydrochloride (prepared from nicotine) in *N*-HCl was treated at 0° with amyl nitrite until complete solution had been effected. The solution was then boiled with EtOH (large excess) until evolution of N ceased. After removal of EtOH the solution was made alkaline with NH_3 aq. and extracted with $CHCl_3$, and the latter on evaporation gave a liquid base, which was converted into a cryst. hydrochloride (yield, 2·45 g.). The base distilled readily under reduced press. but could not be obtained cryst. The whole of the hydrochloride was dissolved in a very little H_2O and treated with sat. sodium picrate solution until no further pptn. occurred. The *picrate* (3·8 g.) required 750 c.c. of H_2O for crystn. and separated in glistening leaflets, m. p. 194—195°. The picrate also crystallises in needles [Found (micro.): C, 42·9; H, 3·2; H_2O, 3·4. $C_8H_7N_3,C_6H_3O_7N_3,H_2O$ requires C, 42·9; H, 3·1; H_2O, 4·6%]. That the salt was a monopicrate was confirmed by nitron estimation (Found: picric acid, 57·4; monopicrate monohydrate requires picric acid, 58·4%). The *flavianate* crystallised in stout orange needles, m. p. 229° (decomp.), very readily sol. in hot H_2O [Found (micro.): C, 43·6; H, 3·5; N, 14·1; H_2O, 7·0. $C_8H_7N_3,C_{10}H_6O_8N_2S,2H_2O$ requires C, 43·6; H, 3·5; N, 14·1; $2H_2O$, 7·3%].

The base was recovered from the picrate (1·0 g.) by means of $CHCl_3$ and $NaHCO_3$ aq. and

distilled under reduced press. It was boiled with excess of MeI in MeOH for 2 hrs., and the solution evaporated to a small vol. The ***methiodide*** (0·45 g.) separated in large hexagonal tablets, m. p. 217·5° [Found (micro.): C, 37·6; H, 3·5. $C_9H_{10}N_3I$ requires C, 37·6; H, 3·5%]. The ***methopicrate***, a felt of fine needles from H_2O, had m. p. 185° [Found (micro.): C, 46·3; H, 3·4; N, 21·3. $C_{15}H_{12}O_7N_6$ requires C, 46·4; H, 3·1; N, 21·6%].

β-*Pyridoylacetone*.—Ethyl nicotinate (15 g.) and dry acetone (7·5 g.) in 50 c.c. of dry Et_2O were cooled in ice and treated with Na wire (2·3 g.). After remaining for an hr. at room temp., the mixture was warmed on the water-bath for a few mins. and the solid sodium salt was collected and dried (yield, 15·2 g.). It was dissolved in H_2O (100 c.c.) and the solution was saturated with CO_2 and extracted with Et_2O. The cryst. residue (7·35 g.) obtained on evaporation of the Et_2O was distilled under reduced press. and showed b. p. 153°/13 mm. It had the m. p. and properties recorded by Ferenczy (*Monatsh.*, 1897, **18**, 673).

3-*Methyl*-5-(3-*pyridyl*)*pyrazole*.—β-Pyridoylacetone (4·65 g.), dissolved in EtOH (25 c.c.), was added to a solution of hydrazine sulphate (4·1 g.) and hydrated sodium acetate (8·6 g.; 2 mols.) in H_2O (25 c.c.) and refluxed for 2 hrs. After removal and washing of the separated Na_2SO_4 with EtOH the liquid was evaporated to a small vol. and treated with 5% NaOH aq. (10 c.c.) and H_2O (100 c.c.). The oil which separated solidified rapidly and was removed by filtration (4·65 g.). A small amount of material was obtained from the mother-liquor by saturation with NaCl. This appeared to be the sodium salt of the pyrazole, since, on neutralisation with AcOH, it yielded the free *pyrazole*. The combined products crystallised from warm H_2O (140 c.c.) in large stout plates, which melted at 81—83°, lost H_2O, resolidified, and then melted at 137—138° (Found: loss at 100°, 12·4. Found in dried material: N, 26·1. $C_9H_9N_3,1\frac{1}{2}H_2O$ requires H_2O, 14·5. $C_9H_9N_3$ requires N, 26·4%). The *monopicrate* crystallised from H_2O in large balls of fine needles, m. p. 202—203° (Found: N, 21·5. $C_9H_9N_3,C_6H_3O_7N_3$ requires N, 21·6%), and the *hydrochloride* from 50% aq. acetone in long fine needles, m. p. 214—216° (Found: N, 21·2. $C_9H_9N_3$,HCl requires N, 21·5%).

5-(3-*Pyridyl*)*pyrazole*-3-*carboxylic Acid*.—3-Methyl-5-(3-pyridyl)pyrazole (1 g.), dissolved in H_2O (50 c.c.), was oxidised on a boiling water-bath by the dropwise addition of $KMnO_4$ (2 g.) in H_2O (100 c.c.) during 2 hr., while CO_2 was passed through the solution. This was then boiled for a further 20 min. and, after destruction of the faint red colour by addition of a few drops of MeOH, filtered from MnO_2, neutralised to Congo-paper, and evaporated to 25 c.c. 5-(3-*Pyridyl*)*pyrazole*-3-*carboxylic acid*, m. p. 308—310° (efferv.), which separated almost completely when the solution was kept in the ice chest over-night, was removed (0·45 g.): a portion (0·1 g.), cryst. from boiling H_2O (25 c.c.) for analysis (Found: N, 22·4. $C_9H_7O_2N_3$ requires N, 22·2%), separated in small aggregates of fine needles. The *picrate*, m. p. 242—245°, formed small clusters of hair-like needles (Found: N, 20·3. $C_9H_7O_2N_3,C_6H_3O_7N_3$ requires N, 20·1%).

5-(3-*Pyridyl*)*pyrazole*.—The foregoing acid (0·35 g.) was heated at about 310° until evolution of gas was complete. The tube was connected to a water-pump, and the decarboxylated product distilled from the small dark residue. The distilled product (0·15 g.) was freed from traces of acidic substances by solution in dil. NH_3 aq. and extraction with $CHCl_3$. The extract was washed twice with NH_3 aq. and H_2O, and the base removed from it by washing with dil. HCl. Evaporation of this extract to dryness yielded a hydrochloride (0·25 g.), crystallising in pointed plates which could not be recrystallised in any simple manner. The hydrochloride was therefore converted into the picrate (0·35 g.) by the addition of aq. sodium picrate. This, recryst. from boiling H_2O (90 c.c.), yielded thin leaflets and sometimes needles (0·3 g.), m. p. 194—195° [Found (micro.): C, 42·9; H, 3·1. Calc.: C, 42·9; H, 3·1%].

The product from decarboxylation of a further amount of the acid (0·4 g.) in a similar way was divided into two equal parts and one was converted into the flavianate, which, after two crystns. from H_2O, formed stout needles, m. p. 229° (decomp.) [Found (micro.): C, 44·1; H, 3·5; H_2O, 5·5. $C_8H_7N_3,C_{10}H_6O_8N_2S,1\frac{1}{2}H_2O$ requires C, 44·4; H, 3·3; H_2O, 5·5%]. The second portion of the distilled base was boiled with an excess of MeI for ¾ hr., the solution evaporated to dryness, and the cryst. residue dissolved in the minimum vol. of MeOH. On cooling, large tablet-shaped crystals of the methiodide separated, m. p. 217°. These were converted by solution in H_2O and addition of sodium picrate into the methopicrate, m. p. 184—186°, which crystallised in long stout needles [Found (micro.): C, 46·5; H, 3·3. Calc.: C, 46·4; H, 3·1%].

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