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A NEW METABOLITE FROM AN UNIDENTIFIED ASPERGILLUS SPECIES

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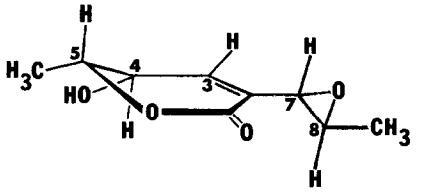
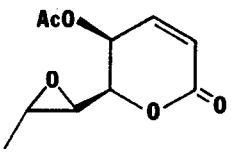
A new fungal lactone (I) has been isolated from an unidentified penicillic acid producing Aspergillus species. We wish to report the structure of this weak broad-spectrum antibiotic and the base catalyzed contraction of its lactone ring. I, $C_9H_{12}O_4$[m/e 184, mp 110-112°, $[\alpha]_D^{25}$ -16.5° ($CHCl_3$)] exhibited spectral properties indicative of an α,β - unsaturated six-membered lactone with infrared absorption ($CHCl_3$) at 5.81 and 6.08 μ and an ultraviolet maximum at 204 mμ (ε 12,000) in methanol. In this respect, I is related to two previously reported fungal lactones, asperline (1) (II) and desacetyl-6,7-deoxy-asperline (2).



I



II

Structure I was suggested by examination of the NMR spectrum* of the lactone (Fig. 1), the relative stereochemistry being derived from a consideration of the coupling constants, and the absolute configuration of the lactone ring from optical rotatory dispersion (ORD) data.

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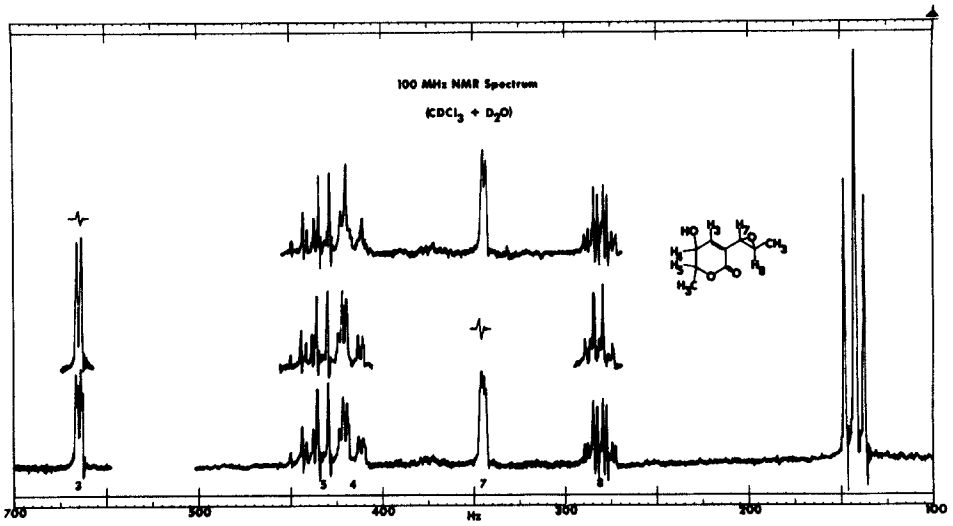
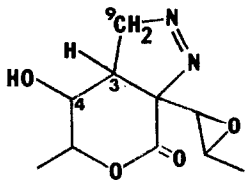
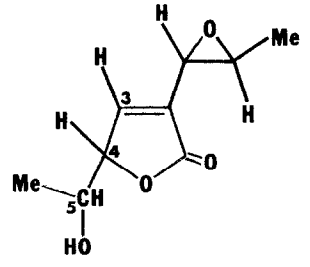
*NMR spectra were recorded with a Varian HA 100 in $CDCl_3$ with an internal TMS standard. Coupling patterns were analyzed by double resonance spin decoupling. Satisfactory elemental and/or mass spectral analyses were obtained for all compounds reported.



The vinyl proton H_3 was observed as a 1-proton quartet at 6.65 ppm. ($J_{4,3}$ = 2.5 Hz and $J_{7,3}$ = 1.0 Hz) consistent with a β-olefinic proton of an α,β-unsaturated δ-lactone (1). This assignment is confirmed by the I-diazomethane addition product (III) in which H_3 appears as a complex multiplet at 2.64 ppm. and is now coupled only to H_4 and the diazole ring methylene protons ($J_{4,3}$ = 5.0 Hz).



III



IV

The coupling between H_4 and H_3 is 2.5 Hz in I indicating that H_4 is pseudo-axial (3). $J_{4,5}$ is 9.0 Hz and dictates that H_5 is also pseudo-axial.

The negative Cotton effect at 263 mμ ([Φ]=-1341) in the ORD curve of I (4) suggests that the absolute configuration at C_5 is (R). From the relative stereochemistry discussed above it follows that C_4 is also (R). In asperline C_4 and C_5 are both of the (S) configuration and H_4 and H_5 are pseudo-equatorial and pseudo-axial respectively (2).

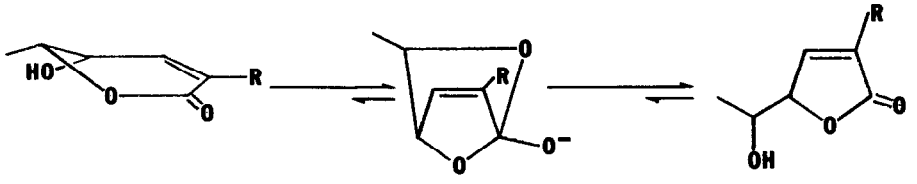
Further confirmation of the size of the lactone ring was obtained through the NMR spectrum of the phenylurethane derivative of I. H_4 was observed as a 1-proton quartet (the homo-allylic coupling with H_7 is small) at 5.27 ppm. a shift of 111 Hz downfield from that of the parent lactone. The rest of the urethane NMR spectrum is essentially that of the parent (I).

H_7 was observed as a 1-proton multiplet at 3.44 ppm. and H_8 as a 1-proton octet at 2.80 ppm. indicative of a propylene oxide side chain at C_2 (1,5). The coupling between H_7 and H_8 ($J_{7,8}$ ($J_{7,8}$ = 2.0 Hz) dictates a trans relationship for these protons. H_8 exhibits only one other coupling ($J_{Me,8}$ =5.0 Hz), while H_7 exhibits an allylic coupling with H_3 and a homo-allylic coupling with H_4 ($J_{4,7}$ = 0.6 Hz). The parent lactone gave a periodate number of 2 consistent with structure I.

Treatment of I with 1 N sodium hydroxide at room temperature for 30 min. gave IV, the γ-lactone analog, $C_9H_{12}O_4$[m/e 184, oil, 5.68 μ and 6.02 μ]. H_3 now appears at 7.28 ppm. to further confirm an α,β-unsaturated γ-lactone. H_4 has also shifted downfield and was observed as a 1-proton sextet at 4.85 ppm. (Δ69 Hz; $J_{3,4}$ = 1.8 Hz, $J_{5,4}$ = 4.5 Hz, and $J_{7,4}$ = 1.5 Hz), while H_5 had shifted upfield to 4.00 ppm. (Δ 32 Hz).

The γ-lactone nature of the isomer (IV) was further confirmed by the NMR spectrum of its phenylurethane derivative. H_4 and H_5 were observed as a complex 2-proton multiplet near 5.1 ppm., a shift for H_5 of approximately 110 Hz downfield from that of the parent (IV), which dictates an isocyanate substituent at C_5. The rest of the urethane NMR spectrum is essentially that of the parent (IV).

This ring contraction would appear to be related to that suggested for the saturated aldonolactones (6) in which interconversion proceeds via an intramolecular attack by a



hydroxyl group to give a bicyclic intermediate. The γ-lactone (IV) is perhaps favored in the equalibrium by relief of strain on the double bond and by relief of the interaction

between the carbonyl group and the planar C_2 substituent. This interconversion is probably unrelated to that in the saturated asperline series which involves an acetoxy-lactone interchange (2).

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REFERENCES

1. A. D. Arquodelis, et al., "Antimicrobial Agents and Chemotherapy", p. 801 (1965).
2. R. H. Evans, et al., Tetrahedron Letters, 1791, (1969).
3. E. W. Garbisch, J. Am. Chem. Soc., 86, 5561 (1964).
4. G. Snatzke, Angew. Chem. Internat. Edit., 7, 14 (1968).
5. R. H. Bible, "Interpretation of NMR Spectra", Plenum Press, New York, 1965.
6. B. Capon, Chem. Rev., 69, 407 (1969).