The Brevianamides: a New Class of Fungal Alkaloid

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Summary Formulae are suggested for brevianamide-A and brevianamide-E.

PENICILLIUM BREVI-COMPACTUM gives a low yield of a mixture of related neutral compounds, mostly pigments, brevianamides A—E. Brevianamide-A is a yellow pigment, $C_{21}H_{23}N_3O_3$, with a ψ-indoxyl chromophore, the presence of which is confirmed by borohydride reduction and acid dehydration to deoxybrevianamide-A.[1] Chemical and spectral evidence was obtained for the presence of a 2,3-disubstituted indole ring in the latter. No double bonds other than those in the ψ-indoxyl system could be detected in brevianamide-A, and ozonolysis and methylation gave $C_{17}H_{24}N_2O_6$, as expected for fission of the pyrrole ring, loss of the benzene ring and indolic N.

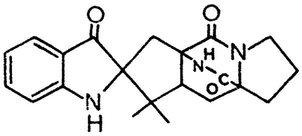
Amide bands at 1670 and 1690 cm.$^{-1}$, lack of the amide-II band, and reduction by diborane of deoxybrevianamide-A to the basic $C_{21}H_{27}N_3$, suggested the presence of a diketopiperazine ring. Hydrolysis gave no simple amino-acids, but base gave an amino-acid which rapidly regenerated brevianamide-A on acidification. No evidence for the NCHCO unit of a diketopiperazine could be obtained (τ 5·5—6·1 absent); there was no exchange with MeOD and base, and no racemisation. With six rings to be expected, these positions were assumed to be involved in ring-closures.

Chemical and spectral evidence of possible biogenetic precursors was sought. The presence of CMe_2 in brevianamide-A (τ 8·70, 9·10), with differences in environment, obliterated in deoxybrevianamide-A (τ 8·48), indicates proximity of the Me_2 to the CO and NH of the ψ-indoxyl system. Both compounds show spectral evidence for an isolated CH_2 group, which in the latter compound is adjacent to the aromatic ring. Lack of other CMe resonances and the presence of a resonance at τ 6·7 (2H) similar to that due to NCH_2 in proline dimer suggested a possible proline unit. The mass spectrum showed a major loss of C_5H_9 and suggested a terpene unit.

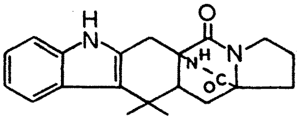
The evidence above, biogenetic considerations, and relations to known fungal metabolites suggested a number of possible formulae including (I). Feeding experiments were conducted with [3-^{14}C]tryptophan, [2-^{14}C]mevalonic lactone, [2-^{14}C]acetate, [*Me*-^{14}C]methionine and L-[U^{14}C]-proline (incorporations 0·6, 0·003, 0·025, 0·000, and 0·09% respectively). In view of the low yields (2—10 mg./l.) the positive incorporations were considered to be significant.

Examinations in detail of mass spectra and ^{1}H n.m.r. spectra, checked by irradiation, strongly support (I) for brevianamide-A and (II) for deoxybrevianamide-A. Notably dibromination of the aromatic ring, and methylation of the CONH and exchange with MeOD, permitted assignments of many mass spectral peaks.

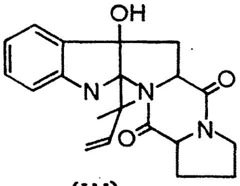
The colourless brevianamide-E, $C_{21}H_{25}N_3O_3$, has an indoline chromophore, unaffected by acid or base. It contains OH (3600 cm.$^{-1}$), NH (3370 cm.$^{-1}$), and amide (1680, 1690 cm.$^{-1}$) but lacks the amide-II band at 1550 cm.$^{-1}$, indicating the likelihood of the presence of a diketopiperazine ring. In this case the NCHCO hydrogens are detectable in the ^{1}H n.m.r. spectrum, one coupled to the non-equivalent protons of an otherwise isolated CH_2 (ABX system J_{AB} 13, J_{AX} 11, J_{BX} 8Hz.). Hydrolysis gave one molar equivalent of proline. The terpene unit is present as $CMe_2CH{:}CH_2$; τ 8·75 s (2Me) and three vinylic H which could be assigned to $CH{:}CH_2$, confirmed by hydrogenation to Et. The mass spectrum shows a major loss of 69 units, increased to 71 in the dihydro-derivative. Reduction with zinc and acetic acid gave deoxybrevianamide-E with removal of one oxygen and production of an indole chromophore. We consider brevianamide-E to be (III) and this is supported by detailed spectra.



(I)



(II)



(III)

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[1] B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.*, 1951, **73**, 2188.