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Synthesis of Isoxazolo[3,4-*b*]pyridin-3(1*H*)-one and Isoxazolo[5,4-*b*]-pyridin-3(2*H*)-one

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α-(*N'*-Hydroxyamidino)acetohydroxamic acid (I) and 5-aminoisoxazol-3(2*H*)-one (V) were each condensed with acetylacetone to yield 2-hydroxyamino-4,6-dimethylpyridine-3-carboxylic acid (II) and 4,6-dimethylisoxazolo[5,4-*b*]pyridin-3(2*H*)-one (VIa) respectively. Compound (II) gave isoxazolo[3,4-*b*]pyridin-3(1*H*)-ones (III) on acetylation, benzoylation, and bromination. The structures of (II) and (VIa) were confirmed by their conversion into known products.

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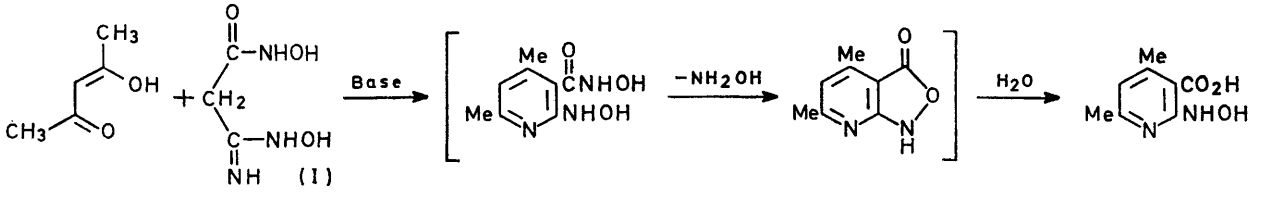
ETHYL CYANOACETATE and hydroxylamine react together to yield a number of products [1,2] depending upon the reaction conditions. One of these products, the cyanoacetohydroxamic acid, gave a cyclic hydroxamic acid on condensation with acetylacetone under alkaline conditions.[3,4] The other two products, α-(*N'*-hydroxyamidino)acetohydroxamic acid (I) and 5-aminoisoxazol-3(2*H*)-one (V) also undergo a similar reaction with acetylacetone to give new pyridine compounds. This provides a route to the hitherto unknown isoxazolo-[5,4-*b*]pyridin-3(2*H*)-ones.

When acetylacetone was refluxed with (I) in aqueous medium with catalytic amounts of a base, a yellow compound (II), $C_8H_{10}N_2O_3$, was obtained in high yields. Compound (II) dissolved in 5% sodium hydrogen carbonate solution with evolution of carbon dioxide, and had a very broad i.r. absorption at 2500—3100 cm^{-1}, thus suggesting the presence of a carboxylic group. On reaction with nitrous acid (II) gave the known 1,2-dihydro-4,6-dimethyl-2-oxopyridine-3-carboxylic acid,[5] and it could be reduced with hydrazine hydrate and also with zinc and sodium hydroxide to another known product, 2-amino-4,6-dimethylpyridine-3-carboxylic acid.[6] We thus suggest that compound (II) is 2-hydroxyamino-4,6-dimethylpyridine-3-carboxylic acid which can be visualised as arising *via* a Hantzsch–Knoevenagel reaction to give an intermediate which loses a molecule of hydroxylamine to yield an unstable isoxazolopyridinone which then reacts with water to give (II) (Scheme).

The dibenzoate of (I),[2] which cannot lose hydroxylamine, failed to condense with acetylacetone under alkaline conditions.

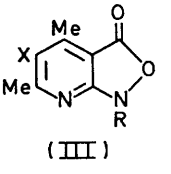
On acetylation and benzoylation (II) gave the side-chain *N*-acyl derivatives which were readily dehydrated *in situ* to yield (IIIa and b). The *N*-acylation is indicated by the absence of the NH absorption in the i.r. spectrum. The acyl group could easily be removed under alkaline conditions to generate the yellow material.

Bromination of (II) in acetic acid caused substitution in the 5-position of the pyridine ring and was again accompanied by cyclisation of the isoxazolone ring, to yield (IIIc). The position of bromine in this compound was confirmed by its reaction with nitrous acid to give 5-bromo-1,2-dihydro-4,6-dimethyl-2-oxopyridine-3-carboxylic acid.[7] The bromo-compound was also *N*-acetylated. Compound (II) also reacted with copper(II) chloride to produce a copper salt (IV).



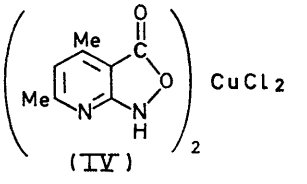
SCHEME

Compound (II) dissolved in concentrated sulphuric acid to give a colourless solution, and on dilution with water the original compound was recovered. Unlike the hydroxyaminobenzoic acid [8] it failed to reduce Fehling's solution, but did reduce Tollens' reagent on warming.



(III)

a; R = Ac, X = H
b; R = Bz, X = H
c; R = H, X = Br
d; R = Ac, X = Br



(IV)

Reaction of acetylacetone with 5-aminoisoxazol-3(2*H*)-one in the presence of a base in aqueous medium gave a white crystalline product (VIa) which was insoluble in dilute acids and bases and gave no colour with iron(III) chloride. The structure (VIa) was based

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[4] M. A. Khan and F. K. Rafla, *J.C.S. Perkin I*, 1974, 327.
[5] A. Dornow and E. Neuse, *Chem. Ber.*, 1951, **84**, 296.
[6] A. Dornow and P. Karlson, *Ber.*, 1940, **73**, 545.
[7] U.S.P. 2,516,673/1950 (*Chem. Abs.*, **45**, 670h).
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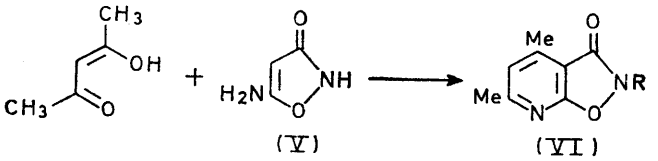
on its elemental analysis, its spectra (see Experimental section), and its reaction products. On reduction with hydrazine hydrate and with zinc and sodium hydroxide, (VIa) gave 3-carbamoyl-4,6-dimethylpyridin-2(1*H*)-one,[9] and on treatment with nitrous acid it yielded 1,2-dihydro-4,6-dimethyl-2-oxopyridine-3-carboxylic acid. Treatment with acetic anhydride gave the *N*-acetyl derivative (VIb).



(V) (VI)

a; R = H
b; R = Ac

EXPERIMENTAL

I.r. spectra were run on a Perkin-Elmer 521 spectrophotometer. Known compounds obtained from (II) and (V) were identified by comparison (spectra and mixed m.p.s) with authentic samples. Elemental analyses were performed by Alfred Bernhardt, West Germany.

1-*Hydroxyamino*-4,6-*dimethylpyridine*-2-*carboxylic Acid* (II).—The hydroxyamidino-hydroxamic acid (I) (1·3 g, 0·01 mol) in water (30 ml) was refluxed with acetylacetone (1 g, 0·01 mol) in the presence of piperidine (1 ml) for 15 min. On cooling a yellow solid separated (1·5 g, 85%) and crystallised from dilute methanol as *needles*, m.p. 204°, $\nu_{max.}$ (KBr) 3100—3520s,br, 2500—3100v,br, 1835w, and 1660s cm^{-1} (Found: C, 52·8; H, 5·3; N, 15·6. $C_8H_{10}N_2O_3$ requires C, 52·7; H, 5·5; N, 15·4%).

Acetylation of (II).—A solution of (II) (2 g) in pyridine (6 ml) was treated with acetic anhydride (4 ml). An exothermic reaction occurred during which the yellow colour of the solution disappeared and 1-*acetyl*-4,6-*dimethylisoxazolo*[3,4-b]*pyridin*-3(1H)-*one* (IIIa) separated on cooling. The white solid was filtered off and crystallised from benzene (2 g), m.p. 195° (decomp.), $\nu_{max.}$ 1780s, 1710m, 1618m, and 1590s cm^{-1} (Found: C, 58·3; H, 4·9; N, 13·6. $C_{10}H_{10}N_2O_3$ requires C, 58·3; H, 4·9; N, 13·6%).

Benzoylation of (II).—A solution of (II) (1·5 g) in 5% sodium hydroxide (2 g, in 40 ml water) was stirred with benzoyl chloride (4·5 ml) for 1 h. 1-*Benzoyl*-4,6-*dimethylisoxazolo*[3,4-b]*pyridin*-3(1H)-*one* (IIIb) (1·7 g) was filtered off and crystallised from benzene–methanol as needles, m.p. 163°, $\nu_{max.}$ (KBr) 1855w, 1770s,br, and 1690m cm^{-1} (Found: N, 10·3. $C_{15}H_{12}N_2O_3$ requires N, 10·4%).

Bromination of (II).—A solution of (II) (1·8 g) in glacial acetic acid (20 ml) was treated with bromine (1·6 g), warmed on a steam-bath for 15 min, and then diluted with water. 5-*Bromo*-4,6-*dimethylisoxazolo*[3,4-b]*pyridin*-3(1H)-*one* (IIIc) precipitated as brown solid which crystallised from methanol in brown prisms, m.p. 194° (decomp.), $\nu_{max.}$ 1730s, 1660s, and 1600m cm^{-1} (Found: C, 39·5; H, 3·1; N, 11·4; Br, 32·8. $C_8H_7BrN_2O_2$ requires C, 39·5; H, 2·9; N, 11·5; Br, 32·8%).

Reduction of (II).—(a) *With hydrazine hydrate*. A mixture of hydrazine hydrate (3 ml; 98%), methanol (5 ml), and (II) (2 g) was heated on a steam-bath for 10 min. The yellow colour of the solution soon disappeared. The solvent was evaporated off under reduced pressure to give a solid which was dissolved in a small amount of hot water. On acidification, the aqueous solution gave 2-amino-4,6-dimethylpyridine-3-carboxylic acid (1·5 g), m.p. 258° (from hot water) (lit.,[6] 258°).

(b) *With* Zn–NaOH. A solution of (II) (4 g) in 10% aqueous sodium hydroxide (50 ml) was refluxed with zinc dust (4 g) for 2 h. The mixture was left overnight at room temperature and filtered, the filtrate was acidified with conc. hydrochloric acid, and on cooling a hydrochloride separated which was suspended in a small quantity of water and neutralised with ammonia; the acid obtained had b.p. 258°. The picrate of the above acid was prepared and had m.p. 227—228°. The acid was also converted by the method of Dornow and Willie [10] in 2,5,7-trimethylpyrido[2,3-*d*][1,3]oxazin-4-one, m.p. 124° (lit.,[10] 122—124°).

Action of Nitrous Acid on (II).—A stirred solution of (II) (1·8 g) in concentrated sulphuric acid (5 ml) was treated with solid potassium nitrite (1·8 g), gently warmed on a steam-bath for 5 min, and poured into ice–water to yield 1,2-dihydro-4,6-dimethyl-2-oxopyridine-3-carboxylic acid, m.p. 254—255° (lit.,[5] 257—258°).

Action of Nitrous Acid on (IIIc).—The bromo-derivative was treated with nitrous acid as for (II) to give 5-bromo-1,2-dihydro-4,6-dimethyl-2-oxopyridine-3-carboxylic acid, m.p. 260—262° (decomp.) (lit.,[7] 262°).

Copper Salt of (II).—Solutions of (II) (0·5 g) and copper(II) chloride (0·5 g) in hot methanol (10 ml each) were mixed and left to cool when the *salt* (IV) crystallised as brown prisms. The analytical sample was purified by washing with methanol (Found: C, 41·3; H, 3·8; N, 12·0; Cl, 15·4. $C_{16}H_{16}N_4O_4,CuCl_2$ requires C, 41·5; H, 3·5; N, 12·1; Cl, 15·3%).

4,6-*Dimethylisoxazolo*[5,4-b]*pyridin*-3(2H)-*one* (VIa).—A solution of 5-aminoisoxazol-3(2*H*)-one (1 g, 0·01 mol) in water (30 ml) was refluxed with acetylacetone (1 g, 0·01 mol) in the presence of piperidine (1 ml) over a small flame for 15 min. The mixture was cooled, acidified with acetic acid, and left for 30 min at room temperature when (VIa) separated (1 g, 61%), and gave *needles*, m.p. 206° (decomp.) (from aqueous methanol), $\nu_{max.}$ 3200—3500v,br, 1685w, and 1625br cm^{-1} (Found: C, 58·7; H, 4·8; N, 16·9. $C_8H_8N_2O_2$ requires C, 58·5; H, 4·9; N, 17·9%).

Acetylation of (VIa).—Acetylation as above gave the *acetate* (VIb), m.p. 139—140° (from dilute methanol), $\nu_{max.}$ 1725sh, 1630m, and 1590s cm^{-1} (Found: C, 58·1; H, 4·8; N, 13·6. $C_{10}H_{10}N_2O_3$ requires C, 58·25; H, 4·9; N, 13·6%).

Reduction of (VIa).—Reduction was carried out by (*a*) hydrazine hydrate and (*b*) Zn–NaOH as described for (II) and gave crystals of 3-carbamoyl-4,6-dimethylpyridin-2(1*H*)-one, m.p. 222° (decomp.) (lit.,[10] 222°).

Action of Nitrous Acid on (VIa).—Reaction as described for (II) gave 1,2-dihydro-4,6-dimethyl-2-oxopyridine-3-carboxylic acid, m.p. 256° (lit.,[5] 257—258°).

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