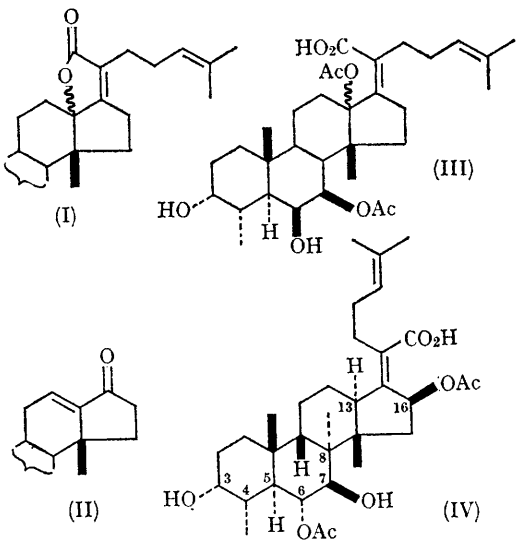
Cephalosporin P_1

By T. G. HALSALL, SIR EWART R. H. JONES, G. LOWE, and C. E. NEWALL
(*The Dyson Perrins Laboratory, Oxford University*)

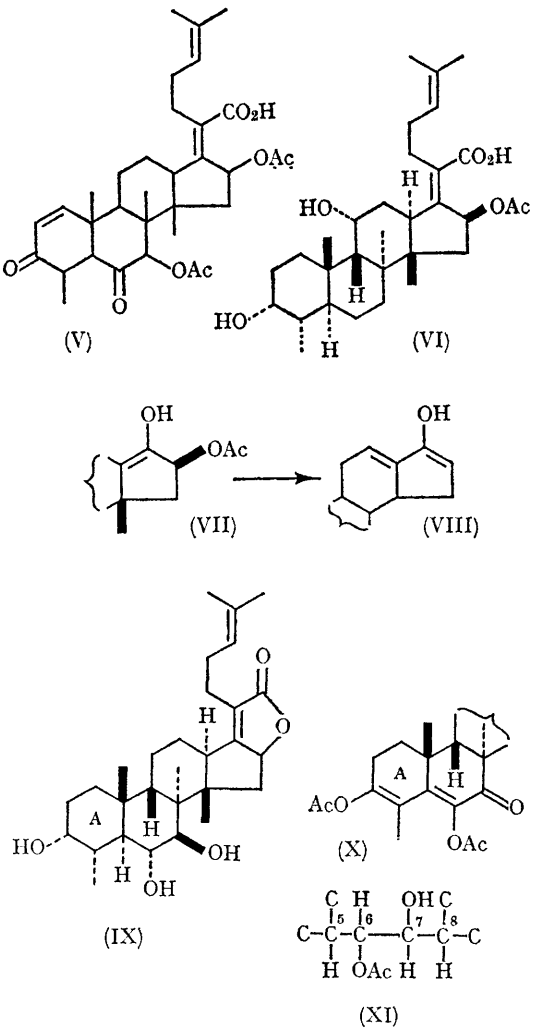
THE early work[1] on cephalosporin P_1, an antibiotic produced by a strain of *Cephalosporium* indicated that it had the formula $C_{32}H_{48}O_8$ and that it was a tetracyclic monounsaturated acid with two hydroxyl groups and two acetoxyl groups, one of which was easily hydrolysed. Complete hydrolysis gave a lactone believed[2] to have partial structure (I) since ozonolysis afforded

a ketone which with acid, but not base, gave a *cisoid* $\alpha\beta$-unsaturated ketone (partial structure II). This evidence together with other results appeared[2] to be consistent with structure (III) for cephalosporin P_1.



Subsequent mass spectral[3] and n.m.r. data require a revision of structures (I) and (III) and now lead to structure (IV) for cephalosporin P_1. They show that cephalosporin P_1 has the formula $C_{33}H_{50}O_8$ and contains an additional methyl group (six in all, of which three are tertiary) and *two* secondary acetoxyl groups. One of the $H\text{–}\overset{|}{\underset{|}{C}}\text{–OAc}$ protons in the methyl ester gives rise to a doublet at τ 5·84 (J 8·5 c./sec.) identical[4] to that found in the methyl esters of the closely related steroid antibiotics, helvolic acid (V)[5] and fusidic acid (VI),[6] indicating that the more hindered acetoxyl group in cephalosporin P_1 is at C-16′, and not C-13. The formation of the *cisoid* $\alpha\beta$-unsaturated ketone (II) is explained by assuming that the enol (VII) of the ozonolysis product undergoes *acid*-catalysed elimination to give the dienol (VIII) of the $\alpha\beta$-unsaturated ketone (II).

The diol-monoacetate group present in cephalosporin P_1 must be in ring-B at C-6 and C-7, and there must be a hydrogen atom at C-5 since the dideacetyl lactone [now formulated as (IX)] gave[2] on oxidation of its tetrahydro-derivative a yellow triketone which afforded a dienol-diacetate (X). N.m.r. data now reveal that the diol-monoacetate group is in the environment shown in (XI).



In the spectrum (determined for acetone solution) of cephalosporin P_1 in which the hydroxyl protons have been replaced by deuterons, the proton of the $H\text{–}\overset{|}{\underset{|}{C}}\text{–OAc}$ group in the diol-monoacetate system gives rise to a doublet at τ 5·43 (J = 10 c./sec.; $W^h/_2$ = 5 and 5·5 c./sec. for the two peaks) and the proton of the $H\text{–}\overset{|}{\underset{|}{C}}\text{–OD}$ group gives rise to a broadened singlet at τ 6·50 ($W^h/_2$ = 3·5 c./sec.). When the signal at τ 6·50 is saturated the doublet at τ 5·43 remains (J = 10 c./sec.) but the band widths decrease to $W^h/_2$ = 3 and 3·5 c./sec. These results show that the proton on the carbon carrying the acetate group is coupled with two protons, one being the hydrogen

atom on the carbon carrying the hydroxyl group, and that the one on the carbon carrying the hydroxyl group is not coupled to any other proton. It follows that the acetate group is at C-6 and the hydroxyl group at C-7 and that C-8 is fully substituted. C-8 must therefore carry a methyl group as in fusidic acid (VI) and helvolic acid (V). The large coupling constant (J = 10 c./sec.) of the proton at C-6 after it has been decoupled from the proton at C-7 implies that it is diaxially coupled with the proton at C-5 and hence β in configuration. The small decrease in band width indicates a small coupling constant of *ca.* 2 c./sec. between the protons at C-6 and C-7. If one assumes that ring-B in cephalosporin P_1 is in a boat conformation, as it is in fusidic acid (V), this coupling constant can only correspond to a dihedral angle of about 110° between the C–H bonds (and not to one of 65°) and shows that the hydrogen at C-7 is α in configuration. The diol-monoacetate group in ring-B is therefore *trans*.

In our original Communication[2] the diol-monoacetate group was considered to be *cis* because monodeacetylcephalosporin P_1 methyl ester formed an acetonide and underwent rapid fission with lead tetra-acetate (k_{25} 430 l. mole^{-1} min.$^{-1}$ in acetic acid) typical of a *cis*-glycol group in a chair ring.[7] The *cis*-glycol groups in boat rings of the camphane-*exo*- and -*endo*-2,3-diols react with lead tetra-acetate very much faster, whereas the *trans*-camphane-2,3-diols react much more slowly.[8] The ring system of the *trans*-camphane-2,3-diols is much more rigid however than ring-B of cephalosporin P_1. In our diol the strain resulting from the 1,3-interactions between the C-4 α-methyl group and the C-6 α-oxygen atom and between the C-7 β-oxygen atom and the C-14 β-methyl group may set up strain which would be relieved on oxidation.

These results together with those already described, and the rational assumption of a close relationship to fusidic acid (VI), lead to the modified structure (IV) for cephalosporin P_1.

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