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SYNTHESIS OF SHOWDOMYCIN

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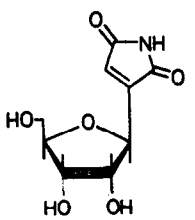
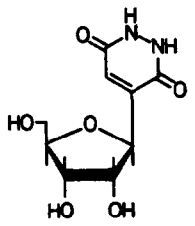
We wish to report herein the synthesis of showdomycin[1] the structure of which has been recently established as I (ref. 2,3).



I

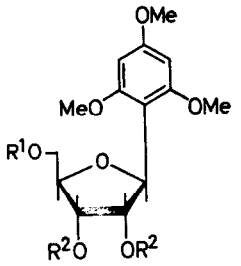


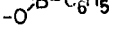
IX

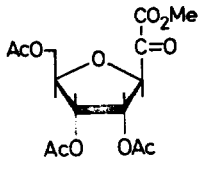
We proceeded from 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4,6-trimethoxybenzene (II, $C_{35}H_{32}O_{10}$, $[\alpha]_D^{25}$ -41.6° c 0.5 in ethyl acetate) which is accessible by condensation of 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide with 1,3,5-trimethoxybenzene in the presence of zinc oxide in benzene at room temperature. (Formation of C-glycosides derived from D-glucopyranose under similar conditions has been reported by Treibs[4].) By treatment of II with sodium methoxide in methanol 1-β-D-ribofuranosyl-2,4,6-trimethoxybenzene (III, $C_{14}H_{20}O_7$, m.p. 102-103° from ethyl acetate, $[\alpha]_D^{25}$ -37.8° c 0.5 in water, λ max in water 212 nm, 237 nm, 270 nm, log ε 4.33, 3.94, 2.90) was obtained and characterized as 2′,3′-phenylboronate (IV, $C_{20}H_{23}BO_7$, m.p. 136-137° from n-propyl ether-light petroleum). The infrared spectrum of IV (10^{-3}M in tetrachloromethane) exhibits the strong band of hydroxyl group at 3533 cm^{-1}. This band may be ascribed to the intramolecular hydrogen bonding due to the interaction of primary hydroxyl group with aromatic ring.

Acetylation of III with acetic anhydride-pyridine mixture led to the

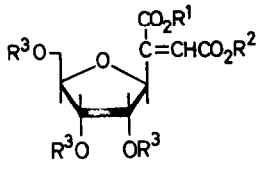
syrupy 2′,3′,5′-tri-O-acetyl derivative V ($C_{20}H_{26}O_{10}$, $[\alpha]_D^{25}$ -19.3° c 0.5 in ethyl acetate, λ max in ethanol 214 nm, 238 nm, 270 nm; log ε 4.31, 3.96, 2.80) which was further subjected to ozonolytical cleavage in ethyl acetate at -25°. The resulting ozonide was treated with dimethyl sulfide at 0° according to the procedure of Pappas[5]. The keto acid VI was treated without isolation with carboethoxymethylene triphenylphosphorane in refluxing benzene to give unsaturated ester VII which was purified by silica gel chromatography (benzene--acetone 9:1) and high vacuum distillation (at 0.05 mm Hg, 185-190° bath temperature). The NMR spectrum of the isolated product was in an agreement with the proposed structure VII ($C_{18}H_{24}O_{11}$, $[\alpha]_D^{25}$ -8.1 c 0.7 in chloroform). By means of GLC (QF1, at 200°), VII was shown to be a mixture of two components VIIa and VIIb in ration 10:1. By alkaline hydrolysis, VII was converted into a mixture of the free acids VIIIa and VIIIb which are separable by ion exchange chromatography (Dowex 1, formate) or by electrophoresis in 0.1 M formic acid. The higher electrophoretical mobility of the major component VIIIa in comparison to that of VIIIb allowed us to assign VIIIa the cis--arrangement on the double bond.



II $R^1=R^2=Bz$
III $R^1=R^2=H$
IV $R^1=H$; $2:R^2=$ 
V $R^1=R^2=Ac$



VI

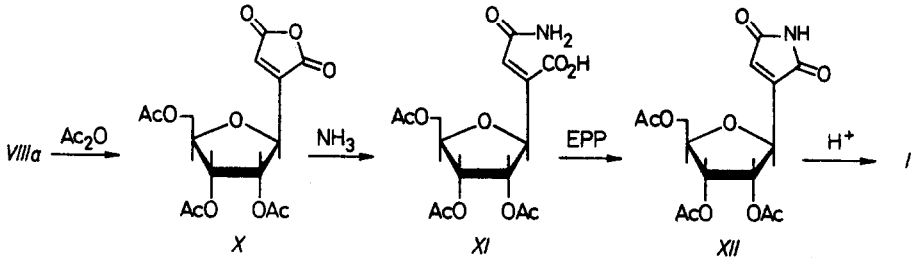


VIIa (cis), *VIIb* (trans): $R^1=Me$; $R^2=Et$; $R^3=Ac$
VIIIa (cis), *VIIIb* (trans): $R^1=R^2=R^3=H$

The mixture VIIIa and VIIIb when treated with hydrazine dihydrochloride in aqueous solution at 100° for 5 hours, afforded 4-(β-D-ribofuranosyl)-1,2,3,6-tetrahydropyridazine-3,6-dione (IX) which was obtained after ion exchange chromatography (Dowex 1, formate) in the crystalline form. $C_9H_{12}N_2O_6$,

m.p. 218-219° (water), $[\alpha]_D^{25}$ +30.2° (c 0.5 in water), λ max in 0.1 M HCl 212 nm, 299 nm (log ε 4.15, 3.51); λ max in 0.05 M NaOH 222 nm, 327 nm (log ε 4.28, 3.49).

Treatment of VIIIa (containing 10% of VIIIb) with acetic anhydride in the presence of 2% trifluoroacetic acid at 50° for one hour afforded the maleic acid derivative X which was characterized after high vacuum distillation (0.07 mm Hg, 170-180° bath temperature) by infrared spectrum in tetrachloromethane ($\nu_{asym.}$ (C=O) 1847 cm^{-1}, $\nu_{sym.}$ (C=O) 1776 cm^{-1}, ν (C=O, acetyl) 1749 cm^{-1}). X was reacted with ammonia in benzene solution at room temperature to give a maleamic acid derivative to which the structure XI was tentatively assigned.



EPP = Ethyl polyphosphate

The attempts to transform the amide XI into the maleimide derivative XII using acetic anhydride as a dehydrating agent, were not successful. The failure of this reaction was not unexpected in view of the recent paper of Cotter and co-workers[6] on the formation of N-substituted isomaleimides from appropriate maleamic acids. To our knowledge there is no report on the cyclisation of maleamic acid into maleimide under mild conditions. (Maleimide was prepared by Rinkes[7] by distillation of maleamic acid with zinc chloride in 10% yield.) The preparative methods for maleimide published[8,9] recently are too complicated for to be applied for conversion of XI into XII. In order to overcome these difficulties, we elaborated a convenient preparative method for maleimide, involving treatment of maleamic acid with suspension of phosphorus pentoxide in dimethylformamide at 80° for 3 hours. The yields of chromatographically pure maleimide ranged from 60-65%. For cyclisation of XI, the above methode was modified using ethyl polyphosphate in dimethylformamide at

80° for 3 hours. The crude product XII was purified via column chromatography on silica gel (benzene-ethyl acetate 7:3) and subjected to acid methanolysis (0.1 M HCl in methanol at 25° for 24 hours) to yield after chromatography on a silica gel column (ethyl acetate-acetone 7:3) a crystalline material ($C_9H_{11}NO_6$) which was proved to be in all respects identical with an authentic sample of showdomycin (m.p., $[\alpha]_D^{25}$, IR, UV, ORD* and mass spectra, and chromatographical and electrophoretical mobilities).

Starting from 800 mg of the mixture VIIIa and VIIIb (10:1), we obtained 110 mg of the crystalline showdomycin melting at 152-153° (ethanol-ethyl ether).

Compounds of which the empirical formulae are given in the present paper were analysed and gave satisfactory elemental analyses.

Inhibitory activity of synthetical showdomycin on the growth of Escherichia coli was indistinguishable from that of the authentic sample.

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* ORD spectrum of showdomycin (not yet reported): $[\phi]_{256\ nm}$ -8780°, $[\phi]_{292\ nm}$ 0°, $[\phi]_{315\ nm}$ 3320° (in water).