Grisorixin, a New Antibiotic Related to Nigericin

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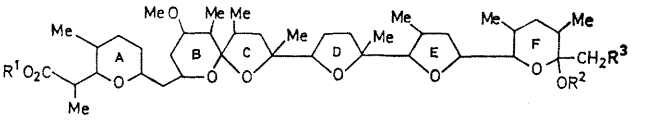
Summary The structure of a new antibiotic Grisorixin has been determined by physical and chemical methods.

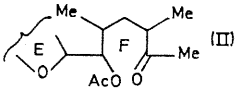
FROM cultures of a strain of *Streptomyces griseus*, we have isolated a biologically active compound we named grisorixin. It shows activity against Gram-positive bacteria, and antifungal and cytotoxic properties which will be described in a further paper. We describe here our chemical investigation on the structure of this antibiotic.

Grisorixin (Ia) ($C_{40}H_{68}O_{10}$)† (*M* 708)‡ is an amorphous solid very soluble in most organic solvents and insoluble in water, m.p. 75—80°; $[\alpha]_{578}^{20}$ + 16° (*c* 4, acetone); pK_a = 7·05 (ethanol–water, 1 : 1, v/v); i.r. (KBr): ν_{max} 3500—3440, [OH] and 1725 cm^{-1} [C=O]; n.m.r. (CCl_4): δ 3·33 (3H, s, OMe) and 6·60 (2H, broad signal, OH); u.v. (ethanol): no absorption above 210 nm. It is a polycyclic polyether with a hydroxy-group, a carboxy-group, and a methoxy-group. Its structure (Ia) is similar to the structures of nigericin (Ib),[1,2] and monensin.[3]

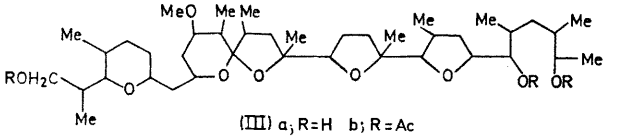
Treatment of (Ia) with diazomethane yields the methyl ester (Ic), $C_{41}H_{70}O_{10}$, m.p. 55—63°, which on acetylation with acetic anhydride–pyridine affords an acetate $C_{43}H_{72}O_{11}$ n.m.r.§: δ 2·08 and 2·14 (each 3H, s, OAc and CO·Me); ν_{max}



(I) a; R^1=R^2=R^3=H c; R^1=Me; R^2=R^3=H
b; R^1=R^2=H; R^3=OH d; R^1=R^2=Me; R^3=H



(II)



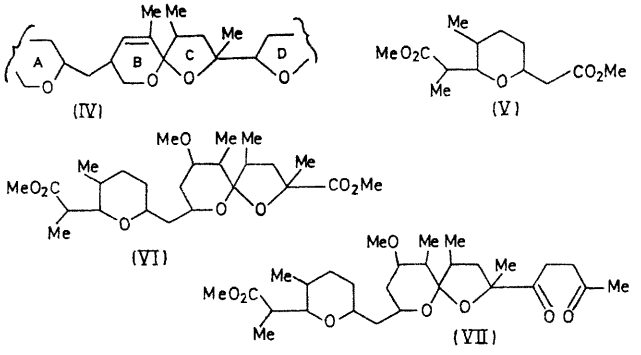
(III) a; R=H b; R=Ac

† Satisfactory elemental analyses have been obtained for all compounds whose molecular formulae are given.
‡ The mass spectrum of grisorixin does not exhibit any peak for the molecular ion. The highest mass peak (*m/e* = 690) corresponds to the loss of one molecule of water.
§ N.m.r. spectra were recorded in CCl_4 solution with Me_4Si as the internal reference.

(KBr), 1740 and 1718 cm^{-1} (C=O). The structure of this compound (II) corresponds to the opening of the hemiacetal ring F.

Reduction of grisorixin (Ia) with $LiAlH_4$ in diethyl ether gives an amorphous solid¶ $C_{40}H_{72}O_9$ (IIIa), which on acetylation with acetic anhydride–pyridine yields a triacetate (IIIb) $C_{46}H_{78}O_{12}$, n.m.r.: δ 2·00 (9H, broad singlet, 3 × OAc).

Treatment of the methyl ester (Ic) with 1N-sulphuric acid in methanol affords two products. The n.m.r. spectrum of the first, $C_{42}H_{72}O_{10}$ (Id), shows the presence of two methoxy-groups (δ 3·16 and 3·27, s, each 3H). The presence of the methoxy-group signal at δ 3·16 suggests an etherification of the tertiary hydroxy-group of ring F.



The n.m.r. spectrum of the second product $C_{41}H_{68}O_9$ reveals one ethylenic proton (δ 5·62, broad signal), an ethylenic methyl-group (δ 1·60, broad singlet, 3H) and only one methoxy-group (δ 3·16, s, 3H). These data suggest the structure (IV), which corresponds to the loss of one molecule of MeOH from ring B of the spiro-acetal group of grisorixin.

Oxidation of the methyl ester (Ic) with chromic acid in aqueous acetic acid yields a number of products, which have been separated into two fractions, one neutral and the other acidic. From treatment of the acidic fraction with diazomethane, we isolated two dimethyl esters. The first one $C_{13}H_{22}O_5$ has the structure (V). Its n.m.r. spectrum is consistent with this structure. The second one $C_{25}H_{42}O_8$ has the structure (VI); n.m.r.: δ 3·67 and 3·70 (each 3H, s, CO_2Me) and 3·30 (3H, s, OMe).

From the neutral fraction, we isolated one product $C_{28}H_{46}O_8$ (VII), n.m.r.: δ 3·72 (3H, s, CO_2Me), 3·33 (3H, s, OMe), and 2·14 (3H, s, CO·Me).

Crystalline metallic salts of grisorixin have been prepared; the sodium salt (m.p. 242—246°) and the silver salt (m.p. 147—153°) are soluble in most organic solvents and insoluble in water.

The complete structure of grisorixin has been determined by *X*-ray crystallographic analysis of its silver salt.[4]

One of us (P.G.) thanks l'Institut National de la Santé et de la Recherche Medicale for support of this work.

(*Received, July 20th*, 1970; *Com.* 1188.)

¶ All the products derived from grisorixin, except for the metallic salts, were obtained as amorphous solids and foams.

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