Tetrahedron Letters No.22, pp. 1791-1794, 1969. Pergamon Press. Printed in Great Britain.

TWO NEW METABOLITES FROM AN UNIDENTIFIED NIGROSPORA SPECIES

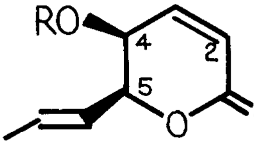
R. H. Evans, Jr., G. A. Ellestad and M. P. Kunstmann

Lederle Laboratories, A Division of American Cyanamid Company

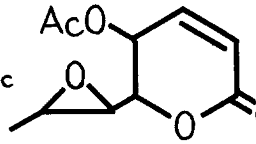
Pearl River, New York

(Received in USA 8 March 1969; received in UK for publication 9 April 1969)

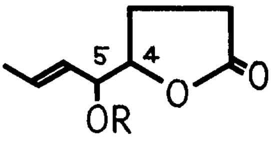
We wish to report the structure of two new fungal lactones I and IV which were isolated from an unidentified Nigrospora species and, in addition, to describe a novel ring contraction of the acetate of tetrahydro I. I, $C_8H_{10}O_3$ $\left[m/e\ 154,\ \text{m.p. } 50\text{-}53^\circ,\ [\alpha]^{25}_{D} + 175^\circ\ (CHCl_3)\right]$ exhibited spectral properties indicative of an α,β-unsaturated six-membered lactone with infrared absorption at 5.85 and 6.00 μ and an ultraviolet maximum at 204 mμ (ϵ 12,000). Examination of the nmr spectrum* of the acetate (II) suggested that I was the corresponding C_4-hydroxy-C_6,C_7-deoxy analog of asperline (III).[1] This was confirmed by oxidation of II with m-chloroperbenzoic acid which gave two diastereoisomeric epoxides one of which had identical physical constants with those for asperline.



I R=H
II R=Ac



III



IV R=H
V R=Ac
VI R=$COC_6H_4NO_2$

Consideration of the J values in the nmr spectrum of II suggested the relative stereochemistry as shown. The coupling between H_3 and H_4 is 5.6 Hz indicating that H_4 is quasi-equatorial and hence that the allylic acetoxy group is quasi-axial.[2,3] $J_{4,5}$ is 3.2 Hz and is not definitive with regard to the stereochemical nature of H_5 but steric considerations almost certainly dictate that the propylene side chain is quasi-equatorial with H_5 quasi-axial.

The positive Cotton effect at 265 mμ in the circular dichroism curve of II[4] suggested that the absolute configuration at C_5 is (S). From the relative stereochemistry discussed above it follows that C_4 is also (S). Hence, the absolute configuration at C_4 and C_5 in asperline is also defined.

---

* Nmr spectra were recorded with a Varian HA 100 in $CDCl_3$; shifts are expressed as Hz (cycles per second) from tetramethylsilane as internal standard and coupling constants (J) are expressed in Hz. Satisfactory analyses (elemental or mass spectral or both) were obtained for all compounds reported.

IV, isolated as an oil, $C_8H_{12}O_3$ $\left[m/e\ 156,\ [\alpha]_D^{25} + 49.5^\circ\ (CHCl_3)\right]$ contains a 5-membered lactone (5.6 μ), an isolated double bond $\left[6.0\ \mu\right.$; end absorption at 200 mμ (ϵ1,780); consumption of one mole of hydrogen to give VIII$\left.\right]$ and a hydroxyl group as evidenced by the formation of a non-crystalline acetate V, $[\alpha]_D^{25}$ + 50.3° ($CHCl_3$) and a crystalline p-nitrobenzoate VI, m.p. 108-109°, $[\alpha]_D^{25}$ + 6.5° ($CHCl_3$). The strong peak at m/e 85 (m-113) in the mass spectrum of V was most suggestive of the fragmentation shown below where R is an acetoxy-butylene side chain. Supporting evidence for this conclusion as well as evidence for the substitution pattern of the side chain could be drawn from the 100 mc nmr spectrum of V (Fig. 1) The methyl group was observed as a 3-proton quartet at 173 Hz ($J_{7,8}$ = 6.5 Hz and $J_{6,8}$ = 1.6 Hz) consistent with a terminal methyl group on a disubstituted double bond. The H_6 and H_7 vinyl protons were observed at 548 and 583 Hz as complex multiplets with $J_{6,7}$ = 14.6 Hz indicating these protons to be <u>trans</u> to each other. The H_5 signal at 528 Hz appears as a quartet with $J_{5,6}$ = 7.5 Hz and $J_{4,5}$ = 5.2 Hz. In the spectrum of IV the H_5 signal is found at 408 Hz thus indicating the acetate moiety to be joined to the side chain at C_5. The H_4 signal at 455 Hz indicates it to be on the lactone terminus and is additionally coupled to the upfield half of a highly complex A_2B_2 system (214 and 249 Hz) assigned to the C_2, C_3 methylene protons.

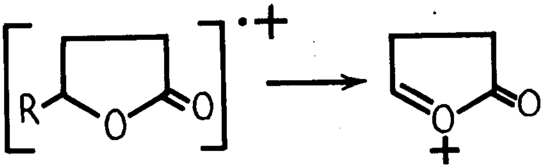
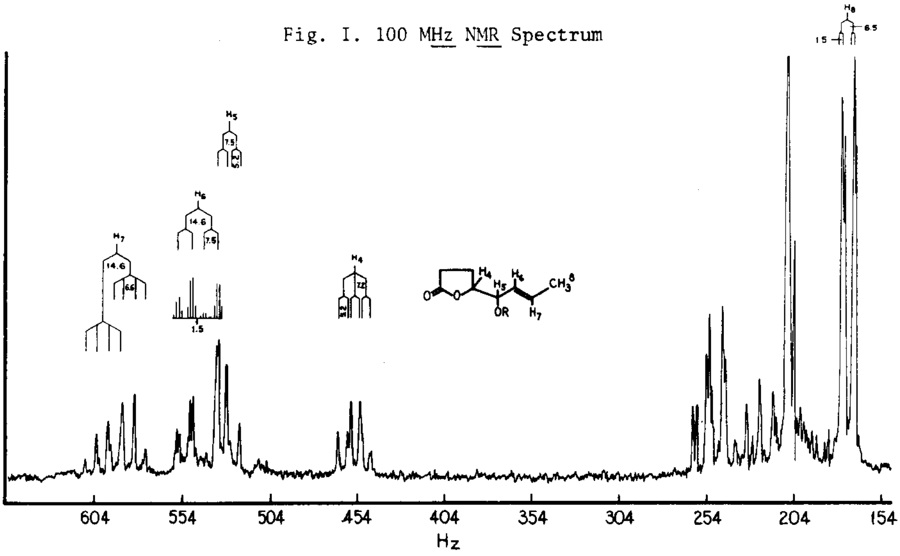
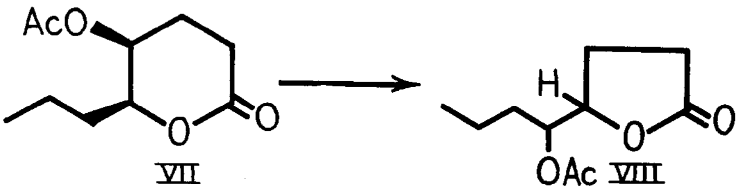


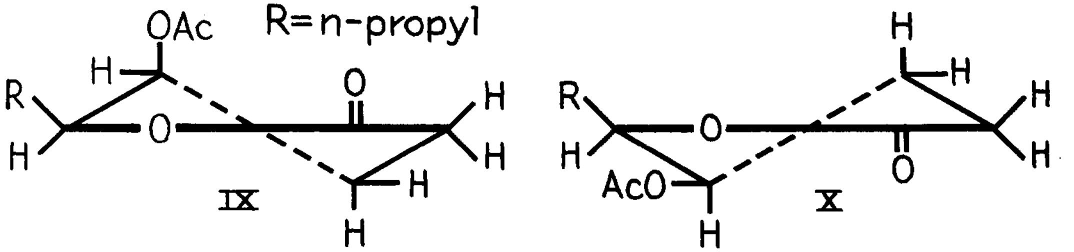
Fig. I. 100 MHz NMR Spectrum



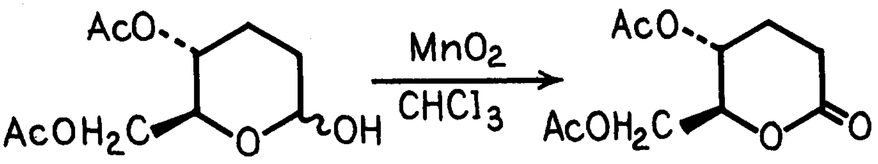
Hydrogenation of II with 5% Rh/Al_2O_3 provided VII in good yield as a highly mobile liquid. However, prolonged standing at room temperature (three months) gave most unexpectedly VIII as indicated by IR and nmr analysis and by comparison with an authentic sample prepared by catalytic hydrogenation of V.



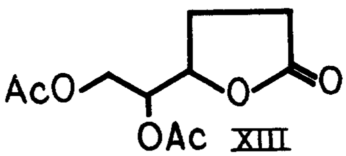
This transformation appears to be a unique example of an acetoxy-lactone interchange with concomitant ring contraction. The driving force is the greater stability of the 5-membered lactone. Rearrangement is essentially complete in three days by heating at 106° and occurs almost immediately with dry hydrogen chloride in chloroform. The stereochemical disposition of the reacting groups in VII is <u>cis</u> and hence conformational inversion to effect <u>trans</u>-coplanarity appears necessary. Although the nmr spectrum of VII provides no indication of a mixture of conformers, it seems possible that even though the equilibrium probably exclusively favors IX, the existence of a very small amount of X would be sufficient for the reaction to occur even at room temperature.



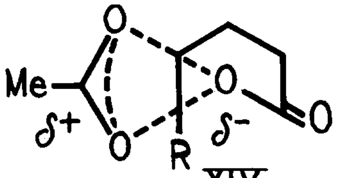
In order to test the generality of this transformation in conjunction with some synthetic studies, we prepared XI by published procedures.[5] Manganese dioxide oxidation of XI gave XII which was even more labile than VII. Indeed XII could not be distilled or allowed to stand at room temperature for more than a day without some rearrangement to XIII taking place. The greater instability of XII is easily understandable since the acetoxy and lactone groupings are already <u>trans</u>-coplanar.



XI XII



XIII



XIV

A possible mechanism, shown in XIV, is related to that suggested by Barton and King[6] for the diaxial-diequatorial halogenohydrin ester rearrangement in steroids. Thus one might expect the configuration at C_4 and C_5 in VIII (obtained from VII) to be opposite to that in I and also the stereochemistry of IV to be the same as in VIII (from VII) on the basis of the possibility that IV is derived from I by a related rearrangement during the fermentation. However, the optical rotations ($[\alpha]_D$) of VIII (-0.477°) obtained from VII and VIII (-1.84°) from IV are too low for making stereochemical correlations with any certainty especially without optically pure specimens for comparison.

ACKNOWLEDGEMENTS

We wish to thank Mr. L. Brancone and staff for elemental analyses, Mr. W. Fulmor, Mr. G. Morton and staff for some of the spectra and helpful discussions, Dr. J. Lancaster for the 100 Mc spectra and Dr. J. Karliner for mass spectra. Also we would like to thank Dr. W. J. McGahren of these laboratories for the circular dichroism curve, Dr. M. Goodman of the Brooklyn Polytechnic Institute for the use of his instrument (Cary Spectropolarimeter), Dr. P. Shu and colleagues for the many fermentations and Dr. H. Tresner for identifying the culture.

REFERENCES

1. A. D. Argoudelis, J. H. Coats and R. R. Herr, Antimicrobial Agents and Chemotherapy, p. 801 (1965); S. P. Owen and B. K. Bhuyan, ibid, p. 804 (1965); A. D. Argoudelis and J. F. Zieserl, Tetrahedron Letters, No. 18, 1969 (1966).
2. R. J. Ferrier and G. H. Sankey, J. Chem. Soc., (C), 2345 (1966).
3. E. W. Garbisch, J. Am. Chem. Soc., 86, 5561 (1964).
4. G. Snatzke, Angew Chem. Internat. Edit., 7, 14 (1968).
5. M. Bergman, Ann. 443, 223 (1925).
6. D. H. R. Barton and J. F. King, J. Chem. Soc., 4398 (1958).