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THE CONSTITUTION OF MONORDEN, AN ANTIBIOTIC WITH TRANQUILISING ACTION

Frank McCapra and A. I. Scott

Chemistry Department,
University of British Columbia,
Vancouver, Canada.

P. Delmotte and J. Delmotte-Plaquée*

National Centre for Multiple Sclerosis,
Melsbroek, Belgium

N. S. Bhacca

Varian Associates, Palo Alto, California.

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The isolation of a new antibiotic from Monosporium bonorden was described earlier[1] and, on the basis of preliminary analytical data, the compound was assigned the molecular formula $C_{17}H_{16}O_7$, containing phenolic, acidic and unsaturated functions, with optical activity ($[\alpha]_D$ + 203°). Re-examination of the antibiotic, which we have named monorden, at Vancouver, by spectroscopic techniques[2] has now led to a revision of the formula to $C_{18}H_{17}O_6Cl$, and further, to the proposal of a complete structure (I) for the antibiotic.

Elemental analysis and inspection of the mass spectrum[3] showed that monorden is in fact $C_{18}H_{17}O_6Cl$. (Found: C, 59.05; H, 4.80; Cl, 9.54%; M 364; $C_{18}H_{17}O_6Cl$ requires C, 59.34; H, 4.94; Cl, 9.60%; M 364).

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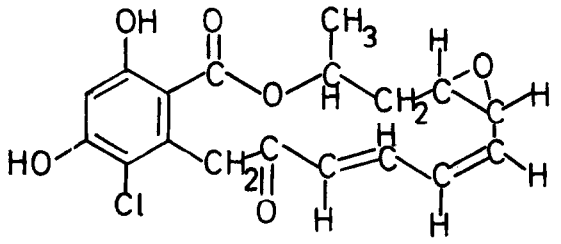
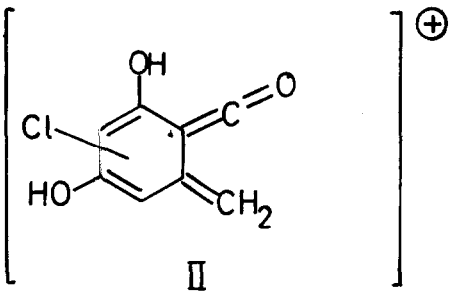
* Present address: Laboratory for Chemical Research, Ministry of Agriculture, Tervuren, Belgium



I



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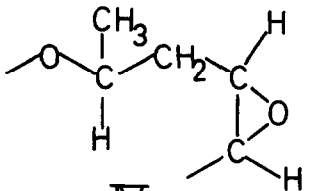

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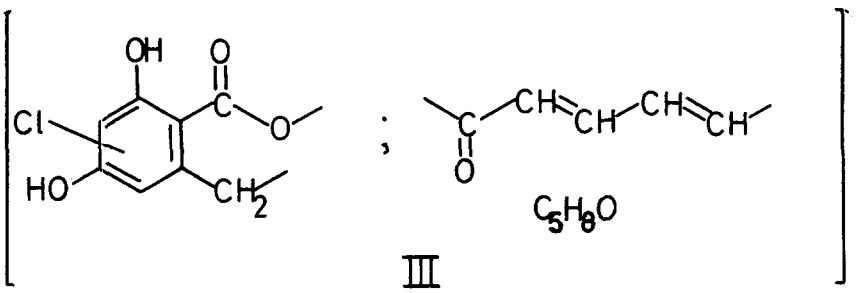


III

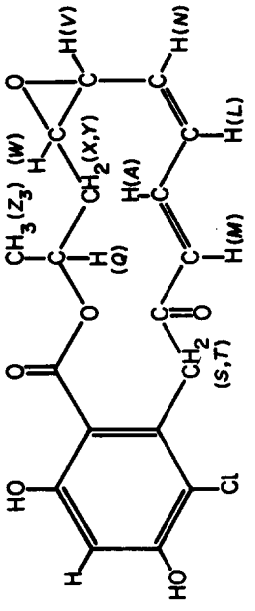
The infra-red spectrum (KBr disc) exhibited a broad band at 3500 cm^{-1} ascribable to a phenolic hydroxyl group[1]. Incompletely resolved bands in the carbonyl region, at 1630 cm^{-1} and 1650 cm^{-1} were not readily identifiable until the spectrum of the diacetate was considered. Monorden diacetate[1] (m.pt. 185-7°) showed peaks at 1775 cm^{-1}, 1780 cm^{-1} (phenolic diacetate groupings) 1730 cm^{-1} (aromatic ester, now free of hydrogen bonding) and 1665 cm^{-1} (dienone). Both monorden and its diacetate had bands in the 1600 - 1620 cm^{-1} region, ascribable to aromatic and/or double bond functions.

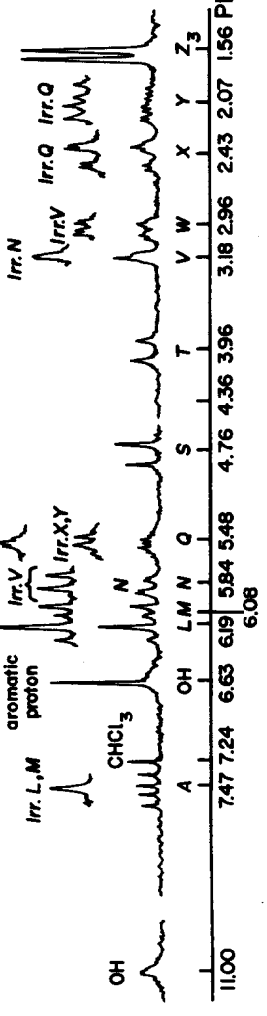
The ultra-violet spectrum of monorden displayed maxima at 264 mμ (ε 13,200), 272 mμ (ε 13,100) and 315 mμ (shoulder; ε 2,800) in ethanol. The presence of a 2,4-dihydroxy-6-alkylbenzoic ester chromophore was suggested by the double maxima at 264 mμ and 315 mμ (calculated[4] 263 mμ and 319 mμ for this partially ionised grouping). This assignment was further confirmed by the disappearance[4b] of these features from the spectrum of monorden diacetate (λ_{max} 275 mμ , ε , 13,000; hepta-3,5-dien-2-one has λ_{max} 270 mμ [5]). Another dienone in a similar, macrocyclic environment has λ_{max}, 273 mμ [6].

The main feature of the mass spectrum of monorden was an ion of mass 184, which from inspection of the intensity of its companion peak at 186 indicated retention of the chlorine atom in the aromatic fragment. A likely structure for this fragment is represented in II, consistent with the known[7] behaviour of aromatic esters of this type and confirming the spectroscopic evidence presented above.

On the basis of the data so far discussed we can propose partial structure III for monorden, thus accounting for five of the six oxygen functions. The nature of this last oxygen and that of the C_5 unit, with their relationship to the rest of the molecule follows unambiguously from a consideration of the 100 m.c. double resonance N. M. R. spectrum

Fig. 1


H(V)
H(N)
H(W)
H(L)
H(A)
H(Q)
H(M)
HO
Cl
HO
H


Irr.N
Irr.V
Irr.Q
Irr.Q
Irr.T
Irr.Z3
Irr.V
Irr.X,Y
Irr.L,M
aromatic proton
OH
CHCl3
A
OH
L M N Q
S
T
V W
X
Y
Z3
11.00
7.47 7.24
6.63
6.19
5.84 5.48
6.08
4.76
4.36 3.96
3.18 2.96
2.43
2.07
1.56 PPM (δ, from T.M.S.)

(Fig. 1). Two labile protons at δ 6.63 and δ 11.00 are the phenolic hydroxyl protons. The proton resonating at δ 11.00 is hydrogen bonded[8] to the ester carbonyl. The tall doublet (δ 1.56) represents three protons and is due to a secondary methyl group. This is confirmed by observing the multiplet at Q (one proton attached to carbon bearing oxygen) while irradiating[9] the protons, Z_3, resulting in a triplet for Q. The coupling constant is 7 cps. At δ 2.07 and 2.43 are the methylene protons X and Y which by coupling with Q give rise to the residual triplet mentioned above, with coupling constant of 3 and 4 cps respectively. X and Y are coupled in geminal fashion (15 c.p.s.), and with a further proton, W, (δ 2.96) with vicinal coupling constants 3.2 and 8.5 c.p.s. respectively. W is coupled in turn to V (δ 3.18) with a constant of 2.8 cps. W and V, from their chemical shifts, are probably methine protons of an epoxide, thus satisfactorily accounting for the remaining oxygen atom. We have, thus far, the expression IV for this group of protons. The proton V is coupled to one of a series of vinylic protons, N (δ 5.84), M (δ 6.08), L (δ 6.19) and A (δ 7.47). The coupling constant between protons N and V is 2.5 c.p.s. Similarly N is coupled to L (11 cps). L is coupled to A with a spin coupling constant of 8 cps and A is also coupled to M (16 cps). From the positions of these protons and their respective coupling constants it is obvious that we must extend partial expression IV by the dienone chromophore. The relatively large coupling constant between protons A and M suggest a trans-configuration for this double bond, while assignment of configuration to bond LN (11 c.p.s.) is likely to be more ambiguous. There remain three protons for consideration, and the AB pattern centred at δ 4.36 is easily ascribed to the benzylic methylene group (S,T) whose protons are non-equivalent. Confirmation of the assignment of this isolated methylene is obtained from the

slight coupling observed between one of these protons and the vinylic proton L_1 as shown by the double resonance trace. Finally, the single aromatic proton (δ 6.63) can be placed between the hydroxyl groups[10]. This latter conclusion had already been made by positioning the chlorine atom by analogy with similar groupings in other mould products, and the known reactivity of substituted resorcinols.

Indeed the total structure I is particularly satisfactory as another example of an acetate-derived mould metabolite. The resemblance to the (hypothetical) precursor[11] of the tetracyclines has already been noted, with evidence that certain reactions of monorden give rise to polycyclic material. This aspect is under active investigation.

An earlier report[1] described this metabolite as having strong antifungal properties, and this has since been confirmed. It shows[12] remarkably low toxicity, while acting as a potent sedative without other obvious effect on the nervous system. Direct comparison between radicicol (see following paper) and monorden showed their complete identity.

Editor's note: This manuscript was intended for simultaneous publication with the companion paper, "The Constitution of Radicicol" by R.N.Mirrington, E.Ritchie, C.W.Shoppee, W.C.Taylor and S.Sternhell, Tetrahedron Letters No.7, pp. 365-370, 1964, but was received too late for inclusion in issue No.7.

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1. P. Delmotte and J. Delmotte-Plaquée, Nature, 171, 344 (1953).
2. The amount of monorden available to us during this study was 86 mg.
3. We thank Dr. J. M. Wilson, (Stanford University) for his very kind determination of this spectrum.
4. (a) A. I. Scott, Experientia 17, 68 (1961), (b) idem, "Interpretation of the Ultraviolet Spectra of Natural Products", Pergamon, Oxford, 1964 (Ch. 3).
5. E. A. Braude and J. C. Coles, J. Chem. Soc., 2078 (1951).
6. R. B. Woodward, Angew. Chem., 69, 50 (1957).
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8. See, for example, spectrum no. 259, Varian N.M.R. Spectra Catalogue.
9. N. S. Bhacca, M. E. Wolff and R. Kwok, J. Am. Chem. Soc., 84, 2976 (1962)
10. See, for example, Varian N.M.R. Spectra Catalogue, Vol. 2, nos. 635-678.
11. A. J. Birch, G. F. Snell, and P. J. Thomson, J. Chem. Soc. 425 (1962); S. Gatenbeck, Biochem. Biophys. Res. Comm. 6, 422 (1961/62).
12. Work carried out at the "Laboratoire de Pharmacodynamie" Tours, France.