X-Ray Crystallographic Determination of the Structure of the Antibiotic Aphidicolin: a Tetracyclic Diterpenoid Containing a New Ring System

By K. M. BRUNDRET, W. DALZIEL, and B. HESP*
(*Imperial Chemical Industries Limited, Pharmaceuticals Division, P.O. Box* 25, *Mereside, Alderley Park, Macclesfield, Cheshire*, SK10 4TG)
J. A. J. JARVIS
(*Imperial Chemical Industries Limited, Corporate Laboratory, P.O. Box* 8, *The Heath, Runcorn, Cheshire*)
and S. NEIDLE
(*Queen Mary College, Mile End Road, London*, E1 4NS)

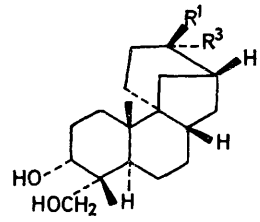
Summary Aphidicolin, an antibiotic produced by *Cephalosporium aphidicola* Petch, is shown to contain a novel tetracyclic diterpenoid ring system.

APHIDICOLIN,[1] $C_{20}H_{34}O_4$, m.p. 227—233°, $[\alpha]_D^{27}$ + 12° (*c* 1·0, MeOH), is a new antiviral diterpenoid, produced by *Cephalosporium aphidicola* Petch C.M.I. 68,689(ii) grown on a medium containing Czapek–Dox salts plus 5% "Cerelose" and 0·1% yeast extract ("Oxoid"). Aphidicolin has been shown to have structure (Ia), containing a new ring system. We propose that the hypothetical parent hydrocarbon (II) be named aphidicolane and numbered as shown. Thus aphidicolin is (+)-3α,16,17,18-tetrahydroxyaphidicolane. Possible biogenetic pathways to aphidicolin, *via* the tricyclic intermediate (III), are readily derivable by minor modifications of the accepted pathways to the more common members of the tetracyclic diterpenoid series.[2]

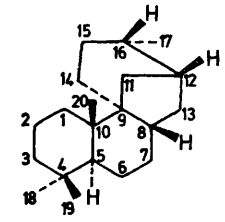
Chemical and spectroscopic evidence was consistent with structure (Ia, without the detailed stereochemistry shown) or (IV) for aphidicolin, both of which were acceptable on biogenetic grounds. Final assignment of structure (Ia) to aphidicolin was made by *X*-ray analysis of the bis-acetonide (V), m.p. 145—146°.

Crystal data: $C_{26}H_{42}O_4$; M = 418·6; orthorhombic, space group $P2_12_12_1$ with a = 10·58(1), b = 14·09(1), c = 16·07(2) Å; U = 2395 Å^3; D_m = 1·14 g cm^{-3}, Z = 4, D_c = 1·158 g cm^{-3}; F (000) = 920.

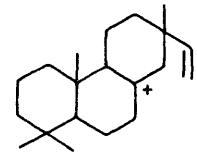
A total of 1130 independent reflections were measured on a Picker automatic four-circle diffractometer using Mo-K_α (Nb filter) radiation (λ = 0·7107 Å). The initial trial structure was based on the strongest 19 peaks on an *E*-map whose phases were determined by the tangent formula using 193 *E*-values ⩾1·5. Two cycles of structure factor



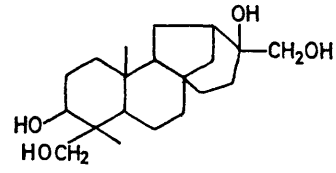
(I) a; R^1 = OH, R^2 = CH_2OH
b; R^1, R^2 = O



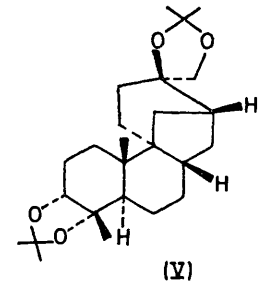
(III)



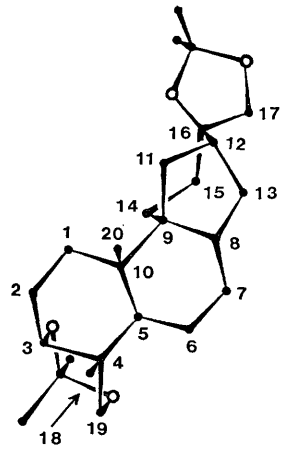
(III)



(IV)



(V)



FIGURE

Fourier synthesis located all 30 atoms (excluding hydrogen), and least-squares refinement of these as carbon atoms with individual isotropic temperature factors gave an R value of 0·110. Substitution of correct form factors for oxygen atoms, identified by lower temperature-factors, and inclusion of hydrogen atoms in calculated positions, gave an R value of 0·071. The three dimensional structure so obtained is shown in the Figure. All six-membered rings are in the chair form. C–C and C–O bond distances lie within the ranges 1·52 to 1·58 Å and 1·41 to 1·44 Å, respectively. Angles C(19)–C(4)–C(5), and C(4)–C(5)–C(10) are both 116° and the C(19), C(20) separation is 3·23 Å.

Aphidicolin is active against a range of DNA-containing viruses, *e.g. Herpes simplex*, and acts by inhibiting the synthesis of viral DNA.[3] On a molar basis aphidicolin and 5-iodo-2-deoxyuridine are equiactive, *in vitro*, against *Herpes simplex*.

(*Received, 5th July* 1972; *Com.* 1171.)

[1] United Kingdom Patent Application No. 3280/71.
[2] E. Wenkert, *Chem. and Ind.*, 1955, 282.
[3] R. B. Bucknall, to be published.