405. *The Preparation and Properties of Pyridino*(1′ : 2′-2 : 3)-1-*oxa*-2 : 4-*diazol*-5-*one*.

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Heating 2-ethoxycarbonylaminopyridine 1-oxide gives the compound named in the title, the first example of a 1 : 2-pyridino-bicyclic system containing a potential pyridine 1-oxide group. The preparation and some properties of two homologues are described.

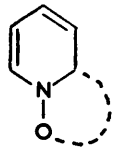
RING systems containing a pyridine 1-oxide group as part of a 1 : 2-pyridino-bicyclic system [as in (I)] have not hitherto been described. They are being sought because of the theoretical interest in pyridine 1-oxides;[1] the present paper records the synthesis of pyridino(1′ : 2′-2 : 3)-1-oxa-2 : 4-diazol-5-one (II).

2-Aminopyridine and ethyl chloroformate in pyridine gave 2-ethoxycarbonylaminopyridine and some *NN*′-di-2-pyridylurea, for the crude product with hydrogen peroxide gave, together with the expected urethane oxide (III), a sparingly soluble by-product which was proved to be *NN*′-di-2-pyridylurea 1 : 1′-dioxide by its synthesis from *NN*′-di-2-pyridylurea.[2] When heated at 140—150°, the urethane oxide (III) lost one mol. of ethanol and gave a compound $C_6H_4O_2N_2$. This could only have been the pyridino-oxadiazolone (II) or 2-*iso*cyanatopyridine 1-oxide; the latter was eliminated because the compound did not show the intense absorption at 2269 ± 6 cm.$^{-1}$ characteristic of *iso*cyanates,[3] and because it crystallised unchanged from water or ethanol.

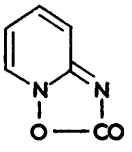
Starting from 2-amino-4- and -6-methylpyridine, similar reactions led to 4′- and 6′-methylpyridino(1′ : 2′-2 : 3)-1-oxa-2 : 4-diazol-5-one. Although Adams and Miyano [4] found

[1] See, *e.g.*, Jaffé, *J. Amer. Chem. Soc.*, 1954, **76**, 3527; 1955, **77**, 4448.
[2] Camps, *Arch. Pharm.*, 1902, **240**, 345.
[3] Davison, *J.*, 1953, 3712.
[4] Adams and Miyano, *J. Amer. Chem. Soc.*, 1954, **76**, 2785.

that 2-acetamidopyridine 1-oxides might be freed from acetic acid by distilling off the latter, in this work better results were obtained by removing acetic acid with potassium carbonate; in the 6-methyl series omission of this treatment gave the urethane oxide acetate. Attempted cyclisation of a crude urethane oxide acetate at 150° *in vacuo* led to explosive decomposition.



(I)



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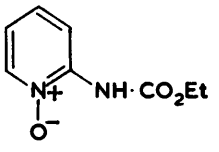

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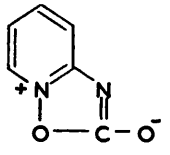

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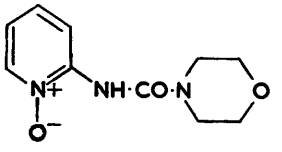

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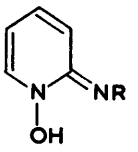

(VI)

The considerable stability of the new bicyclic system to heat and oxidising agents (see Experimental section) reflects the fact that the representation (II) is only one of several contributors to the resonance hybrid. The compound may be described as aromatic, for sextets of eletrons are associated with both rings, as is seen in the canonical form (IV). Hydrochloric acid cleaved the pyridino-oxadiazoles to 2-aminopyridine 1-oxides which do not form stable picrates [5] but were converted into picrolonates, which have proved suitable for characterisation of other pyridine 1-oxides.[6] Heating the pyridino-oxadiazolone (II) with sodium ethoxide also gave 2-aminopyridine 1-oxide in poor yield (and, presumably, ethyl carbonate) and, similarly, heating with aniline gave carbanilide. With morpholine, the pyridino-oxadiazolone (II) gave 2-morpholinocarbonylaminopyridine 1-oxide (V).

As noted by Newbold and Spring [5] and by Adams and Miyano [4] 2-aminopyridine 1-oxides give an intense blue ferric chloride test. The urethanes (as III) from them give an intense red colour and the derived urea (V) gives a violet colour with the same reagent. All these compounds also gave green colours with cupric ions, but did not change the colours of solutions of Ni^{++}, Co^{++}, or Mn^{++} salts.

2-Hydroxypyridine 1-oxide exists as 1-hydroxypyrid-2-one,[7] and possibly 2-aminopyridine 1-oxide and/or the urethanes and ureas derived from it similarly exist in tautomeric forms (VI). This would show 2-aminopyridine 1-oxide as a cyclic amidoxime and bring out the relations between the pyrido-oxadiazolones described in this paper and the azoximes (1-oxo-2 : 4-diazoles); [8] these matters are under investigation.

Experimental

2-Ethoxycarbonylaminopyridine 1-Oxide.—Ethyl chloroformate (75 g., 66 c.c.) was added dropwise at 0° to 2-aminopyridine (50 g.) in pyridine (150 c.c.) with constant shaking. After 12 hr., pouring the mixture into water gave 2-ethoxycarbonylaminopyridine (60·8 g. 70%), m. p. 98—101°, raised by recrystallisation from ethanol–water (3 : 1) to 102—103·5° (lit.,[2] m. p. 105°).

The crude urethane (18 g,) in acetic acid (35 c.c.) was heated with 30% aqueous hydrogen peroxide (16·5 c.c.) at 70° overnight. Volatile matter was removed at 100°/20 mm., chloroform (150 c.c.) was added to the residue, and *NN'*-di-2-pyridylurea 1 : 1'-dioxide (0·68 g.) filtered off.

[5] Newbold and Spring, *J.*, 1949, S 133.
[6] Katritzky, *J.*, 1956, 2404.
[7] Shaw, *J. Amer. Chem. Soc.*, 1949, **71**, 67; Cunningham, Newbold, Spring, and Sharp, *J.*, 1949, 2091.
[8] See, *e.g.*, Tiemann, *Ber.*, 1889, **22**, 2391.

The chloroform solution was digested with potassium carbonate (10 g.). Filtration and removal of solvent gave the crude *urethane* 1-*oxide* (19·2 g., 97%) which after two recrystallisations from ether formed needles, m. p. 88·5—90° (Found : C, 52·6; H, 5·7. $C_8H_{10}O_3N_2$ requires C, 52·7; H, 5·5%). Light absorption : max. at 2300, 2650, 3050 Å (ε 30,000, 7550, 2950) in neutral MeOH; 2300, 2950 (ε 16,300, 6030), infl., at 2700 (ε 3680), in *ca.* 0·1N-methanolic sulphuric acid. The compound gave an intense red colour with aqueous ferric chloride.

The *picrolonate* separated from ethanol in buff laths, m. p. 135° (decomp.) (Found : C, 48·6; H, 4·2. $C_{18}H_{18}O_8N_6$ requires C, 48·4; H, 4·0%).

NN′-*Di*-2-*pyridylurea* 1 : 1′-*Dioxide*.—*NN*′-Di-2-pyridylurea (0·53 g.), acetic acid (2·5 c.c.), and 30% aqueous hydrogen peroxide (0·8 c.c.) were heated for 12 hr. at 70°. Dilution of the semisolid product with ethanol and filtration gave the *urea* 1 : 1′-*dioxide* (0·61 g., 100%) as needles, m. p. 235—237° (decomp.), raised by two recrystallisations from acetic acid to 236—237° (decomp.) (immersion at 220°) (Found, after drying at 130°/14 mm. : C, 53·6; H, 4·2. $C_{11}H_{10}O_3N_4$ requires C, 53·7; H, 4·1%). This was identical with the by-product mentioned above (m. p., mixed m. p., and infrared spectra).

Pyridino(1′ : 2′-2 : 3)-1-*oxa*-2 : 4-*diazol*-5-*one* (II).—2-Ethoxycarbonylaminopyridine 1-oxide (3 g.), heated at 140—150° for 1 hr., gave ethanol (0·68 g., 90%) [identified by b. p. (77·5°) and conversion into ethyl 3 : 5-dinitrobenzoate (2·77 g., 78%), m. p. and mixed m. p. 91—92°] and a residue of *pyridino-oxadiazolone* (2·24 g., 100%) which crystallised from ethanol in colourless needles, m. p. 203—205° (Found : C, 53·3; H, 3·2; N, 20·2. $C_6H_4O_2N_2$ requires C, 53·0; H, 2·9; N, 20·6%). Light absorption : max. at 2450, 3100 Å (ε 17,170, 4030) in MeOH. The compound was readily soluble in hot water. It dissolved in hydrochloric acid and was reprecipitated by sodium hydroxide. It sublimed unchanged at 220°/12 mm., gave no colour with ferric chloride, did not decolorise bromine or acid permanganate, and reacted with alkaline permanganate only on warming.

The yellow *picrolonate*, separated from ethanol, had m. p. 125—126° (decomp.) (Found : C, 48·2; H, 3·2. $C_{16}H_{12}O_7N_6$ requires C, 48·0; H, 3·0%).

4′-*Methylpyridino*(1′ : 2′-2 : 3)-1-*oxa*-2 : 4-*diazol*-5-*one*.—2-Amino-4-methylpyridine similarly gave 2-*ethoxycarbonylamino*-4-*methylpyridine* (66%), needles (from ethanol), m. p. 124—126·5° (Found : C, 60·0; H, 6·7; N, 16·0. $C_9H_{12}O_2N_2$ requires C, 60·0; H, 6·7; N, 15·6%). Oxidation of the crude urethane gave, as by-product, the urea dioxide (see below), and 2-*ethoxycarbonylamino*-4-*methylpyridine* 1-*oxide* (70%), plates (from ether), m. p. 80—81°, giving an intense red ferric chloride colour (Found : C, 54·8; H, 6·3. $C_9H_{12}O_3N_2$ requires C, 55·1; H, 6·1; N, 14·3%). Heating the latter as before afforded the *methylpyridino-oxadiazolone*, needles (from ethanol), m. p. 155·5—157° (Found : C, 56·0; H, 4·2. $C_7H_6O_2N_2$ requires C, 56·0; H, 4·0; N, 18·7%). Light absorption : max. at 2455, 3050 Å (ε 14·680. 3920) in MeOH. The *picrate* separated from ethanol in yellow needles, m. p. 120—121° (Found : C, 40·9; H, 2·3; N, 18·5. $C_{13}H_9O_9N_5$ requires C, 41·2; H, 2·4; N, 18·5%).

2-Ethoxycarbonylaminopyridine (1 g.) and 2-aminopyridine (1·2 g.) were boiled over a small flame for 8 min.; the product, recrystallised from ethanol, gave NN′-*di*-(4-*methylpyrid*-2-*yl*)*urea* (1·48 g., 69%) in needles, m. p. 220—223° raised by further recrystallisation to 222—224° (Found : C, 64·3; H, 6·0; N, 23·2. $C_{13}H_{14}ON_4$ requires C, 64·5; H, 5·8; N, 23·1%). Oxidation as described above gave the corresponding *dioxide* (88%), needles (from acetic acid), m. p. 235—236° (decomp.) (varies with the rate of heating) (Found : C, 57·2; H, 5·2. $C_{13}H_{14}O_3N_4$ requires C, 56·9; H, 5·1%). This was shown to be identical with the by-product mentioned above (mixed m. p. and infrared spectrum).

6′-*Methylpyridino*(1′ : 2′-2 : 3)-1-*oxa*-2 : 4-*diazol*-5-*one*.—2-Amino-6-methylpyridine similarly gave a *urethane* (90%), which formed laths, m. p. 56—58°, from ethanol (Found : C, 60·1; H, 6·8%). Oxidation as before gave (without a by-product) the *urethane* 1-*oxide* (97%), needles (from ether), m. p. 65—66·5°, giving an intense red ferric chloride test (Found : N, 14·7%). Omission of the treatment with potassium carbonate gave the corresponding *acetate* (28%), prisms (from ether), m. p. 68—70° (Found : C, 51·6; H, 6·0. $C_{11}H_{16}O_5N_2$ requires C, 51·6; H, 6·2%). Heating the urethane oxide gave the *pyridino-oxazolone* (77%), laths (from ethanol), m. p. 182—183·5° (Found : C, 55·6; H, 3·7; N, 19·0%). Light absorption : max. at 2440, 3125 Å (ε 19·270, 5610) in MeOH.

Conversion of Pyridino-oxadiazolones into 2-*Aminopyridine* 1-*Oxides*.—Pyridino(1′ : 2′-2 : 3)-1-oxa-2 : 4-diazol-5-one (2·24 g.) was refluxed with concentrated hydrochloric acid (8 c.c.) and water (8 c.c.) overnight. Aqueous sodium hydroxide (30%) was added to alkalinity, then hydrochloric acid to acidity. Extraction with chloroform (10 × 100 c.c.) gave, after drying of the extracts (K_2CO_3) and removal of solvent, 2-aminopyridine 1-oxide (1·28 g., 71%), m. p.

159—160·5°, raised by recrystallisation from ethanol–ethyl acetate to 161—162° (lit.,[4,5] m. p. 161—163° and 164—165°). The *picrolonate* separated from ethanol in yellow needles, m. p. 221° (decomp.) (Found : C, 48·5; H, 4·1. $C_{15}H_{14}O_6N_6$ requires C, 48·1; H, 3·7%).

The following were similarly prepared : 2-amino-6-methylpyridine 1-oxide (82%), prisms (from ethanol–ethyl acetate), m. p. 153—154·5° (lit.,[5] 153—154°); *picrolonate*, needles (from ethanol), m. p. 221—223° (decomp.) (Found : C, 49·6; H, 4·1. $C_{16}H_{16}O_6N_6$ requires C, 49·5; H, 4·1%).

Reaction of the Pyridino-oxadiazolones with Bases.—Pyridino(1′ : 2′-2 : 3)-1-oxa-2 : 4-diazol-5-one (1 g.) was refluxed with ethanolic sodium ethoxide (from 0·05 g. of sodium and 10 c.c. of ethanol) for 8 hr. Carbon dioxide was passed into the product from which, after treatment with charcoal, 2-aminopyridine 1-oxide (0·18 g., 22%), m. p. and mixed m. p. 159—161°, was isolated.

Pyridino(1′ : 2′-2 : 3)-1-oxa-2 : 4-diazol-5-one (1 g.) was refluxed with aniline for 4 hr. under nitrogen. On cooling, carbanilide (1·32 g., 85%) separated; it had m. p. 230—240°, raised by recrystallisation from water to 241—242° (lit., 244°) (Found : C, 73·7; H, 5·8; N, 13·2. Calc. for $C_{13}H_{12}ON_2$: C, 73·6; H, 5·7; N, 13·2%). 4′-Methylpyridino(1′ : 2′-2 : 3)-1-oxa-2 : 4-diazol-5-one similarly gave carbanilide.

Pyridino(1′ : 2′-2 : 3)-1-oxa-2 : 4-diazol-5-one (1 g.) was refluxed with morpholine (5 c.c.) under nitrogen for 18 hr.; on cooling, 2-*morpholinocarbonylaminopyridine* 1-*oxide* (0·74 g., 45%) separated; it crystallised from ethyl acetate in needles, changing to plates, m. p. 129·5—131° (Found : C, 54·1; H, 5·76; N, 19·0. $C_{10}H_{13}O_3N_3$ requires C, 53·8; H, 5·8; N, 18·8%). It gave an intense violet colour with ferric chloride.

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