X-Ray Structure of Oxaline: a Novel Alkaloid from *Penicillium oxalicum*

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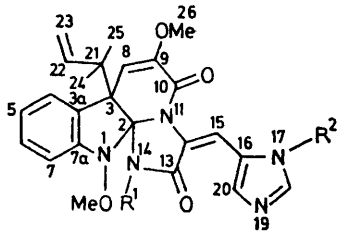
Summary The structure of oxaline, the main alkaloid of *Penicillium oxalicum* has been established as (**1a**) by *X*-ray methods.

CULTIVATION of a toxigenic strain of *Penicillium oxalicum* in bulk on sterilized maize meal yielded the toxin, secalonic acid D[1], and oxaline as the main alkaloid. Oxaline (**1a**), $C_{24}H_{25}N_5O_4$ crystallised from nitromethane, m.p. 220—221° and had $[\alpha]_D^{22}$ − 45° (*c* 0·3 in MeOH); c.d. (MeOH): λ/nm (Δε) 420 (0), 343 (−7·8), 309 (0), 275 (+13·05), 259 (+11·60), 247 (+13·75), 237 (0), 223 (−32·25), and 208 (0); λ_{max} (MeOH) 228 and 347 nm (log ε 4·32 and 4·39); ν_{max} ($CHCl_3$) 3425 [N(14)-H], 3182 [N(17)-H], 2985, 2942, 1710, 1705, 1686, and 1640 cm^{-1}. High resolution mass spectral studies showed a major fragmentation *via* loss of C_5H_8 (isoprene side-chain) from the molecular ion.

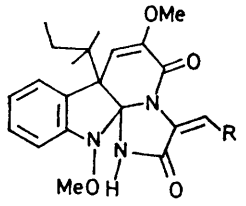
Single-crystal *X*-ray analysis of oxaline was successful. The crystals are orthorhombic, space group $P2_12_12_1$ with $a = 10{\cdot}84$, $b = 15{\cdot}70$, $c = 13{\cdot}24$ Å, $Z = 4$. Intensity data for 1232 reflections were recorded at low temperature on an automated single-crystal diffractometer with graphite-monochromated Mo-K_α radiation. The structure was determined by direct methods applying the multiple solution approach.[2]

All the hydrogens were found from a difference map calculated after refinement by full-matrix least-squares methods with anisotropic thermal parameters.[3] The hydrogen atoms were included isotropically in the final refinement which gave a residual of 0·041. The structure

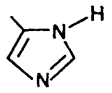
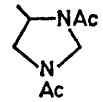


(1)

a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = Ac$
c; $R^1 = Me$, $R^2 = H$



(2)

a; R =  b; R = 

and conformation of oxaline is shown by the perspective drawing[4] in the Figure. Individual bond lengths and angles agree well with accepted values. There were no abnormally short intermolecular distances indicative of hydrogen bonding. The ^1H and ^{13}C n.m.r. spectra of oxaline were consistent with its structure.

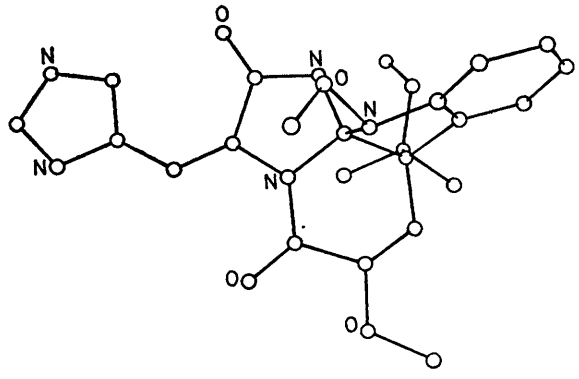


FIGURE. Perspective drawing of the molecular conformation of oxaline.

Upon acetylation of (**1a**) with acetic anhydride–pyridine a labile *N*-acetyl derivative (**1b**), $C_{36}H_{27}N_5O_5$, ν_{max} [N(14)-H] 3425 cm^{-1}, δ 2·59 (*N*Ac) was obtained. Treatment of oxaline with ethereal diazomethane effected methylation of N(14) and yielded *N*-methyloxaline (**1c**), $C_{25}H_{27}N_5O_4$, m.p. 214—215°, ν_{max} [N(17)-H] 3190 cm^{-1}, δ 2·48 (*N*Me). Prolonged hydrogenation of oxaline under pressure in acetic acid over PtO_2 gave only dihydro-oxaline (**2a**), $C_{24}H_{27}N_5O_4$, m.p. 254—255°. However, hydrogenation of oxaline in acetic anhydride-acetic acid (1 : 1) over PtO_2 gave hexahydro-*NN'*-diacetyloxaline (**2b**), $C_{28}H_{35}N_5O_6$ as the major product. The latter reduction is characteristic of the imidazole system.[5]

Oxaline is labile towards very dilute mineral acid, but it is stable towards drastic treatment with aqueous NaOH or $LiAlH_4$ in tetrahydrofuran. *N*-Methyloxaline (**1c**) reacts readily with $LiAlH_4$ in tetrahydrofuran at room temperature by reduction of the 13-CO group to a secondary alcohol, $C_{25}H_{29}N_5O_4$.

Oxaline contains several unique structural features, *e.g.* the *NO*-Me group; the unusual coupling of tryptophan and histidine (the presence of the dehydrohistidine unit is uncommon); the location of the isoprene unit (linked in the reverse fashion) at C(3) of tryptophan [C(2) is the more common location as in the brevianamides,[6] austamide,[7] and echinulin[8]]; and furthermore the C(2) carbon atom bearing three nitrogen functionalities.

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