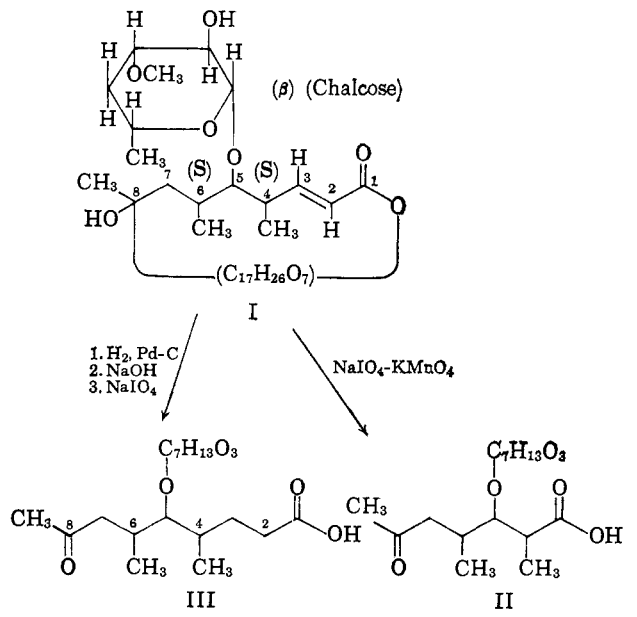
Partial Structure of Chalcomycin. I. A C_{18} Chalcosyloxy Moiety

Sir:

Previous communications have reported that acid degradation of the antibiotic chalcomycin[1] (I) yields chalcose[2] (4,6-dideoxy-3-*O*-methyl-D-glucose) and mycinose[3] (6-deoxy-2,3-di-*O*-methyl-D-allose), and that periodate–permanganate oxidation gives 2,4-dimethyl-3-chalcosyloxy-6-oxoheptanoic acid (II).[4] We now wish to present evidence which assigns the partial structure I to chalcomycin.



One of the possible formulas, $C_{35}H_{56}O_{14}$ (mol. wt. 700.8), is compatible with elemental analyses (*Anal.* Calcd.: C, 59.98; H, 8.06. Found: C, 59.84; H, 8.06) and molecular weight determinations (X-ray crystallography, mol. wt.[5] 701 ± 7; osmometric determinations, 725 ± 15 (butyl acetate) and 716 ± 14 (benzene); isothermal distillation (methanol), 575–592) of chalcomycin. This formula is also compatible with the elemental analyses of several derivatives and degradation products of chalcomycin.

The presence of an α,β-unsaturated lactone (or ester) in chalcomycin (I) is indicated by its ultraviolet spectrum (λ_{max}^{EtOH} 218 mμ (ε 22,770)) and infrared absorption peaks (5.84, 6.03 μ). The infrared peaks remained essentially unchanged by sodium borohydride reduction (5.84, 6.05 μ), but were replaced by a single peak (5.80 μ) upon hydrogenation (Pt, acetic acid). The n.m.r. spectrum of I in deuteriochloroform indicates the presence of a proton on C-2 coupled to a proton on C-3, $J_{2,3}$ = 15.6 c.p.s., typical of a *trans* olefinic function.[6] The C-3 proton appears as a quartet, indicating the presence of a single proton on C-4, $J_{3,4}$ = 9.8 c.p.s. Spin-decoupling studies[7,8] verify these assignments and further indicate that the C-4 proton appears at δ 2.68, as expected from a methinyl proton. The C-2 proton doublet and the C-3 proton quartet are also shown by the sodium borohydride reduction product of I.

Hydrogenation of I (Pd–C, ethanol) followed by saponification and subsequent periodate oxidation yielded, as one of the major products, a C_{18} acid (III). Acid III remained oily after purification by countercurrent distribution (200 transfers, K = 1 in chloroform–water system) but gave good analyses for $C_{18}H_{32}O_7$ (*Anal.* Calcd.: C, 59.97; H, 8.95. Found: C, 59.82; H, 9.26). The n.m.r. spectrum of III in deuteriochloroform indicates the presence of three C-methyl doublets, one methyl ketone singlet, and one O-methyl singlet. Oxidation of III with sodium hypoiodite gave iodoform and a diacid IV (infrared peak at 5.85 μ); acid hydrolysis of IV yielded chalcose and a γ-lactonic acid V (infrared peaks at 5.66, 5.83 μ). On the other hand, acid hydrolysis of III did not give a γ-lactone (5.82 μ). Hence chalcose is γ- to the methyl ketone group in III, and the established structure of II[4] allows assignment of partial structure from C-4 to C-9 of III.

Nitric acid oxidation of III yielded (+)-2-methylglutaric acid[9] (identified by comparison of infrared and n.m.r. spectra, melting point, and optical rotation with authentic (−)-2-methylglutaric acid and by elemental analyses), which established the partial structure of III from C-1 to C-4. The known absolute configuration of (+)-2-methylglutaric acid shows that the absolute configuration at C-4 in III is *S*.[10] The previously reported isolation of (+)-2,4-dimethylpentane-1,3,5-triol[4] from C-1 to C-5 of II reveals the relative configuration of the two asymmetric carbons corresponding to C-4 and C-6 of III, and thus establishes the configuration at C-6 in III as *S*.

The C-1 anomeric proton of chalcose shows large coupling with the C-2 proton (J = 7.4 c.p.s. in II; J = 7.1 c.p.s. in III), indicative of a diaxial coupling and hence a β-glycosidic configuration.[2b]

Thus, the structure of III is 4,6-dimethyl-5-β-chalcosyloxy-8-oxononanoic acid and allows the structural assignment of C-1 to C-8 in chalcomycin.

(1) Parke, Davis & Company, Belgian Patent 587,213 (Aug. 2, 1960)

(2) (a) P. W. K. Woo, H. W. Dion, and Q. R. Bartz, *J. Am. Chem. Soc.*, **83**, 3352 (1961); (b) P. W. K. Woo, H. W. Dion, and L. F. Johnson, *ibid.*, **84**, 1066 (1962); (c) N. K. Kochetkov and A. I. Usov, *Tetrahedron Letters*, **No. 8**, 519 (1963).

(3) (a) H. W. Dion, P. W. K. Woo, and Q. R. Bartz, *J. Am. Chem. Soc.*, **84**, 880 (1962); (b) J. S. Brimacombe, M. Stacey, and L. C. N. Tucker, *Proc. Chem. Soc.*, 83 (1964).

(4) P. W. K. Woo, H. W. Dion, and Q. R. Bartz, *J. Am. Chem. Soc.*, **84**, 1512 (1962).

(5) We thank Mr. J. Krc and Mr. B. Scott, Parke, Davis & Company, for this determination.

(6) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 85.

(7) (a) W. A. Anderson and R. Freeman, *J. Chem. Phys.*, **37**, 85 (1962); (b) J. D. Baldeschwieler and E. W. Randall, *Chem. Rev.*, **63**, 81 (1963).

(8) We thank Dr. L. Durham, Stanford University, for the spin-decoupling studies.

(9) (a) E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, **77**, 3383 (1955); (b) A. Fredga, *Arkiv. Kemi, Mineral. Geol.*, **24A**, No. 32 (1947); (c) K. Freudenberg and W. Hohmann, *Ann.*, **584**, 54 (1953); (d) J. F. Lane, *Science*, **113**, 577 (1951).

(10) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

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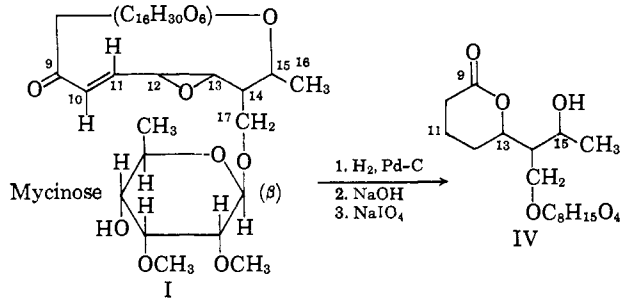
Partial Structure of Chalcomycin. II. A C_{17} Mycinosyloxy Moiety

Sir:

In the preceding communication,[1] the structure and partial configuration of a C_{18} chalcosyloxy moiety in

(1) P. W. K. Woo, H. W. Dion, and Q. R. Bartz, *J. Am. Chem. Soc.*, **86**, 2724 (1964).

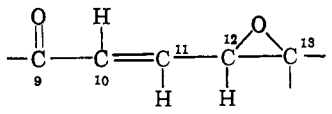
chalcomycin (I) were elucidated. We now wish to present evidence which establishes the remaining C_{17} mycinosyloxy[2] moiety (C-9 to C-16 of I).



The presence of an α,β-unsaturated ketone in chalcomycin (I) is indicated by its ultraviolet (shoulder in the 245 mμ region, ϵ ~13,200) and infrared spectra (peaks at 5.91, 6.14 μ). The latter absorptions disappear when I is reduced with sodium borohydride or hydrogenated with Pd–C–ethanol or Pt–acetic acid.

The presence of an epoxide group is indicated by the fact that while I forms a diacetate (n.m.r., two acetyl singlets), hexahydrochalcomycin (Pd–C–ethanol) gives a triacetate (three acetyl singlets), indicating the hydrogenolysis of an epoxide group. Treatment of I with potassium iodide in acetic acid[3] resulted in the liberation of iodine and the formation of an $\alpha,\beta,\gamma,\delta$-unsaturated ketone (II, λ_{max}^{MeOH} 282 mμ; infrared peaks at 5.96, 6.14, 6.27, 10.0, 10.16 μ) without the elimination of either chalcose of mycinose (n.m.r., three O-methyl singlets). The epoxide is therefore allylic to the α,β-unsaturated carbonyl group (C-9 to C-13 of I). Treatment of II with sodium methoxide in methanol resulted in the simultaneous decrease of the dienone peak at 288 mμ (in 0.01 *N* hydrochloric acid) and the appearance of a new peak at 317 mμ (conjugated trienone), explainable by the elimination of an oxygen function β to the conjugated dienone system in II (β to C-13, *cf.* I).

The presence of three single protons in the α, β, and γ positions of the unsaturated carbonyl group (C-10, 11, 12 of I, grouping A) was established by n.m.r.

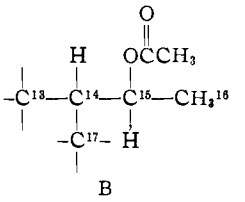


A

studies. In acetone, the C-10 proton appears as a doublet, δ 6.54–6.79, $J_{10,11}$ = 15.5 c.p.s., typical of a *trans* double bond. The C-11 proton appears as a quartet, δ 5.86–6.25, $J_{11,12}$ = 9.0 c.p.s.[4] Spin-decoupling studies[5] show that in deuteriochloroform the C-10 and C-11 protons have identical chemical shifts, and the signals, appearing as double peaks at δ 6.58 with 4.5 c.p.s. separation,[6] are coupled to signals at δ 3.38, where the epoxide proton signal is expected to appear.

Saponification of hexahydrochalcomycin followed by periodate oxidation (1 mole uptake) yielded the previously reported 4,6-dimethyl-5-β-chalcosyloxy-8-oxononanoic acid (III)[1] and a δ-lactone (IV,[7] infrared peak at 5.77 μ). Alkaline treatment of IV generated the sodium salt of the corresponding hydroxy acid, which upon acidification slowly lactonized to give the original lactone IV. Nitric acid oxidation of IV yielded glutaric acid. N.m.r. studies of IV diacetate[7] show the presence of mycinose (two O-methyl singlets), existing in the β-pyranoside form.[8]

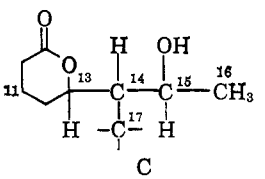
Spin-decoupling studies of IV diacetate show the presence of grouping B. The C-15 proton signal at



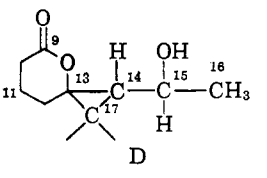
B

δ 4.88–5.32,[9] a 1:4:6:4:1 quintet indicating four adjacent protons, is coupled to a C-methyl at δ 1.32 (doublet) and to the fourth proton at δ 2.14. The high-field position of the fourth proton shows that C-14 is not attached to any oxygen; hence it must be attached to two other carbon atoms, as in grouping B.

Groupings A and B contain a total of ten carbon atoms while the aglycone in IV cannot contain more than nine (chalcomycin, C_{35}; acid III, C_{18}; mycinose, C_8).[1] Two conclusions follow: (1) the precursor to glutaric acid (from nitric acid oxidation of IV, above) originates from hydrogenation and hydrogenolysis of grouping A; and (2) C-13 of A is one of three carbon atoms attached to C-14 in B, such an attachment giving rise to two structural possibilities, groupings C and D.



C



D

In lactone IV and its diacetate, the presence of a proton α to the lactone ring oxygen (on C-13) is indicated by an irregular multiplet[10] at δ ~4.6. This multiplet can be decoupled to a sharp singlet by irradiation at high field, where the C-12 and C-14 signals appear.[11] This multiplet cannot be accounted for by grouping D but is readily explained by grouping C, which is therefore the correct structure.

The only position in C where mycinose may be attached is C-17. Signal integration data of IV diacetate are consistent with this attachment, showing the

(2) H. W. Dion, P. W. K. Woo, and Q. R. Bartz, *J. Am. Chem. Soc.*, **84**, 880 (1962).

(3) S. Bodforss, *Ber.*, **49**, 2795 (1916).

(4) A structural unit in the antibiotic Magnamycin [R. B. Woodward, *Angew. Chem.*, **69**, 50 (1957)], identical with grouping A, exhibits entirely similar n.m.r. absorptions.

(5) We thank Dr. L. Durham, Stanford University, for the spin-decoupling studies.

(6) This signal pattern is that expected from treatment of the C-10, C-11, and C-12 protons as an ABX system with $\nu_{10} = \nu_{11}$ and with $J_{AB} = J_{10,11} = 15.5$ c.p.s., $J_{BX} = J_{11,12} = 9.0$ c.p.s., and $J_{AX} = J_{10,12} = 0$ c.p.s.

(7) The compound is not crystalline but was vigorously purified by silicic acid chromatography and shown to be a single component by thin-layer chromatography.

(8) The H-1, H-2, H-4, and H-6 signals of the mycinose moiety of IV diacetate are almost identical in chemical shifts and splitting patterns with those of the acetate of methyl β-mycinopyranoside.[2]

(9) The corresponding C-15 proton signal in IV is at δ 3.98.

(10) The multiplet consists of broadened absorptions with no discernible pattern. The irregular broadening may be explained by virtual long range coupling [J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962)] with the C-11 protons.

(11) This decoupling study was done on the tetraacetate of the lithium aluminum hydride reduction product of IV, with which this characteristic irregular signal, shifted to δ 5.20, is not complicated by other signals.

two C-17 protons, in addition to H-3 and H-5 of mycinose, in the δ 3.65–4.25 region.

Thus the data above show that IV is 5,7-dihydroxy-6-mycinosyloxymethyloctanoic acid δ-lactone and allows the structural assignment from C-9 to C-16 in I. Additional confirmation by chemical evidence will be presented in the next communication.[12]

(12) P. W. K. Woo, H. W. Dion, and Q. R. Bartz, *J. Am. Chem. Soc.*, **86**, 2726 (1964).

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RECEIVED MAY 8, 1964

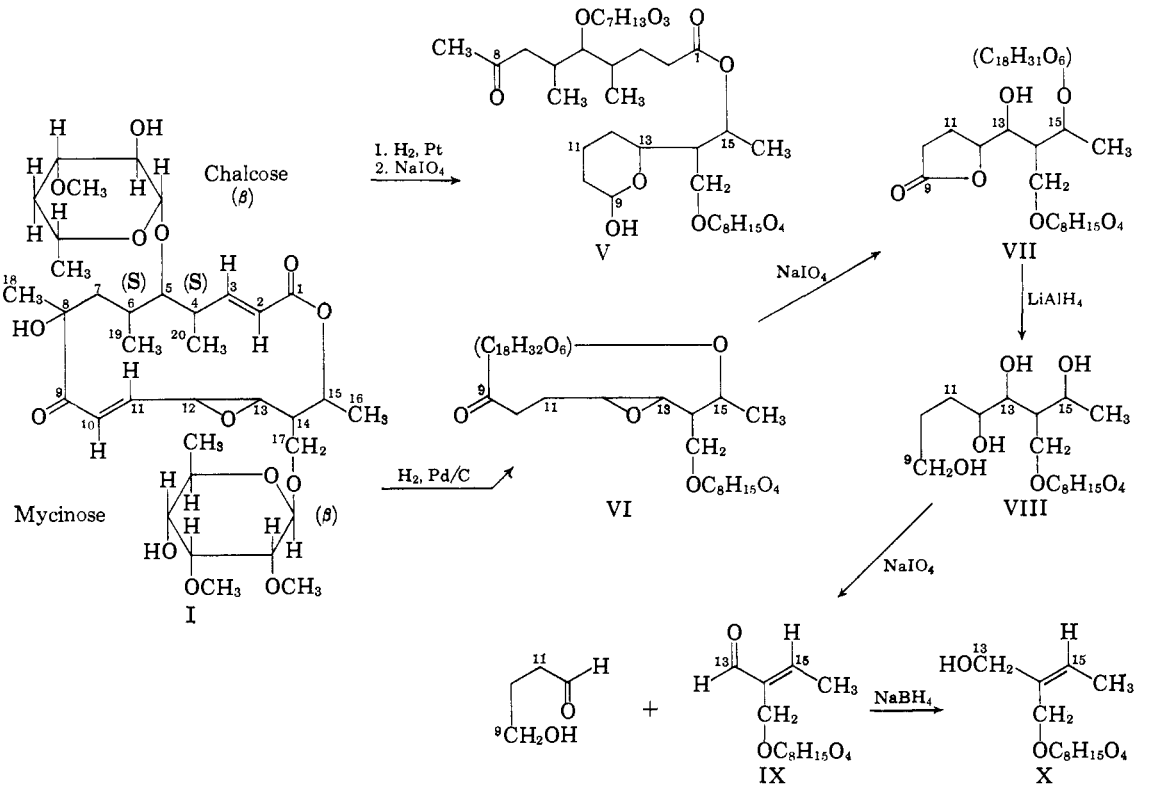
The Structure of Chalcomycin

Sir:

Previous communications on chalcomycin (I) have elucidated the structure of a C_{18} chalcosyloxy (C-1 to C-8)[1] and a C_{17} mycinosyloxy (C-9 to C-16) moiety.[2]

Hydrogenation of I using platinum–acetic acid gave octahydrochalcomycin, which reacted rapidly with periodate to give a neutral compound V, which contains chalcose and mycinose (n.m.r.,[3] three O-methyl singlets), a methyl ketone (singlet at δ 2.10), and a hemiacetal group. The latter is indicated by the fact that V forms a triacetate (three peaks at δ ~2.1, in addition to a methyl ketone singlet), which shows a low-field signal at δ 5.56, corresponding to a proton on the acetylated hemiacetal carbon (C-9). The formation of V provides further evidence that I is a lactone and shows that the α-hydroxy ketone grouping is present as such in I.

Spin-decoupling studies[4] of I indicate that the oxygen on C-15, rather than those in the hydroxyl groups of chalcose and mycinose, is the ring oxygen of the lactone (16-membered). The C-15 proton appears as a superposition of two 1:3:3:1 quartets ($J_{14,15}$ = 10.5 c.p.s., $J_{15,16}$ = 6.4 c.p.s.) at δ ~5.36. This signal at low field, characteristic of a proton α to a lactone



The structures of the corresponding C_{18} methylketonic acid (II)[1] and C_{17} δ-lactone (III)[2] from hexahydrochalcomycin (IV) (alkaline hydrolysis of IV and subsequent periodate oxidation) have been reported. The formation of II and III with 1 mole of periodate uptake shows that an α-methyl-α-hydroxyketone was oxidized, thus establishing the linkage at C-8 and C-9. The presence of three readily acylable hydroxyl groups in II and III (at C-2 of chalcose, C-4 of mycinose, and C-15 of aglycone), but only two in chalcomycin (I), shows that one of these three hydroxyl groups is involved in lactone formation with the C-1 carboxyl group.

(1) P. W. K. Woo, H. W. Dion, and Q. R. Bartz, *J. Am. Chem. Soc.*, **86**, 2724 (1964).

(2) P. W. K. Woo, H. W. Dion, and Q. R. Bartz, *ibid.*, **86**, 2724 (1964).

ring oxygen, collapsed to a singlet by irradiation at the C-methyl region (δ 1.35),[5] as expected for the C-15 proton in I, but not for the proton on C-2 of chalcose or C-4 of mycinose, which is coupled to other protons at low field.

Hydrogenation of I (Pd–C, ethanol) gave, as the minor product, tetrahydrochalcomycin (VI), which formed a diacetate (n.m.r., two O-acetyl singlets), thus indicating that the epoxide remained intact. Periodate oxidation of VI yielded γ-lactone VII (infrared peak

(3) All n.m.r. spectra were determined in deuteriochloroform solution.

(4) W. A. Anderson and R. Freeman, *J. Chem. Phys.*, **37**, 85 (1962).

(5) The C-14 proton is probably shifted upfield to the C-methyl region due to its spatial orientation. Thus the axially oriented C-4 proton of chalcose [P. W. K. Woo, H. W. Dion, and L. F. Johnson, *J. Am. Chem. Soc.*, **84**, 1066 (1962)] also absorbs at the C-methyl region and shows large couplings (*ca.* 11 c.p.s.) with the adjacent protons.