1031. *The Reaction of Nicotinic Acid 1-Oxide and 3-Picoline 1-Oxide with Acetic Anhydride.**

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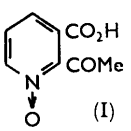
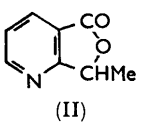
Nicotinic acid 1-oxide reacts with acetic anhydride to give as principal product 2-acetylnicotinic acid 1-oxide; 2-hydroxynicotinic acid and 6-hydroxynicotinic acid are by-products. Nicotinic acid 1-oxide and propionic anhydride give a neutral diketone (III), together with 2- and 6-hydroxynicotinic acid; 2-propionylnicotinic acid 1-oxide is formed when reaction times are very short. Isonicotinic acid 1-oxide and cinchomeronic acid 1-oxide are deoxygenated by acetic anhydride. 3-Picoline 1-oxide and acetic anhydride give 3-methyl-2-pyridone, 5-methyl-2-pyridone, and 3-methyl-1-(5-methyl-2-pyridyl)-2-pyridone. Under the same conditions 3-hydroxypyridine 1-oxide gives 2,3-dihydroxypyridine as the only product isolated. The mechanisms of these reactions are briefly discussed.

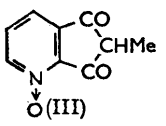
Although the rearrangements of pyridine *N*-oxides have been studied extensively in recent years, there appears to be no record of the behaviour of nicotinic acid 1-oxide towards acetic anhydride. The available evidence relating to the rearrangements of 3-substituted pyridine *N*-oxides (*e.g.*, the reaction of nicotinic acid 1-oxide with phosphorus pentachloride and phosphorus oxychloride,[1] and the reaction of 3-picoline 1-oxide with acetic anhydride [2]) led us, *ab initio*, to expect a preponderance of 2-hydroxynicotinic acid in the product. When nicotinic acid 1-oxide was boiled with acetic anhydride for six hours



(I)



(II)



(III)

2-acetylnicotinic acid 1-oxide (I) (25—30%), 2-hydroxynicotinic acid (10%), and 6-hydroxynicotinic acid (3%) were obtained.

2-Acetylnicotinic acid 1-oxide readily gave the haloform reaction; the major product

* A preliminary account of part of this work has been reported in *Chem. and Ind.*, 1960, 402.

[1] Taylor and Crovetti, *J. Org. Chem.*, 1954, **19**, 1636.
[2] Boekelheide and Linn, *J. Amer. Chem. Soc.*, 1954, **76**, 1286.

was identified as quinolinic acid 1-oxide, which was also prepared by the peracetic acid oxidation of quinolinic acid at room temperature. The *N*-oxide function in (I) was smoothly removed by catalytic hydrogenation, and the product, 2-acetylnicotinic acid, was characterised as the known oxime anhydride [3] and *p*-nitrophenylhydrazone anhydride.[4] When hydrogenation proceeded until 2 moles of hydrogen had been absorbed, the product isolated after sublimation of the crude material was the lactone (II) of 2-1′-hydroxyethylnicotinic acid.

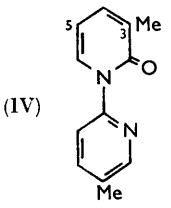
None of the other carboxylic acid *N*-oxides in this series underwent acetylation when heated with acetic anhydride. Isonicotinic acid 1-oxide suffered mainly deoxygenation, but a small yield of 2-hydroxyisonicotinic acid was isolated, together with a substance, $C_9H_9NO_4$, of unknown constitution. Cinchomeronic acid 1-oxide was also deoxygenated under similar conditions. Picolinic acid 1-oxide was readily decarboxylated, hence the products of reaction with acetic anhydride were the same as those obtained from pyridine 1-oxide.[5,6] Similarly, quinolinic acid 1-oxide gave the same products as nicotinic acid 1-oxide.

In an attempt to widen the scope of this reaction we investigated the behaviour of nicotinic acid 1-oxide with propionic anhydride. Under conditions similar to those adopted with acetic anhydride (140° for 4—6 hours) there was no reaction, nicotinic acid 1-oxide being insoluble in propionic anhydride at this temperature. When the mixture was boiled for 3 hours, the acidic products were 2- and 6-hydroxynicotinic acid, but we failed to isolate the expected keto-acid. Instead, we obtained a neutral ketone which we formulate tentatively as (III). When shorter reaction times were used (1 hour at the boiling point), we obtained a non-crystalline, non-acidic fraction which exhibited bands at 1802 and 1764 cm.$^{-1}$ in the infrared spectrum, characteristic of an anhydride grouping. Since the propionic anhydride had been removed at 120°/12 mm. it is probable that this oil consists of anhydrides of nicotinic acid derivatives, contaminated with traces of propionic anhydride. After hydrolysis with water at 100°, the resulting crystalline mixture was separated into 2-propionylnicotinic acid 1-oxide (5%) and 2-hydroxynicotinic acid. The acidic fraction from this reaction contained small amounts of 2- and 6-hydroxynicotinic acid. Since no neutral ketone was isolated under these conditions, whereas ketone but no keto-acid was isolated when using longer reaction times, it seems probable that the initial product of reaction is the keto-acid, which then suffers cyclodehydration to the diketone (III).

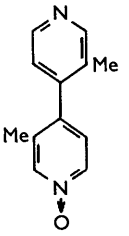
The isolation of the ketones (I) and (III) prompted us to investigate the reactions of other 3-substituted pyridine 1-oxides with acetic anhydride, with particular reference to the possibility of ketone formation. In an earlier study with 3-picoline 1-oxide, Boekelheide and Linn [2] obtained a moderate yield of 2-acetoxy-3-methylpyridine, but they did not account for the remainder of their material. In our experiments with 3-picoline 1-oxide, the crude product was hydrolysed with water, and then chromatographed on neutral alumina. The following products were thus obtained, in order of elution: 3-methyl-1-(5-methyl-2-pyridyl)-2-pyridone (IV) (4%), 3-methyl-2-pyridone (35—40%), and 5-methyl-2-pyridone (35—40%). Neither the crude product nor any of the eluates gave evidence of containing ketonic material, and we believe that if any ketones are formed, they are only present in the product in minimal yield. The infrared spectrum of the minor product (IV) exhibits twin absorption bands at 1277 and 1267 cm.$^{-1}$, which almost coincide with the *N*-oxide bands at 1282 and 1272 cm.$^{-1}$ in the spectrum of 3-picoline 1-oxide. However, this substance did not contain an *N*-oxide function, since it was not hydrogenated under conditions which smoothly reduced the *N*-oxide grouping in 2-acetylnicotinic acid 1-oxide, and it was also stable to nascent hydrogen (iron–acetic acid) under conditions which quantitatively removed the oxygen

[3] Rosenheim and Tafel, *Ber.*, 1893, **26**, 1501.
[4] Wibaut and Boer, *Rec. Trav. chim.*, 1955, **74**, 241.
[5] Boekelheide and Lehn, *J. Org. Chem.*, 1961, **26**, 428.
[6] Sauermilch, *Arch. Pharm.*, 1960, **293**, 452.

atom from 3,3′-dimethyl-4,4′-bipyridyl 1-oxide (V). The chromophore present in (IV) was inferred from a comparison of its ultraviolet absorption with that of 1-2′-pyridyl-2-pyridone,[7] and its constitution was established by synthesis from the sodium salt of 3-methyl-2-pyridone and 2-bromo-5-methylpyridine. 5-Methyl-1-(5-methyl-2-pyridyl)-2-pyridone was also synthesised for reference purposes; we have not observed its formation in the reaction of 3-picoline 1-oxide with acetic anhydride.



(IV)

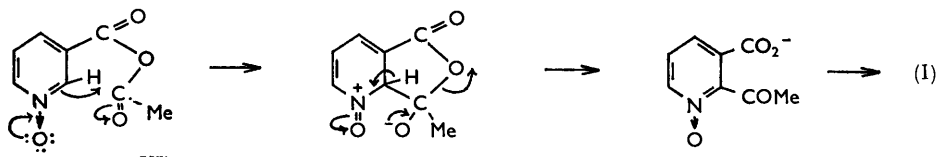


(V)

Finally, we have also examined the rearrangement of 3-hydroxypyridine 1-oxide with acetic anhydride, which gave a moderate yield of 2,3-dihydroxypyridine. We have not found any evidence for the formation of 2,5-dihydroxypyridine or of any ketones in this reaction, which affords a convenient alternative preparation of 2,3-dihydroxypyridine to the one hitherto available.[8]

The direct introduction of an acyl group into the pyridine *N*-oxide nucleus by what is in effect an electrophilic substitution is at present unique. However, the detailed mechanism of the formation of the *N*-oxide (I) is still obscure; it presumably cannot proceed by a Fries-type rearrangement of the 1-acetoxy-3-carboxypyridinium ion for obvious electronic reasons. Also, if such a mechanism operated, we should expect 3-hydroxypyridine 1-oxide to undergo acylation with acetic anhydride, and, indeed to react more readily than nicotinic acid 1-oxide. In addition, neither nicotinic acid 1-oxide nor 3-picoline 1-oxide could be acylated by the Friedel–Crafts reaction; pyridine 1-oxide and 3-methoxypyridine 1-oxide have also been reported to be unreactive.[9]

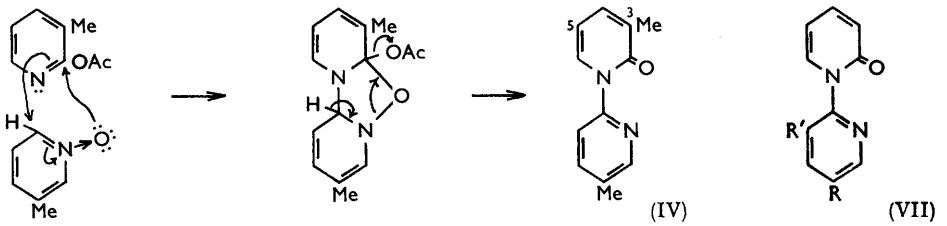
Although the reactions between pyridine *N*-oxides and acetic anhydride frequently show the typical characteristics of free-radical reactions,[10] we do not consider that the formation of the keto-acid (I) can be satisfactorily explained by a free-radical mechanism. It is evident that the keto-acid (I) is formed by a specific process which does not allow the participation of ethyl nicotinate 1-oxide,[5] isonicotinic acid 1-oxide, 3-picoline 1-oxide, or 3-hydroxypyridine 1-oxide. A more likely possibility seems to be intramolecular rearrangement of the mixed anhydride (VI), *via* a cyclic transition state:



(VI)

We envisage the formation of 3-methyl-1-(5-methyl-2-pyridyl)-2-pyridone (IV) in the rearrangement of 3-picoline 1-oxide as arising from reaction of 2-acetoxy-3-methylpyridine with unchanged 3-picoline 1-oxide:

[7] de Villiers and den Hertog, *Rec. Trav. chim.*, 1957, **76**, 647.
[8] Kudernatsch, *Monatsh.*, 1897, **18**, 617.
[9] Mosher and Welch, *J. Amer. Chem. Soc.*, 1955, **77**, 2902.
[10] Boekelheide and Harrington, *Chem. and Ind.*, 1955, 1423; Traynelis and Martello, *J. Amer. Chem. Soc.*, 1958, **80**, 6590; 1960, **82**, 2744.



This possibility is supported by the reaction of 3-picoline 1-oxide with 2-acetoxypyridine at 100°, from which we isolated small yields of 1-(5-methyl-2-pyridyl)-2-pyridone (VII; R = Me, R′ = H), 1-(3-methyl-2-pyridyl)-2-pyridone (VII; R = H, R′ = Me), and 2-pyridone (considerable yields of starting materials were recovered). Clearly the presence of acetic anhydride is not an essential prerequisite for the formation of (VII) or, presumably, of (IV).

The mechanism outlined above involves an initial nucleophilic attack at position 2 in a 2-substituted pyridine by an *N*-oxide function, followed by internuclear transfer of the *N*-oxide oxygen atom. It was first suggested to account for the formation of 1-(5-methyl-2-pyridyl)-2-pyridone (VII; R = Me, R′ = H) in the reaction of 2-bromopyridine with 3-picoline 1-oxide.[11] In the present context internuclear transfer of oxygen cannot readily be demonstrated, and at least one other mechanism can be written which does not involve such a transfer. However, we believe that the analogy is sufficiently close to allow the same mechanism to operate in the reaction of 3-picoline 1-oxide with 2-acetoxypyridine, and in the reaction of 3-picoline 1-oxide with acetic anhydride. The isolation from the former reaction of 1-(3-methyl-2-pyridyl)-2-pyridone (VII; R = H, R′ = Me) is of interest; it indicates that the steric factors invoked by Ramirez and von Ostwalden[11] to account for the non-formation of this substance in the reaction between 3-picoline 1-oxide and 2-bromopyridine are not decisive.

Experimental

Reaction of Nicotinic Acid 1-*Oxide with Acetic Anhydride.*—(*a*) A solution of nicotinic acid 1-oxide (15 g.) in acetic anhydride (150 ml.) was boiled for 6 hr. The solvent was then removed, under reduced pressure, dilute potassium hydroxide solution (90 ml.) was added, and the mixture was heated on the steam-bath for 15 min. An excess of concentrated hydrochloric acid was added. The dark crystalline product was recrystallised from water (charcoal), ethanol, and finally from water. 2-*Acetylnicotinic acid* 1-*oxide* (5·3 g., 27%) was obtained as colourless rhombs, m. p. 247—248° (decomp.), with previous darkening above 230°; $\lambda_{max.}$ (in water) 214·5 and 261 mμ (log ε 4·30 and 3·98); inflexion at 310 mμ (log ε 2·76); ν 1754, 1730, 1242, 784, and 772 cm.$^{-1}$ (potassium chloride disc) (Found: C, 52·95; H, 3·9; N, 7·7. $C_8H_7NO_4$ requires C, 53·05; H, 3·9; N, 7·7%). The acidified mother liquors from the reaction mixture were evaporated to dryness, the residue was extracted repeatedly with boiling ethanol, and the combined extracts were concentrated to crystallisation point. When crystallisation was complete, the dark solid was collected, and crystallised thrice from water (charcoal). The product thus obtained was a mixture of short, dense prisms and fine needles, from which the latter were separated by preferential solution in hot water, followed by decantation. The cooled solution deposited 2-hydroxynicotinic acid, which was recrystallised from water, and obtained as fine needles (1·5 g., 10%), m. p. and mixed m. p. with authentic 2-hydroxynicotinic acid, 260—262° (Found: C, 51·95; H, 3·6; N, 10·1. Calc. for $C_6H_5NO_3$: C, 51·8; H, 3·6; N, 10·1%). Recrystallisation of the short, dense prisms from aqueous acetic acid (1 : 1) gave 6-hydroxynicotinic acid (0·6 g., 3%) as dense, pale brown prisms, m. p. and mixed m. p. with authentic 6-hydroxynicotinic acid, 318—320° (decomp.) with previous darkening >300°. The infrared spectra of 2- and 6-hydroxynicotinic acid thus obtained were identical with those of authentic specimens.

[11] Ramirez and von Ostwalden, *Chem. and Ind.*, 1957, 46; *J. Amer. Chem. Soc.*, 1959, **81**, 156.

(*b*) The following is one example of the many variations which were tried. A solution of nicotinic acid 1-oxide (15 g.) in acetic anhydride (150 ml.) was boiled for 6 hr. The solvent was then removed under reduced pressure, the residue was taken up in methanol (120 ml.) (charcoal), the solution was filtered, and the solvent removed. Repeated fractional crystallisation of the residue from water eventually yielded 2-acetylnicotinic acid 1-oxide (5·0 g., 25%), 2-hydroxynicotinic acid (1·2 g., 8%), and 6-hydroxynicotinic acid (0·4 g., 2%).

2-Acetylnicotinic acid 1-oxide was characterised as its *dinitrophenylhydrazone*, which crystallised from acetic acid as orange rhombs, m. p. 244—245° (decomp.) (Found: C, 46·45; H, 3·2; N, 19·2. $C_{14}H_{11}N_5O_7$ requires C, 46·55; H, 3·05; N, 19·4%). The p-*nitrophenylhydrazone anhydride* was obtained from acetic acid as buff needles, m. p. 266—267° (decomp.) [Found: C, 54·9; H, 4·1; N, 17·1. $C_{14}H_{10}N_4O_4$,0·5AcOH requires C, 54·9; H, 3·7; N, 17·1. Found (after being dried at 116° *in vacuo*): C, 56·6; H, 3·45; N, 18·85. $C_{14}H_{10}N_4O_4$ requires C, 56·4; H, 3·4; N, 18·8%].

Quinolinic Acid 1-Oxide.—(*a*) An ice-cold solution of bromine (1·45 g.) in dilute sodium hydroxide solution (1·1 g. in 10 ml. of water) was added to a solution of 2-acetylnicotinic acid 1-oxide (540 mg.) in dilute sodium hydroxide solution (2N; 5 ml.), with cooling in ice. Almost immediately bromoform began to separate. After 1 hr. at 0°, and 4 hr. at room temperature, the mixture was extracted with ether, and the aqueous layer was acidified (Congo Red) with concentrated hydrochloric acid and kept at 0° overnight. The product was then recrystallised from water. *Quinolinic acid 1-oxide* (430 mg., 80%) was thus obtained as rhombs, m. p. 260—262° (decomp.), alone or in admixture with authentic quinolinic acid 1-oxide (Found: C, 46·05; H, 2·7; N, 7·8. $C_7H_5NO_5$ requires C, 45·9; H, 2·7; N, 7·65%). The infrared spectra of this compound and of quinolinic acid 1-oxide, prepared as described below, were identical.

(*b*) A mixture of quinolinic acid (5 g.), acetic acid (25 ml.), and 40% hydrogen peroxide (25 ml.) was warmed *gently* on the steam-bath until solution was complete, and then kept at room temperature overnight. The solid (quinolinic acid) which separated was removed and the mother liquors were kept at room temperature for 7 days. The solid was then recrystallised from water; quinolinic acid 1-oxide (2·5 g., 50%) was obtained as rhombs, m. p. 260—261° (decomp.) (Found: C, 45·95; H, 2·75; N, 7·7%).

Cinchomeronic Acid 1-Oxide.—A mixture of cinchomeronic acid (5 g.), acetic acid (15 ml.), and 40% hydrogen peroxide (15 ml.) was heated on the steam-bath for 5 hr. The solvent was then removed under reduced pressure, and the residue was crystallised from water. *Cinchomeronic acid 1-oxide* (2·6 g., 47%) was thus obtained as rhombs, m. p. 249—250° (decomp.) (Found: C, 46·1; H, 2·75; N, 7·6%). The m. p. of a mixture with cinchomeronic acid was 230—244°.

2-Acetylnicotinic Acid.—A solution of 2-acetylnicotinic acid 1-oxide (2 g.) in water (60 ml.) was hydrogenated at atmospheric pressure, 5% palladised charcoal catalyst (0·2 g.) being used, until one mole of hydrogen had been absorbed. The catalyst was then removed, the solution evaporated to dryness, and the residue sublimed at 100°/0·03 mm. The sublimate was recrystallised twice from benzene, and 2-acetylnicotinic acid was obtained as needles, m. p. 127—128°; ν 1754, 1710sh, and 789 cm.$^{-1}$ (potassium chloride disc) [Found (after being dried at 78° *in vacuo*): C, 58·1; H, 4·1; N, 8·6. Calc. for $C_8H_7NO_3$: C, 58·2; H, 4·3; N, 8·5%]; Rosenheim and Tafel [3] report m. p. 127°. The oxime anhydride was obtained from ethanol as long needles, m. p. 165—166° (Found: C, 59·55; H, 3·6. Calc. for $C_8H_6N_2O_2$: C, 59·3; H, 3·7%); Rosenheim and Tafel [3] give m. p. 171°. The *p*-nitrophenylhydrazone anhydride crystallised from benzene as pale yellow needles, m. p. 268° (Found: C, 59·35; H, 3·35; N, 19·95. Calc. for $C_{14}H_{10}N_4O_3$: C, 59·6; H, 3·55; N, 19·85%); Wibaut and Boer [4] give m. p. 270°.

Lactone of 2-1′-Hydroxyethylnicotinic Acid.—A solution of 2-acetylnicotinic acid 1-oxide (1·00 g.) in water (30 ml.) was hydrogenated at atmospheric pressure in the presence of 5% palladised charcoal catalyst. When 2 moles of hydrogen had been absorbed the solution was filtered and evaporated to dryness. The reddish-brown semisolid residue (0·8 g.) was sublimed at 110°/0·03 mm. The sublimate was dissolved in boiling benzene (charcoal), the solvent was removed, and the residue was crystallised twice from cyclohexane. The *lactone* (II) of 2-1′-hydroxyethylnicotinic acid (0·38 g.) was obtained as needles, m. p. 77·5—79°; $\lambda_{max.}$ (in ethanol) 270 mμ (log ε 3·71); ν 1767 cm.$^{-1}$ (potassium chloride disc) (Found: C, 64·4; H, 4·75; N, 9·4. $C_8H_7NO_2$ requires C, 64·4; H, 4·73; N, 9·4%).

Reaction of Nicotinic Acid 1-Oxide with Propionic Anhydride.—(*a*) A solution of nicotinic acid 1-oxide (20 g.) in propionic anhydride (200 ml.) was boiled for 3 hr. The solvent was then

removed under reduced pressure, the residue was dissolved in water (400 ml.), and the aqueous solution was extracted with chloroform. The aqueous layer was concentrated until crystallisation began. The solid was fractionally crystallised from water (charcoal), yielding 2-hydroxynicotinic acid (3·6 g.), m. p. and mixed m. p. with authentic material 260—262°, and 6-hydroxynicotinic acid (0·4 g.), m. p. and mixed m. p. with authentic material 318° (decomp.). The chloroform extract was washed with dilute sodium carbonate solution, dried ($MgSO_4$), and evaporated. The crude product was recrystallised repeatedly from ethanol, and the *diketone* (III) (2·0 g.) was obtained as long cream needles, m. p. 160—161°; $\lambda_{max.}$ (in water) 288 (log ε 3·95) and 335 mμ (log ε 3·49); ν 1727, 1670, 1250sh, 1242, and 787 cm.$^{-1}$ (potassium chloride disc) (Found: C, 61·1; H, 4·1; N, 8·2. $C_9H_7NO_3$ requires C, 61·0; H, 3·95; N, 7·9%). This diketone gave an intense green colour with ferric chloride but was insoluble in dilute sodium carbonate solution. With dilute sodium hydroxide solution it gave an orange-red solid, which dissolved when warmed to give a red solution, the colour of which gradually faded to orange. The *dinitrophenylhydrazone* crystallised from acetic acid as orange-brown needles, m. p. 271—272° (decomp.) (Found: C, 50·45; H, 3·4; N, 19·5. $C_{15}H_{11}N_5O_6$ requires C, 50·4; H, 3·1; N, 19·6%).

(*b*) A mixture of nicotinic acid 1-oxide (6 g.) and propionic anhydride (90 ml.) was boiled for 1 hr., and the solvent was removed at 120°/12 mm. The black tarry residue was extracted with chloroform, and the extracts were washed several times with dilute sodium carbonate solution and then with water. The chloroform solution was then dried ($MgSO_4$) and evaporated, yielding a viscous brown oil which exhibited infrared bands at 1802s, 1764s, 1724 infl., and 1664m cm.$^{-1}$. A mixture of this oil and water (100 ml.) was boiled for 2 hr., then treated with charcoal, filtered, and evaporated to dryness. The residue (3·2 g.) crystallised completely on trituration with methylene chloride, and was recrystallised from the same solvent. The product was repeatedly recrystallised from water, yielding 2-*propionylnicotinic acid* 1-*oxide* (5%) as long prisms, m. p. 195—196° (Found: C, 55·4; H, 4·75; N, 7·45. $C_9H_9NO_4$ requires C, 55·4; H, 4·6; N, 7·2%); $\lambda_{max.}$ (in water) 214 and 261 mμ (log ε 4·33 and 3·99), inflexion at 310 mμ (log ε 2·86). The dinitrophenylhydrazone was prepared in ethanol but was amorphous. The methylene chloride mother liquors were evaporated to dryness and the residue was fractionally crystallised from water, yielding 2-hydroxynicotinic acid, m. p. 260—262° (5%), identical (mixed m. p. and infrared spectrum) with authentic material.

In another experiment the mixture was evaporated to dryness and the residue was extracted with boiling water (total volume 150 ml.). The cooled solution was extracted with chloroform, and the aqueous layer was evaporated to dryness. Fractional crystallisation of the residue from water gave small amounts of 2-hydroxynicotinic acid and 6-hydroxynicotinic acid.

Reaction of Isonicotinic Acid 1-*Oxide with Acetic Anhydride.*—A mixture of isonicotinic acid 1-oxide (20 g.) and acetic anhydride (200 ml.) was boiled for 8 hr., then filtered, and the dark brown residue was crystallised repeatedly from water (charcoal). Isonicotinic acid (3·9 g.) was obtained as needles, which darken above 240° and sublime at 310°. The infrared spectrum of this material was identical with that of authentic isonicotinic acid. The acetic anhydride mother liquor was evaporated to dryness under reduced pressure, and the dark residue (7 g.) fractionally crystallised from water (charcoal). The major product was 2-hydroxyisonicotinic acid (1·4 g.) which was obtained as pale yellow-brown needles, which darken above 270° but do not melt below 330° (Found: C, 51·55; H, 3·4; N, 9·65. Calc. for $C_6H_5NO_3$: C, 51·8; H, 3·6; N, 10·05%); Baümler, Sorkin, and Erlenmeyer [12] report m. p. 318—325° (decomp.). The less soluble fractions gave a *substance* $C_9H_9NO_4$ (0·15 g.), obtained as long, colourless needles, m. p. 204—206° (Found: C, 55·4; H, 4·8; N, 7·25. $C_9H_9NO_4$ requires C, 55·4; H, 4·6; N, 7·2%).

Reaction of Cinchomeronic Acid 1-*Oxide with Acetic Anhydride.*—A mixture of cinchomeronic acid 1-oxide (2 g.) and acetic anhydride (20 ml.) was boiled for 2 hr., and the solvent was then removed. The residue was dissolved in water (charcoal), and the solution was filtered and evaporated to dryness. The residue was recrystallised from water, and cinchomeronic acid (1 g.) was obtained as long prisms, m. p. 266—267°, alone or when mixed with authentic cinchomeronic acid. The infrared spectra of the two specimens were identical.

Reaction of 3-*Picoline* 1-*Oxide with Acetic Anhydride.*—A solution of 3-picoline 1-oxide (5 g.) in acetic anhydride (25 ml.) was boiled for 5 hr., and the solvent was removed under

[12] Bäumler, Sorkin, and Erlenmeyer, *Helv. Chim. Acta*, 1951, **34**, 496.

reduced pressure. Water (25 ml.) was then added, and the mixture was heated on the steam-bath for 1 hr. The solution was then evaporated to dryness under reduced pressure, and the residue (5·5 g.) dissolved in light petroleum (b. p. 60—80°) and chromatographed on neutral alumina (200 g.). Elution with light petroleum (b. p. 60—80°) containing benzene (10%) gave 3-*methyl*-1-(5-*methyl*-2-*pyridyl*)-2-*pyridone*, which was obtained from light petroleum (b. p. 60—80°) as plates, m. p. 110—111° (0·18 g., 3·9%); $\lambda_{max.}$ (in water) 264·5, 270, and 303 mμ (log ε 3·7, 3·71, and 3·84); ν 1656, 1613, 1277, and 1267 cm.$^{-1}$ (potassium chloride disc) (Found: C, 72·1; H, 6·1; N, 14·45. $C_{12}H_{12}N_2O$ requires C, 72·0; H, 6·0; N, 14·0%). Elution with light petroleum (b. p. 60—80°)–benzene (3 : 1) furnished 3-methyl-2-pyridone (1·65 g.), m. p. 142—143°, identical (mixed m. p. and infrared spectrum) with authentic material, followed by a mixture (1·53 g.) of 3-methyl- and 5-methyl-2-pyridone. Elution with benzene and with benzene–chloroform then gave 5-methyl-2-pyridone (1·23 g.), m. p. 184—185°, identical (mixed m. p. and infrared spectrum) with authentic material. Rechromatography of the intermediate mixed fraction on neutral alumina (60 g.) yielded more 3-methyl- (0·5 g.) and 5-methyl-2-pyridone (0·3 g.).

3-*Methyl*-1-(5-*methyl*-2-*pyridyl*)-2-*pyridone*.—A mixture of the sodium salt of 3-methyl-2-pyridone (3·22 g.), 2-bromo-5-methylpyridine (4·65 g.), and copper bronze (0·1 g.) was heated at 165° for 5 hr. The cooled mixture was extracted with chloroform, and the extracts were filtered, dried, and concentrated. The residue was recrystallised from light petroleum (b. p. 60—80°) (charcoal); 3-methyl-1-(5-methyl-2-pyridyl)-2-pyridone (2·5 g.) was then obtained as needles, m. p. 110—111°, identical (mixed m. p. and infrared spectrum) with the by-product obtained in the reaction of 3-picoline 1-oxide with acetic anhydride (Found: C, 71·75; H, 5·85; N, 13·95. $C_{12}H_{12}N_2O$ requires C, 72·0; H, 6·0; N, 14·0%).

5-*Methyl*-1-(5-*methyl*-2-*pyridyl*)-2-*pyridone*.—The procedure of the preceding experiment was repeated with the sodium salt of 5-methyl-2-pyridone (1·55 g.), 2-bromo-5-methylpyridine (2·74 g.), and copper bronze (0·1 g.). 5-*Methyl*-1-(5-*methyl*-2-*pyridyl*)-2-*pyridone* (1·0 g.) was obtained as needles, m. p. 102—103°; $\lambda_{max.}$ (in water) 264, 269, and 313 mμ (log ε 3·62, 3·60, and 3·78); ν 1675, 1626, 1613, 1287, and 1266 cm.$^{-1}$ (potassium chloride disc) (Found: C, 72·1; H, 6·15; N, 14·05%). The m. p. of a mixture with the product, m. p. 110—111°, obtained from the reaction of 3-picoline 1-oxide was 85—100°.

3,3′-*Dimethyl*-4,4′-*bipyridyl* 1-*Oxide*.—3,3′-Dimethyl-4,4′-bipyridyl [13] (0·4 g.) was added to a solution of perbenzoic acid (0·3 g.) in chloroform (30 ml.), and the solution kept overnight. It was then extracted with dilute sodium carbonate solution, dried, and evaporated, and the residue recrystallised from benzene (charcoal). 3,3′-*Dimethyl*-4,4′-*bipyridyl* 1-*oxide* (0·3 g.) was obtained as rhombs, m. p. 217—218°; $\lambda_{max.}$ (in water) 263 mμ (log ε 4·30); ν 1616, 1253, 1030, 1018, 872, and 830 cm.$^{-1}$ (potassium chloride disc) (Found: C, 72·25; H, 6·0; N, 14·5%). When a mixture with iron powder and acetic acid was boiled for 1·5 hr. smooth, quantitative reduction took place to 3,3′-dimethyl-4,4′-bipyridyl, m. p. 122—123°, identified by mixed m. p. and infrared spectrum.

2,3-*Dihydroxypyridine*.—(*a*) A solution of 3-hydroxypyridine 1-oxide (1·1 g.) in acetic anhydride (10 ml.) was boiled for 4 hr., and the solvent was removed. Water (25 ml.) was then added, and the mixture boiled (charcoal) and filtered. When cold, the solution was filtered to remove tar, and then evaporated to dryness. The residue was recrystallised from water, and 2,3-dihydroxypyridine was obtained as needles, m. p. 252—253°, with previous darkening above 215°, identical (mixed m. p. and infrared spectrum) with authentic 2,3-dihydroxypyridine; [8] the infrared spectrum had bands at 3150—3080, 1669, 781, and 753 cm.$^{-1}$ (Found: C, 54·1; H, 4·55; N, 12·5. Calc. for $C_5H_5NO_2$: C, 54·1; H, 4·5; N, 12·6%).

(*b*) A mixture of 3-hydroxypyridine (5 g.), acetic acid (40 ml.), and 40% hydrogen peroxide (30 ml.) was heated for 18 hr. on the steam-bath. The solvents were removed under reduced pressure, acetic anhydride (10 ml.) was added, and the solution was evaporated to dryness. Acetic anhydride (50 ml.) was added, and the solution was boiled for 4 hr. The solvent was removed, water (50 ml.) was added, and the mixture was digested on the steam-bath for 0·5 hr. (charcoal), filtered, and evaporated until crystallisation began. The product was recrystallised from methanol; 2,3-dihydroxypyridine (1·2 g.) was obtained as plates, m. p. and mixed m. p. with authentic 2,3-dihydroxypyridine, 252—253°.

Reaction of 3-*Picoline* 1-*Oxide with* 2-*Acetoxypyridine*.—A mixture of 3-picoline 1-oxide

[13] Stoehr and Wagner, *J. prakt. Chem.*, 1893, **48**, 1.

(8·75 g.) and 2-acetoxypyridine (11 g.) was heated at 100° for 4 days, with exclusion of atmospheric moisture. The resulting dark brown oil was then distilled, and the fractions (11·5 g.) boiling below 120°/0·7 mm. were discarded. The residue (6·2 g. of dark brown oil) was dissolved in hot water (20 ml.) (charcoal), the solution was filtered, and the solvent removed. The remaining oil was extracted repeatedly with boiling light petroleum (b. p. 60—80°) (total volume 200 ml.). The cooled extracts (mother liquor A) deposited a mixture (0·75 g.) of colourless crystals and a pale yellow oil. Repeated fractional crystallisation of this mixture alternately from hexane and cyclohexane eventually yielded 1-(5-methyl-2-pyridyl)-2-pyridone, as needles, m. p. 93·5—94·5° (0·25 g.); $\lambda_{max.}$ (in ethanol) 272 and 314 mμ (log ε 3·56 and 3·80); identical (mixed m. p. and infrared spectrum) with authentic 1-(5-methyl-2-pyridyl)-2-pyridone [11] (Found: C, 71·05; H, 5·4; N, 14·85. Calc. for $C_{11}H_{10}N_2O$: C, 70·95; H, 5·4; N, 15·05%). The light-petroleum mother liquors (A) were evaporated to dryness, and the residual mixture (2·5 g.) of oil and crystals was extracted twice with cyclohexane (residue B). Fractional crystallisation of the extracted material (0·6 g.) as before yielded more (0·2 g.) 1-(5-methyl-2-pyridyl)-2-pyridone. The remaining residue (B; 1·9 g.) was dissolved in benzene and filtered through neutral alumina (20 g.). The filtered solution (50 ml.) furnished a pale cream solid (0·55 g.), which was separated by fractional crystallisation from cyclohexane into 1-(5-methyl-2-pyridyl)-2-pyridone (0·2 g.) (less soluble fraction) and 1-(3-methyl-2-pyridyl)-2-pyridone (0·05 g.), m. p. 107·5—108·5°, identical (mixed m. p. and infrared spectrum) with authentic material; [11] $\lambda_{max.}$ 263, 268 infl. and 306 mμ (log ε 3·62, 3·60, and 3·76) (Found: C, 71·2; H, 5·45; N, 14·8%).

The benzene eluates (40 ml.) from the alumina yielded a small quantity (0·46 g.) of greenish-yellow oil, from which 2-pyridone, m. p. and mixed m. p., 106—107·5°, was obtained by crystallisation from benzene–hexane (1 : 4).

(*b*) A mixture of 2-acetoxypyridine (11·0 g.) and 3-picoline 1-oxide (8·75 g.) was heated at 100° for 6 days, with exclusion of atmospheric moisture. The resulting oil was then distilled and the fractions boiling below 117°/0·6 mm. were discarded. The residue was extracted with boiling water (charcoal), the solution was filtered, and the solvent was removed under reduced pressure. The residual oil was extracted exhaustively with cyclohexane, and the extracted material (4·44 g.) chromatographed on neutral alumina (250 g.), benzene–cyclohexane (70 : 30) being used as solvent. Elution was carried out with benzene–cyclohexane mixtures, then benzene, and finally benzene–chloroform (70 : 30), which eluted a broad band exhibiting an intense violet fluorescence. The eluates (5 × 250 ml.) furnished mixtures of 1-(5-methyl-2-pyridyl)-2-pyridone and 1-(3-methyl-2-pyridyl)-2-pyridone, which could not be separated conveniently into their components by fractional crystallisation. All five fractions gave two spots on chromatoplate examination, corresponding in R_F value to the two pure components. The mixture to be analysed was added to the chromatoplate in solution in benzene, and development was carried out by using ethyl acetate. 1-(5-Methyl-2-pyridyl)-2-pyridone was located by its intense fluorescence; both constituents were located as deep orange-yellow spots on a pale orange-brown background after spraying with Dragendorff's reagent.

Vapour-phase chromatography at 204° with a silicone column and helium as carrier gas also demonstrated the presence of two constituents, identified by the addition of authentic material to the chromatographed mixtures as 1-(5-methyl-2-pyridyl)-2-pyridone and its 3-methyl isomer. The composition of the mixtures was determined by estimating the areas of the peaks in each chromatogram, from which the estimated total yields were: 1-(5-methyl-2-pyridyl)-2-pyridone (VII; R = Me, R′ = H), 1·52 g. (10%); and 1-(3-methyl-2-pyridyl)-2-pyridone (VII; R = H, R′ = Me), 0·60 g. (4%).

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