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The Constitution of Resistomycin

By N. A. BAILEY, C. P. FALSHAW, W. D. OLLIS,* and M. WATANABE
(*Department of Chemistry, The University, Sheffield* S3 7HF)

and M. M. DHAR, A. W. KHAN, and V. C. VORA
(*Central Drug Research Institute, Lucknow, India*)

FURTHER examination of the constitution of the antibiotic X-340[1,2] shows that it possesses a novel structure which is tautomerically equivalent to one already suggested for resistomycin.[3–7] The molecular formula, $C_{23}H_{18}O_6$, initially suggested[3–5] for resistomycin was later changed to $C_{22}H_{16}O_6$ with the report of a partial structure quoted by Miller.[6] This partial structure was subsequently developed into a complete structure which has been given in a lecture summary,[7] but the experimental detail for this structural proposal[7] has not yet been published. X-340, initially represented as $C_{23}H_{20}O_6$ [1] and later as $C_{19}H_{16}O_5$,[2] was eventually shown also to have the molecular formula $C_{22}H_{16}O_6$. We therefore suspected that X-340 and resistomycin were identical, but some differences between the chemical behaviour of X-340 and that reported for resistomycin[5] were noted. Recently additional physical data were published on resistomycin,[8] and it is now clear that X-340 and resistomycin are indeed identical; the name resistomycin should have precedence. The constitution now proposed for resistomycin is different from that recently published.[8]

Resistomycin is an orange antibiotic, $C_{22}H_{16}O_6$, which has been characterised by a number of derivatives† including a tetramethyl ether, a tetra-acetate, a triacetate, a monomethyl ether, and a monomethyl ether triacetate. The n.m.r. spectra of these derivatives show only *singlet* signals, but some broadening indicates that one aromatic methyl group is weakly coupled to one aromatic proton. The i.r. spectra of resistomycin and its derivatives show the presence of two conjugated carbonyl groups which are each chelated to hydroxyl groups. Therefore on spectroscopic grounds it was established that resistomycin contained the substituents shown in the partial structure (I) in which one methyl group and three hydrogen atoms were aromatic in type and the four hydroxyl groups were either enolic or phenolic. The association of the two aliphatic methyl substituents in a *gem*-dimethyl group was indicated by their chemical shift equivalence observed in the n.m.r. spectra of many derivatives and transformation products of resistomycin. Thus the hydrocarbon equivalent (see I) of resistomycin was $C_{19}H_{14}$ and in view of the probable association of three hydrogen atoms, one methyl and four hydroxyl substituents with aromatic

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† All new compounds described have been adequately characterised by analysis, u.v., i.r., n.m.r., and mass spectra.

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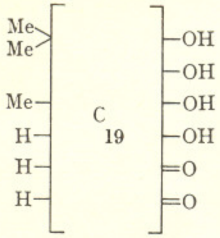
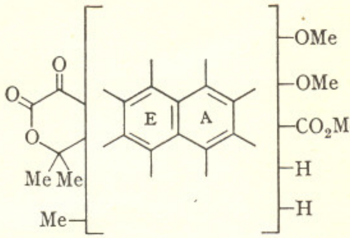
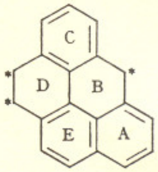


(I)

(II)



(III)



(IV)

rings, the possibility was examined that the undefined nineteen carbon atoms formed the pentacyclic nucleus (II). This is the only arrangement in which the nineteen carbon atoms of $C_{19}H_{14}$ can be accommodated in six-membered rings.

The environment of the two carbonyl groups of resistomycin was now investigated. Sodium borohydride reduction of resistomycin gave the red compound, rescarmone, $C_{22}H_{18}O_5$, which was characterised as the following derivatives: trimethyl ether,‡ dimethyl ether, dimethyl ether diacetate,‡ dimethyl ether monoacetate,‡ triacetate, and diacetate. The n.m.r. spectra of the soluble compounds (marked ‡) showed an additional singlet which could be assigned to a benzylic methylene group. The i.r. spectra of rescarmone and its derivatives showed that the lesser conjugated carbonyl group of resistomycin had been reduced in the formation of rescarmone. The same carbonyl group of resistomycin was also involved in the Dakin oxidation of resistomycin with alkaline hydrogen peroxide. This reaction yielded the yellow lactone, resistomycinolide, $C_{22}H_{16}O_7$, and the deep red compound, resistorubone, $C_{21}H_{16}O_6$. Resistomycinolide gave a tetramethyl ether (ν_{max} in $CHCl_3$, 1744 and 1646 cm.$^{-1}$), a tetra-acetate, and a triacetate. The lactonic nature of resistomycinolide was demonstrated by its reaction with sodium hydroxide and dimethyl sulphate which gave an acidic product characterised as the methyl ester, $C_{22}H_{12}O_2(OMe)_6$, by reaction with diazomethane. Clearly the oxygen atom introduced in the formation of resistomycinolide could provide a phenolic hydroxyl group on hydrolysis of the lactone ring. Oxidation of resistomycinolide tetramethyl ether with alkaline hydrogen peroxide, followed by esterification with diazomethane, gave a product $C_{17}H_{11}O_4(OMe)_3$. On the basis of spectral data, this compound could be formulated as the naphthalene derivative (III).

This demonstration of a naphthalenoid residue in resistomycin encouraged further consideration that the pentacyclic nucleus (II) was present in resistomycin. The most direct correlation between the pentacyclic nucleus (II) and the oxidation product (III) could be achieved in terms of the partial structure (IV) for the C_{19}-nucleus. Thus, only rings A and E (see IV) could directly provide by an oxidative process an appropriately substituted naphthalene (III). A suitable relation to the partial structure (I) for resistomycin could be illustrated, for example, by placing the two carbonyls and the *gem*-dimethyl group at the marked positions on rings B and D (see IV) and thus ring C becomes the third aromatic ring of the resistomycin structure. Unfortunately the formation of the α-keto-lactone (III) from resistomycinolide proceeded in low yield and as other degradations were not rewarding the determination of the complete constitution of resistomycin by *X*-ray crystallography was then considered.

In our search for a suitable derivative of resistomycin, its bromination in methanol was examined. In contrast with the results obtained by Rosenbrook,[8] which form part of the basis for his incorrect structural proposal, resistomycin gave mono-, di-, and tri-bromo-derivatives characterised as their tetramethyl ethers. *X*-Ray crystallographic examination of dibromoresistomycin tetramethyl ether ($C_{26}H_{22}O_6Br_2$) showed that the yellow monoclinic crystals had the unit cell parameters, $a = 14{\cdot}03$, $b = 11{\cdot}87$, $c = 27{\cdot}73$ Å, $\beta = 101° \; 27'$, $Z = 8$ corresponding to two crystallographically independent molecules per equivalent position in the space group, $P2_1/c$. Three-dimensional, room temperature, *X*-ray data to a resolution of $(\sin \theta/\lambda)_{max} = 0{\cdot}5$ were collected with a Phillips automatic diffractometer using monochromated Mo-K_α radiation. Independent reflections numbering 1325, which exceeded the 2σ significant level, were obtained corresponding to a conventional discrepancy index ($R = 0{\cdot}096$).

The skeletal structure (V) was determined by the conventional Patterson and Fourier methods and was refined by least-squares procedures to a final discrepancy index of 0·123; anisotropic thermal parameters were allowed only for the bromine atoms. The two crystallographically independent molecules showed substantially the

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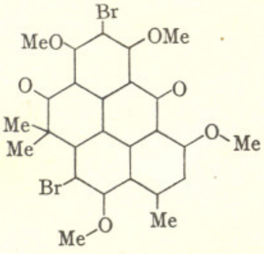

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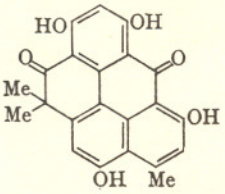

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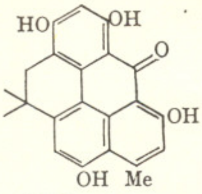

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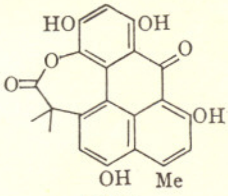
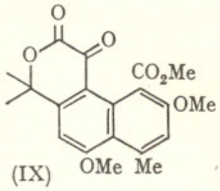


(VIII)

same stereochemistry and development of the skeletal structure (V) gave the constitution (VI), or a tautomeric equivalent, for resistomycin. This constitution permitted the following structural proposals for rescarmone (VII), resistomycinolide (VIII), and the α-keto-lactone (IX) already mentioned.

The formation of resistorubone (X) involves an interesting reaction sequence formulated as follows: (i) hydrolysis of the lactone (VIII) giving resistomycinolic acid, (ii) oxidation of this acid to the quinone (XI), (iii) decarboxylation (arrows XI) giving the quinone-methide (XII) which by the electrocyclic reaction (arrows, XII) gives resistorubone (X). Another interesting transformation product (XIII) was obtained by reduction of resistomycinolide tetramethyl ether (VIII; OH = OMe) with lithium aluminium hydride–aluminium chloride in tetrahydrofuran. The formation of this quinone (XIII) involved oxidation during its isolation and t.l.c. purification.

Resistomycin (VI) represents a new type of pentacyclic polyphenolic microbial metabolite. Its structure has an interesting relation to the natural phenalenones, atrovenetin,[9] herqueinone,[9] and their dimeric equivalents such as duclauxin.[10] The biosynthesis of resistomycin (VI) is most probably related to that established[10,11] for the natural phenalenones. Two polyketide routes (XIV or XV) may be considered and the striking correlation between the oxygenation pattern of resistomycin (VI) and that determined by the operation of either of these biosynthetic programmes is clear.



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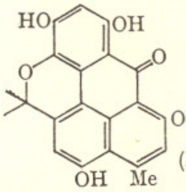

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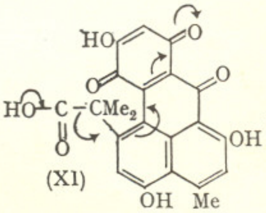

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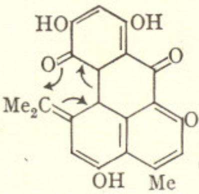

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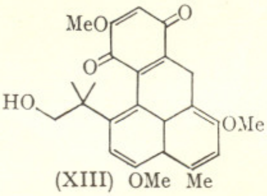

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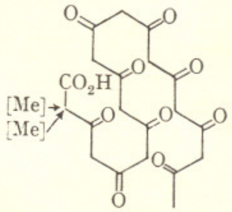

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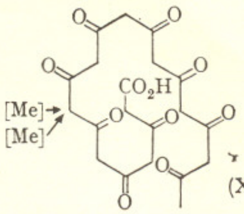

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