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SYNTHESIS OF 6-DEOXY-D-*arabino*-HEXOFURANOS-5-ULOSE, THE SUGAR COMPONENT OF HYGROMYCIN A.

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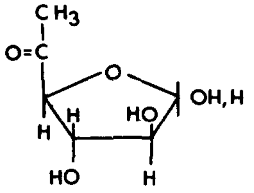
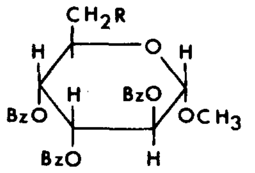
Structure of hygromycin A has been elucidated in 1957. The antibiotic has three principal units and the sugar moiety was found to be 6-deoxy-D-*arabino*-hexofuranos-5-ulose (=5-keto-6-deoxy-D-arabohexose)(I) from the study of the mercaptolysis products of sodium borohydride-reduced hygromycin A and dihydro-deoxyhygromycin A (I).

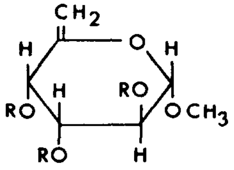
Present communication describes on the synthesis of I and its crystalline derivatives.



I



II Bz = benzoyl
a; R = OTs
b; R = I

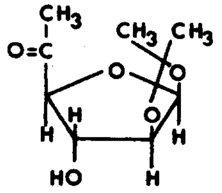


III
a; R = Bz
b; R = H

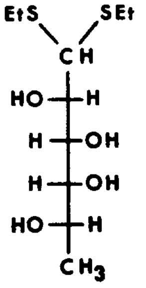
Methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-6-iodo-α-D-altroside (IIb, 0.75g) (2), which was obtained by substitution of *p*-tolylsulfonyloxy group of methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(*p*-tolylsulfonyl)-α-D-altroside (IIa) with iodine, was treated with silver fluoride (1g) in pyridine (5ml) (3). The product was purified by passing through silisic acid column to give colorless syrup (0.57g), $[\alpha]_D^{12}$ -4.8° (c 0.61, chloroform), which showed single spot on t.l.c. (silisic acid). Structure IIIa was assigned spectroscopically to the product which showed IR absorption bands (film) at 1740 cm^{-1} (ester C=O) and 1680 cm^{-1} (C=C). Methyl 2,3,4-tri-O-benzoyl-6-deoxy-α-D-arabino-hex-5-enopyranoside (= methyl 2,3,4-tri-O-benzoyl-5,6-α-D-altrosenide) (IIIa, 2.7g) thus obtained was hydrolyzed with sodium methoxide (1N, 2ml) in methanol (40ml) to methyl 6-deoxy-α-D-arabino-hex-5-enopyranoside (IIIb) which was then hydrolyzed to the corresponding free sugar (I) by heating with IR-120 (H^+form, 5g) in water (50ml). The yellow oily product (I, 0.7g), $[\alpha]_D^{12}$ -4.3° (c 1.88, methanol) was strongly reducing to Fehling's solution. The paper chromatogram of I developed in n-butanol saturated with water showed a yellow spot at Rf 0.38 with aniline hydrogen phthalate spray. Hydrolysis of hygromycin A and subsequent paper chromatography was also carried out in a similar condition as above, and yellow spot appeared at the same position (Rf 0.38).

Structure of I was further confirmed by preparation of crystalline derivatives. Reaction of I (0.2g) with p-nitrophenylhydrazine (0.8g) gave bis-p-nitrophenylhydrazone (0.35g), m.p. 211° (decomp.), $[\alpha]_D^{15}$ +1.1° (c 0.55, pyridine) $\nu_{C=N}$ 1650 cm^{-1}, ν_{NO_2} 1510 cm^{-1}, and ν_{NO_2} 1330 cm^{-1} (nujol mull)*.

As another crystalline derivative, 6-deoxy-1,2-O-isopropylidene-β-D-



IV



V

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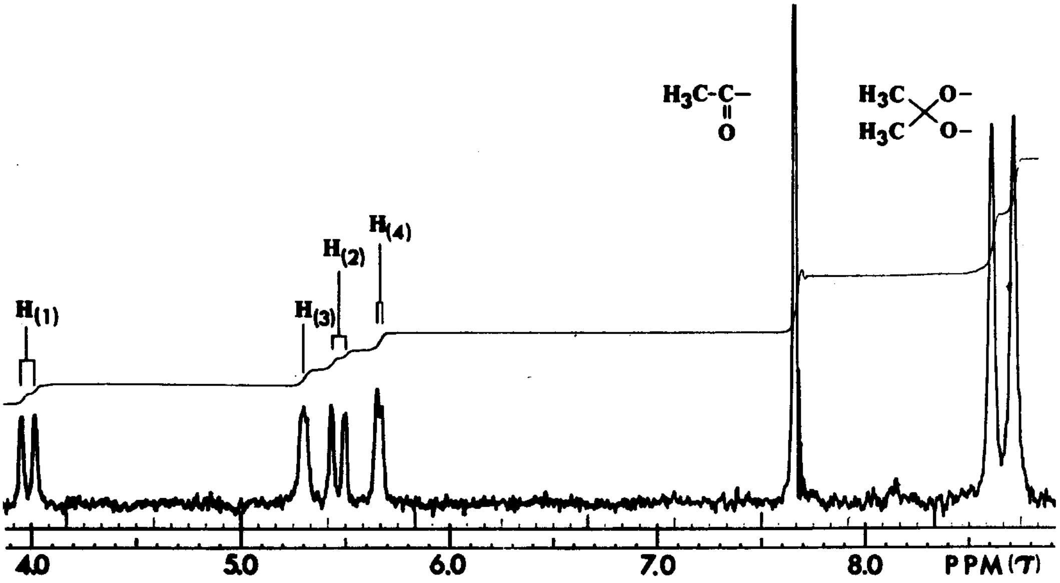
* All compounds for which a melting point is recorded gave satisfactory values in elemental analysis.

arabino-hexofuranos-5-ulose (IV) was obtained. Reaction of I (0.216g) with acetone (20ml) in a presence of anhydrous cupric sulfate (0.2g) and sulfuric acid (1 drop) gave colorless needles (IV, 0.13g), m.p. 85-86°, $[\alpha]_D^{16}$ -18.24° (c 1.0, chloroform), ν_{OH} 3500 cm^{-1}, and $\nu_{C=O}$ 1730 cm^{-1} (KBr pellet). NMR spectrum* of IV showed methyl proton signals at 7.65 ($\underline{H}_3C-\overset{|}{C}=O$), 8.6 and 8.7 ($(CH_3)_2=C=$), and proton signals at 3.99 ($\underline{H}-\overset{|}{\underset{|}{C}}_1-$, doublet, $J_{1,2}$=4 c.p.s.),



NMR spectrum of 6-deoxy-1,2-O-isopropylidene-β-D-arabino-hexofuranos-5-ulose (IV).

5.45 ($\underline{H}-\overset{|}{\underset{|}{C}}_2-$, doublet, $J_{1,2}$=4 c.p.s.), 5.3 ($\underline{H}-\overset{|}{\underset{|}{C}}_3-$, multiplet)** and 5.65 ($\underline{H}-\overset{|}{\underset{|}{C}}_4-$, doublet, $J_{3,4}$=1 c.p.s.).

On the structure studies of hygromycin A, R.L.Mann and D.O.Woolf obtained L-fucose diethylmercaptal (V) from sodium borohydride-reduced hygromycin A (1). Reduction of IV (0.104g) with sodium borohydride (50mg) followed by

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* NMR spectrum was taken in deuteriochloroform solution with tetramethylsilane as internal standard. The τ values were used throughout this communication.

** Multiplet with slight splittings, due to very small coupling constant between $\underline{H}-\overset{|}{\underset{|}{C}}_3-$ and $\underline{H}-\overset{|}{\underset{|}{C}}_2-$ or $\underline{H}-\overset{|}{\underset{|}{C}}_4-$.

treatment of the reduction product (0.10g) with hydrochloric acid (6N, 2ml) and ethylmercaptan (2ml) gave L-fucose diethylmercaptal (0.01g), m.p. 163-165°, which was identified with authentic L-fucose diethylmercaptal obtained from hygromycin A by mixed melting point and IR spectrum.

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References

1. R.L.Mann and D.O.Woolf, J.Am.Chem.Soc., 79, 120 (1957).
2. D.A.Rosenfeld, N.K.Richtmeyer and C.S.Hudson, J.Am.Chem.Soc., 70, 2201 (1948).
3. B.Helferich and E.Himmen, Chem.Ber., 62, 2136 (1929).
   A.Müller, Chem.Ber., 64, 1820 (1931).