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RUTILANTINONE

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DURING a survey of antiphage substances produced by actinomycetes, Dr. I. N. Asheshov of the Lister Institute, London, discovered the rutilantins which are produced by the actinomycete (strain A 220).[1] The rutilantins are a closely related group of deep red antibiotics; they are amphoteric and give salts including hydrochlorides, citrates, and picrates. Mild acid hydrolysis of rutilantin picrate has yielded the aglycone, rutilantinone, and carbohydrates some of which are basic. The determination of the structure of rutilantinone is now described.

Rutilantinone (deep red needles, m.p. 220°, with decomposition and dependence upon rate of heating; Found: C, 61.95; H, 4.70; OMe, 7.16; (C)-Me, 3.33. $C_{22}H_{20}O_9$ requires C, 61.68; H, 4.71; (1)OMe, 7.24; (1)(C)Me, 3.5) contains an acidic group, pKa' = 9.9 (90% ethanol)

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[1] I. N. Asheshov, Private communication.

(equivalent weight = 435 ± 20. $C_{22}H_{20}O_9$ requires 428). Alkaline hydrolysis of rutilantinone yielded a dibasic acid, pKa' 10.2 and 5.7 (90% ethanol) (equivalent weight = 215 ± 20) confirming the presence of an ester group [λ_{max} 1743 cm^{-1} (Nujol)]. This was shown to be a methyl ester since the alkyl iodide produced by hydriodic acid reacted with dimethyl aniline giving $Ph.NMe_3\}$ I which was identified by comparison (m.p. and I.R. spectrum) with an authentic specimen.

The environment of the (C)Me group in rutilantinone was determined by CrO_3 oxidation. This gave a mixture of steam volatile acids which yielded some p-bromophenacyl propionate identified by direct comparison (m.p. and I.R. spectrum). Thus rutilantinone contained a $\geq C\text{-}CH_2\text{-}CH_3$ group.

Rutilantinone tetracetate (m.p. 250°; Found: C, 60.51; H, 4.90; OMe, 5.83; OAc, 38.9. $C_{22}H_{16}O_5(OAc)_4$ requires C, 60.40; H, 4.74; OMe, 5.21; OAc, 39.3) showed complex absorption in the carbonyl region [λ_{max} 1781 cm^{-1} (phenolic acetate), 1743 cm^{-1} (ester), 1683 cm^{-1} (conjugated carbonyl) (in $CHCl_3$)] and it still contained at least one hydroxyl group [ν_{max} 3630 cm^{-1} (in $CHCl_3$)]. The ultra-violet and visible spectra of rutilantinone λ_{max} (ε_{max}) 234 mμ (43,100), 257 mμ (18,100), 293 mμ (7,250), 494 mμ (10,600), 525 mμ (8400) (in EtOH) [λ_{max} (ε_{max}) 234 mμ (50,300), 259 mμ (21,800), 290 mμ (8900), 486 mμ (13,000), 498 mμ (14,400), 520 mμ (12,000), 534 mμ (11,700) (in cyclohexane)] were quite characteristic of the 1,4,5-trihydroxyanthraquinone structure.[2,3]

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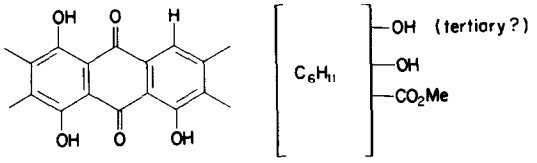
[2] J. H. Birkinshaw, Biochem. J. 59, 485 (1955).

[3] H. Brockmann and W. Muller, Chem. Ber. 92, 1164 (1959).

Its I.R. spectrum [λ_{max} 3520, 3400, 1611, and 1601 cm^{-1} (Nujol)] also showed that rutilantinone was a derivative of 1,4,5-trihydroxyanthraquinone.[4] These results led to the part structure (I) for rutilantinone in which the C_6H_{11} part contains a $-CH_2-CH_3$ unit.



I

When rutilantinone was heated under reflux with toluene and a trace of toluenesulphonic acid, both hydroxyl groups were lost giving bisanhydrorutilantinone (m.p. 239°; yield ~ 80%; Found: C, 67.32; H, 4.09; OMe, 7.80; (C)Me 3.37. $C_{22}H_{16}O_7$ requires C, 67.34; H, 4.11; OMe, 7.92; (C)Me, 3.82). Bisanhydrorutilantinone showed no evidence of unbonded hydroxyl in its I.R. spectrum. Its ultra-violet and visible spectrum [λ_{max} (ε_{max}) 252 mμ (62,500), 275 mμ (36,700), 486 mμ (22,600), 496 mμ (24,200), 508 mμ (20,800), 519 mμ (25,500), 530 mμ (21,800) (in cyclohexane)] is identical in practically all respects with that of 1,4,6- and is different from 1,6,11-trihydroxytetracenequinone.[3]

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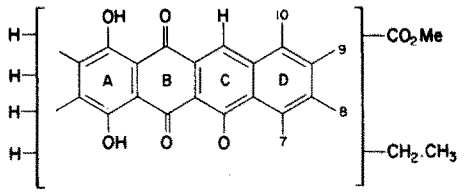
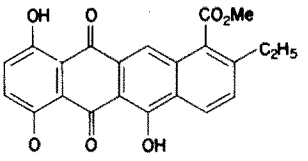
[4] H. Bloom, L. H. Briggs and B. Cleverley, J. Chem. Soc. 178 (1959).

Bisanhydrorutilantinone triacetate (m.p. 215°; Found: C, 64.58; H, 4.40; OMe, 6.07. $C_{28}H_{22}O_{11}$ requires C, 64.86; H, 4.28; OMe, 5.98) has a U.V. spectrum [λ_{max} (ε_{max}) 248 mμ (49,500), 299 mμ (28,500), 391 mμ (6800), 396 mμ (6860) (in MeOH)] almost identical with that of 1,4,6-triacetoxytetracenequinone. These facts lead to the part structure (II) for bisanhydrorutilantinone.

The ester group in bisanhydrorutilantinone (ν_{max} 1724 cm^{-1}) (cf. rutilantinone, ν_{max} 1743 cm^{-1}) cannot be located on ring A because it would then be ortho to a hydroxyl group. For this and other reasons it must be located on ring D. The ester group is so stable to hydrolysis by 2 N alkali that it must be flanked by two ortho substituents; it must be in positions 7 or 10 with the ethyl group correspondingly placed on 8 or 9. In all our experiments there has been no evidence for lactone formation so that position 10 for the $-CO_2Me$ group is preferred. This leads to structure (III) for bisanhydrorutilantinone which is also preferred on other grounds (vide infra).

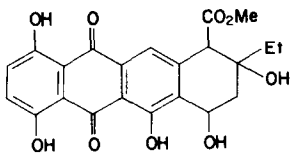


II



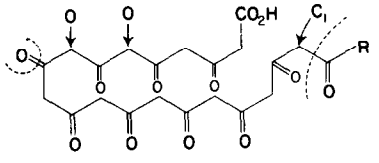
III

Concerning rutilantinone several experiments, not given here for reasons for brevity, have shown that base catalysed elimination of the alcoholic groups occurs easily thereby placing one of these hydroxyl groups β to the $-CO_2Me$. The other hydroxyl group was placed using biogenetic arguments giving structure (IV) for rutilantinone. These arguments utilize Birch's poly-β-keto acid precursor hypotheses and the oxygenation pattern in a precursor such as (V) does lead to (IV) for rutilantinone. The transformation (V ⟶ IV) involves biochemically and mechanistically reasonable processes including introduction of oxygen para to a potential or actual phenolic hydroxyl, introduction of a C_1 unit, loss of a -CO-R unit; the loss of phenolic oxygen is unexceptional.



IV

Rutilantinone

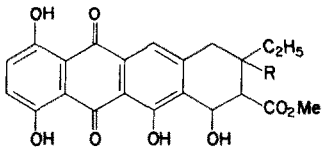


V

If these structures are correctly based, then (III) on oxidation could yield benzene-1,2,3,4-tetracarboxylic acid. Alkaline potassium permanganate oxidation of bisanhydrorutilantinone has in fact yielded this acid characterized as its tetramethyl ester, m.p. 130°, by comparison (m.p. and I.R. spectrum) with an authentic specimen. Thus structure (III)

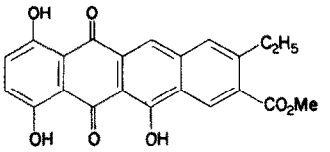
is confirmed.

Just after the completion of this work three papers appeared on the constitutions of some other antibiotics whose structures are remarkably similar to our structures for rutilantinone (IV) and bisanhydrorutilantinone (III). It has been shown that various Streptomyces strains have yielded ε-, ξ-, and η-pyrromycinones with the structures given below, and the glycoside, pyrromycin.[5,6,7]



VI

ε-Pyrromycinone, VIa; R=OH
ξ-Pyrromycinone, VIb; R=H



VII

η-Pyrromycinone

ε-Pyrromycinone (VIa) is isomeric with rutilantinone (IV) and η-pyrromycinone (VII) is isomeric with bisanhydrorutilantinone (III) and the same biogenetic precursor and transformations which have been indicated (see V) could give rise to all of them. It may be mentioned

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[5] L. Ettlinger, E. Gaumann, R. Hutten, W. Keller-Schierlein, F. Kradolfer, L. Neipp, V. Prelog, P. Reusser and H. Zahner, J. Chem. Soc. 1867 (1959).

[6] H. Brockmann and W. Lenk, J. Chem. Soc. 1880 (1959).

[7] H. Brockmann and W. Lenk, J. Chem. Soc. 1904 (1959).

that our biogenetic arguments do differ significantly from those of Prelog, Brockmann and their collaborators, in that we suggest that the introduction of a C_1 unit involving a β-diketone structure (see V) might be more likely than terminal C-methylation or its equivalent. It would appear that an argument based on biogenesis has been important in the location of substituents in the pyrromycinone structures. The crucial experiment on η-pyrromycinone corresponding to our oxidation of bisanhydrorutilantinone to benzene-1,2,3,4-tetracarboxylic acid has not been reported.

It is likely that the pyrromycinones and rutilantinones belong to a new group of antibiotics of common biosynthetic origin and just as pyrromycin, cinerubin A and cinerubin B are glycosides of ε-pyrromycinone (VIa), so the rutilantins are probably similarly derived from rutilantinone (IV).

We would like to acknowledge the help which we have received from the ultra-violet spectra given in two of Professor Brockmann's earlier publications.[3,8] We thank Professor W. Baker for his interest, and Mr. B. K. Kelly, The Director of the Antibiotic Research Station, Clevedon, and Dr. I. N. Asheshov for encouraging our collaboration.

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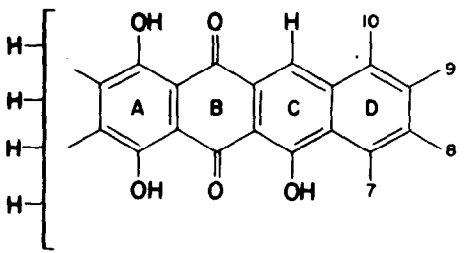
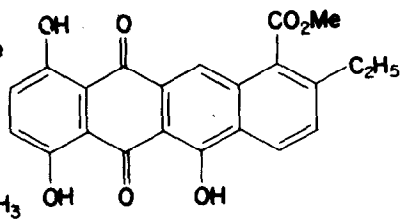
[8] H. Brockmann, L. Costa Pla and W. Lenk, Angew. Chem. 69, 477 (1957); H. Brockmann and W. Lenk, Ibid. 69, 477 (1957).

2. W. D. OLLIS, I. O. SUTHERLAND and J. J. GORDON: Rutilantinone, Tetrahedron Letters No. 16, 17-23 (1959).

An OH group was missing from formula II (Ring C) and from formula III (Ring A) in the above article. This has now been rectified and the corrected formulae are reproduced below.



II



III