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N-DIOXIDES, A NEW CLASS OF AMINE OXIDES

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Recently Myxin[+], a potent broad-spectrum antibiotic from a Sorangium species was described (1). This has now been shown to belong to a new class of compounds, the N-dioxides, and its synthesis has been achieved.

Myxin (I, red needles from acetone, m.p. 120-130° dec.) analysed correctly for $C_{13}H_{10}N_2O_4$. Its infrared spectrum lacked carbonyl absorption, while the weak CH stretching bands and strong signals between 1550 and 1640 cm^{-1} indicated a highly aromatic character. Its ultraviolet and visible spectrum[*] ($\lambda\lambda$ max 283 (97,000), 340 (5400) and 505 mμ (6500) resembled that of a phenazine. Its n.m.r. spectrum contained signals for one methoxyl (δ 4.07) 6 aromatic hydrogens (δ 6.9-8.3) and a very strongly hydrogen-bonded hydroxyl group (δ 14.7).

Stannous chloride in ethanol reduced myxin to an orange compound II ($C_{13}H_{10}N_2O_3$)[**] with m.p. 227-9° and $\lambda\lambda$ max 277 (98,000), 386 (2700) and 478 (3500). Its infrared and n.m.r. spectra were almost identical to those of myxin except for an

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[1]Contribution No. 602.

[+]Previously referred to as "3C antibiotic", now named "myxin".

[*]The ultraviolet spectra were determined of solutions in 0.1N hydrochloric acid; n.m.r. spectra are for deutero-chloroform solutions, with tetramethylsilane as internal reference.

[**]All compounds gave satisfactory carbon-hydrogen analyses.

upfield shift of the hydroxyl signal to δ 13.7. Catalytic hydrogenation of this compound over palladium on charcoal resulted in the uptake of two moles of hydrogen, producing a colorless product (the dihydrophenazine) which oxidized rapidly on exposure to air to a yellow compound III, m.p. 190-191°. This had λλ max 272 (56,000), 283 (56,000), 430 (7300), 480 (1800), 525 (1100). Again the infrared and n.m.r. spectra were little changed, except that the hydroxyl signal was now broad and much displaced (centered at δ 8.0). Compound III was identified by conversion to the known 1,6-dimethoxyphenazine.

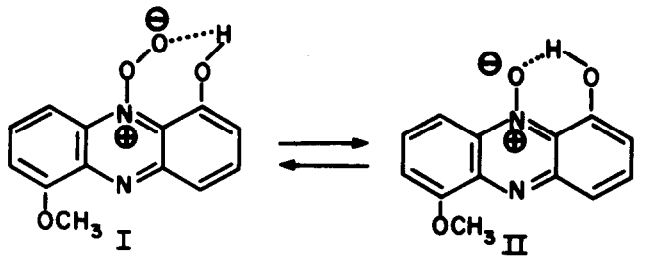
Since the spectra showed that the phenazine nucleus was unchanged throughout the series, it followed that myxin was one of the N-dioxides I or IV, the N,N-dioxide V or the N-oxide hydroperoxides VI and VII.

The fact that the ultraviolet and visible spectra of myxin, II and III all show striking reversible bathochromic shifts in alkali demonstrates the presence of the free phenolic hydroxyl. Hence VI and VII are eliminated from consideration. A sparingly soluble purple isomer of myxin appeared as a minor fermentation product. This could also be reduced to III, and by analogy to the deeply colored N,N-dioxide iodinin (2) was most probably V. Of the two remaining possibilities, IV would have the weak internal hydrogen bonding characteristic of III. Hence myxin is 1-hydroxy-6-methoxyphenazine-10-dioxide (I).

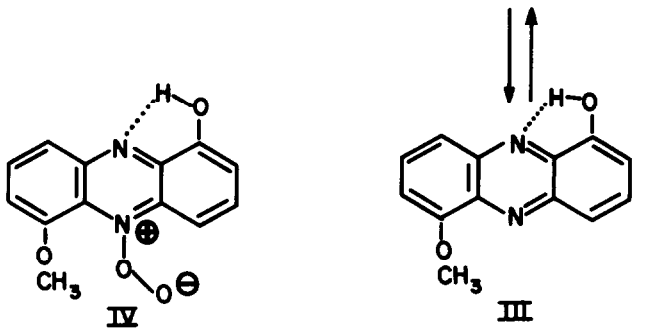
Synthesis of I was effected by partial demethylation of 1,6-dimethoxyphenazine to III, using thiophenoxide ion in dimethylformamide, followed by oxidation with m-chloroperbenzoic acid in benzene. Similarly II could be oxidized to a mixture of I with a trace of V.

Confirmation of these oxidation states has been provided by polarographic reduction studies.* For example

*We are most grateful to Dr. R.M. Elofson, Research Council of Alberta, for this evidence.

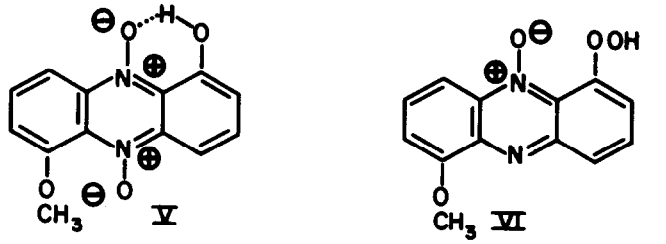


I ⇌ II

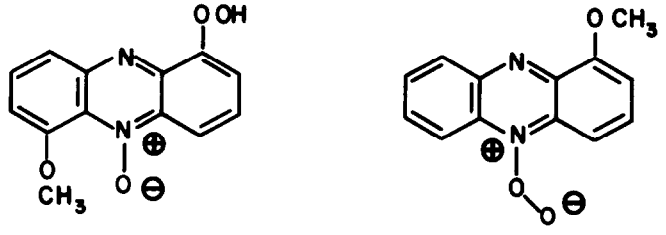


II ⇌ III

III, IV



V, VI



VII, VIII

myxin in 71% aqueous 2-propanol at pH 4.76 gave three two-electron waves at +0.30, -0.102 and -0.308 volts relative to the standard calomel electrode.

A simpler analogue of myxin, 1-methoxyphenazine-5-dioxide (VIII) m.p. 200°, has also been prepared, showing that the hydroxyl was not critical for N-dioxide formation and stability. The electronic factors influencing the formation of the N-dioxides are under investigation.

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