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THE STRUCTURE OF MYXIN

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Myxin, a newly discovered antibiotic (1) was recently reported (2) to possess formula I, a most unusual structure which contains an "N-dioxide" function*. It appeared to us that the reported experimental evidence was insufficient to secure this structure, particularly since it did not rule out with certainty the alternative formula II**. We have now synthesized compound II by several, unambiguous routes and wish to report that this substance is identical with myxin.

Oxidation of 1,6-dimethoxyphenazine (III) (3) with m-chloroperbenzoic acid in benzene solution afforded a mixture of two new products which were separated by chromatography on Florisil. One of these products was identified as 1,6-dimethoxyphenazine 5-oxide (IV; yellow plates from methanol, m.p. 192°, dec.), the other as 1,6-dimethoxyphenazine 5,10-dioxide (V; orange needles from acetone, m.p. 190-192°, dec.). Their elemental compositions*** were corroborated by mass spectroscopy which showed for IV a molecular ion at m/e 256 and a significant peak at m/e 240 (loss of an oxygen); the molecular ion of V appeared at m/e 272 with two concomitant peaks at m/e 256 and 240, indicating the successive loss of two oxygens.

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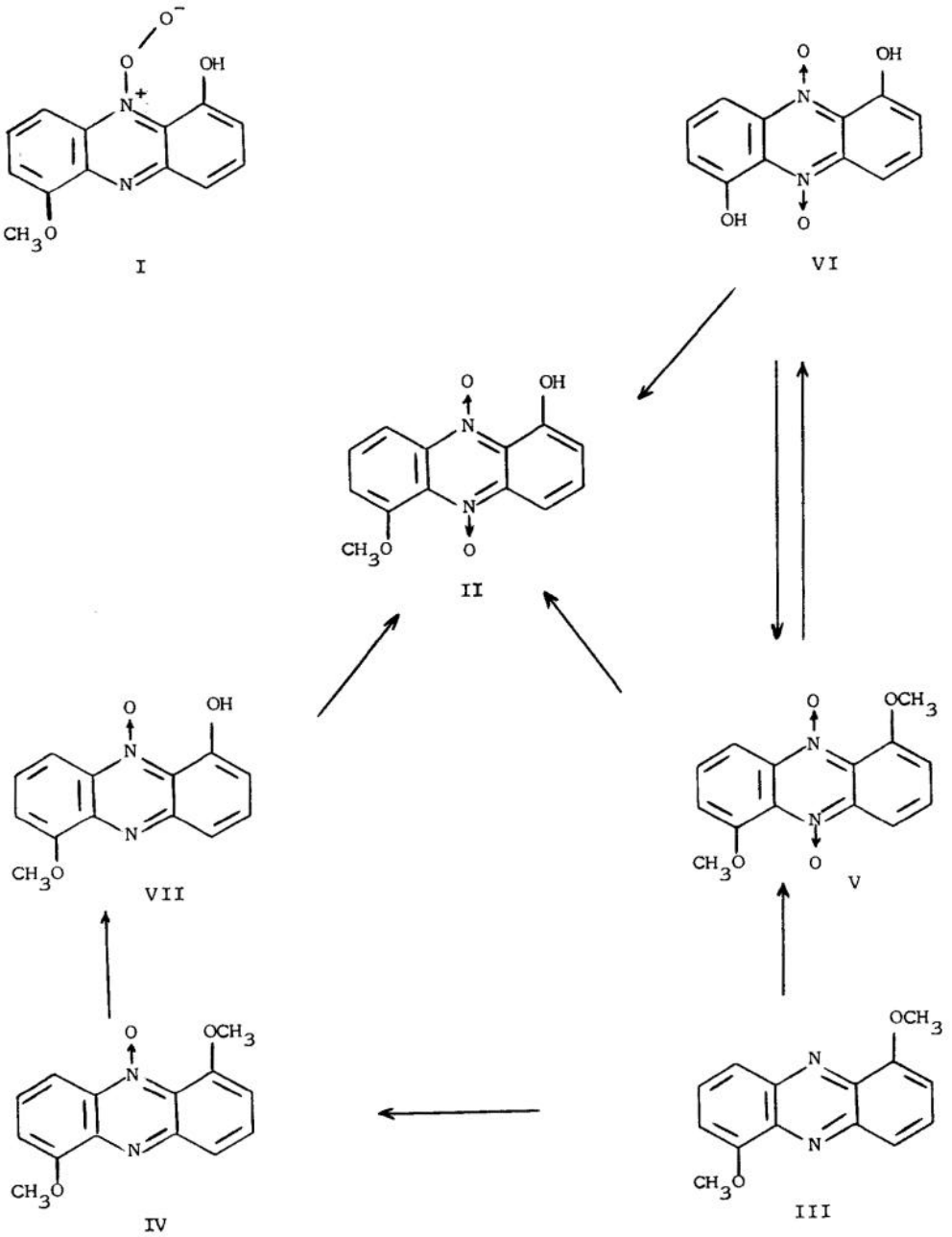
* Molecular arrangements of this type have been postulated as short lived intermediates in the deoxygenation of certain N-oxides by hydroperoxides (3,4), but have never been observed directly.

$$(R_3N\rightarrow O \;+\; HO^{+} \longrightarrow R_3\overset{+}{N}\text{-}O\text{-}O\text{-}H \longrightarrow R_3N \;+\; O_2 + H^{+})$$

** This alternative structure was ruled out by Edwards et al. (2) because "most probably" it corresponded to a minor fermentation product which was isolated along with myxin.

*** All of the compounds reported here gave satisfactory elemental analyses.


I
VI
II
VII
V
IV
III

The basic nature of compound IV was apparent from its ultraviolet and visible absorption spectrum which was greatly dependent upon the nature of the solvent used [$\lambda_{max}^{CH_3OH}$ mμ (ε): 278 (133,500), 328 (3820), 366 (2390), 387 (2040) and 456 (5880); $\lambda_{max}^{0.1\underline{N}\ HCl}$ 278 (65,300), 292 (68,100), 325 (5500), 332 (5500), 382 (4150) and 556 (2700)]; by comparison, the neutral compound V showed only relatively insignificant spectral changes [$\lambda_{max}^{CH_3OH}$ mμ (ε): 284 (89,500), 359 (4320), 410 (3455), 473 (9760), and 500 (13,600); $\lambda_{max}^{0.1\underline{N}\ HCl}$ 283 (120,000), 352 (5600) and 502 (8200)]. The symmetrical nature of the di-N-oxide V was clearly revealed by the simplicity of its 100 MHz n.m.r. spectrum* which contained only one signal (δ 4.03) for both methoxyl groups and only one AMX pattern corresponding to the aromatic protons [H_2 and H_7 at δ 7.04 (J=8 and 1 cps), H_3 and H_8 at δ 7.57 (J=8,9), H_4 and H_9 at δ 8.27 (J=9,1)]. The same n.m.r. pattern was observed for III [methoxyl groups at δ 4.11; aromatic protons H_2 and H_7 at δ 7.03 (J=7,1), H_3 and H_8 at δ 7.67 (J=7,9), H_4 and H_9 at δ 7.95 (J=9,1)]. In contrast, the mono-N-oxide IV exhibited a much more complex spectrum, since two methoxy signals (at δ 4.01 and 4.08) and two nonequivalent AMX patterns [H_2, H_3, H_4 at δ 6.96 (J=8,1), 7.57 (J=8,9), 7.87 (J=9,1) and H_7, H_8, H_9 at δ 7.01 (J=8,1), 7.53 (J=8,9), 8.17 (J=9,1)] were observed.

Partial demethylation of V by the use of aluminum chloride in ether solution afforded in over 50% yield the desired 6-methoxy-1-phenazinol 5,10-dioxide (II; red needles from acetone, m.p. 130-135°, dec.). The spectroscopic properties of this compound not only corroborated our structure assignment (e.g. the mass spectrum showed the molecular ion at m/e 258 and two prominent peaks at m/e 242 and 226) but also fully agreed with the corresponding data reported (2) for myxin.

Compound II was also obtained from iodinin (VI), a well-known antibiotic (5) which in turn could be prepared from V by exhaustive demethylation with aluminum bromide in benzene

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* The n.m.r. spectra were recorded in $CDCl_3$ solution on a HA-100 spectrometer; chemical shifts are reported in p.p.m. (δ) downfield from an internal tetramethylsilane reference.

solution*. Methylation of iodinin with dimethyl sulfate in the presence of alkali produced the desired compound II as the major product along with a minor amount of V.

Still another synthetic route led to the preparation of compound II. Partial demethylation of IV with aluminum bromide in benzene solution afforded as the only product 6-methoxy-1-phenazinol 10-oxide (VII; orange needles from ethanol, m.p. 220°, dec.), the structure of which was clearly indicated by its spectroscopic properties (e.g. the n.m.r. showed the methoxyl group at δ 4.10 and the phenolic proton at δ 13.6). Compound VII has been reported (2) to yield myxin on oxidation with m-chloroperbenzoic acid, a reaction which in our hands gave compound II as the major product; hence, compound II is myxin**.

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* This synthetic iodinin was identified by direct comparison with authentic material which was kindly provided by Drs. Mary P. Lechevalier and Nancy N. Gerber, Rutgers, The State University, New Brunswick, N.J.

** We are greatly indebted to Dr. O.E. Edwards for providing us with a sample of authentic myxin which was identical in all respects (m.p., mixture m.p., thin layer chromatography, spectral data, microbiological activity) with our synthetic samples of II.

References

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