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CHROMOSE A

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ACID hydrolysis of the antitumor substance chromomycin A_3[1,2] m.p. 183°, afforded a reducing sugar, $C_7H_{14}O_4$, m.p. 151° $[\alpha]_D^{22°}$ + 93° (c 1.0, in H_2O) (immediately after preparation), $[\alpha]_D^{22°}$ + 77° (after 1 hour and 1 day), which has been designated chromose A (I); 2,4-dinitrophenylhydrazone (II), $C_{13}H_{16}N_4O_6$ (one C-Me and O-Me), m.p. 146-147°, λ_{max}^{EtOH} 374 mμ (ε 31,000), $\lambda_{max}^{0.25\ N\ NaOH\text{-}EtOH}$ 460 mμ (ε 30,000). The analysis and UV spectroscopic properties of the hydrazone indicated that its formation was accompanied by dehydration of chromose A and that it was an α,β-unsaturated aldehyde derivative. Oxidation of I with one mole of bromine yielded

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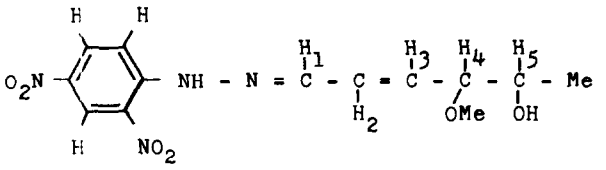
[1] M. Shibata, K. Tanabe, Y. Hamada, K. Nakazawa, A. Miyake, H. Hitomi, M. Miyamoto, and K. Mizuno, J. Antibiotics Ser. B, 13, 1 (1960).

[2] S. Tatsuoka, M. Miyake, and K. Mizuno, ibid. 329, 332, 335, (1960). K. Mizuno, ibid. in press.

a δ-lactone, b.p. 169-172°/2 mmHg, ν_{max}^{liq} 1733 cm^{-1}, which gave a positive iodoform reaction after alkaline hydrolysis. These facts in conjunction with the NMR experiments[3] established the structure of II as follows:



II

H_1 at 7.90(d), J_{12} 8 cps

H_2 at 6.11(q), J_{23} 16 cps

H_3 at 6.08(q), J_{34} 7 cps

Respective peaks of the AB type quartet (H_2 and H_3) are further split into doublets by coupling with H_1 and H_4.

H_4 and H_5 at ca. 3.6

O-Me at 3.41(s)

C-Me at 1.17(d), J_{H_5Me} 6 cps

OH at ca. 2.70(s)

The NMR of the hydrazone moiety was similar to other hydrazones[4].

It follows that chromose A can be represented by the 2-desoxypyranose structure Ia; this was confirmed by its NMR

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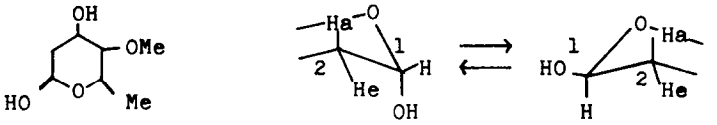
[3] NMR spectra were obtained on Varian A-60 and HR-100 spectrometers with TMS as internal reference. Chemical shifts are expressed in ppm. Decoupling experiments were carried out with the latter model as described in Varian Technical Information Bulletin, Vol. III No. 3 ins. 1471. Abbreviations used in the paper: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

[4] cf. Chart 293 in N. S. Bhacca, L. F. Johnson and J. J. N. Schoolery, "NMR Spectra Catalog," Varian Associates, 1962.

spectrum measured in D_2O. Since there are two anomers present H_1 exhibits two resonance patterns corresponding respectively to H_1 being equatorial (H_{1e}) or axial (H_{1a}). The former H_{1e} (Ib) is coupled to H_{2a} and H_{2e} with an identical spin-coupling constant of 3 cps which results in a three line pattern. However, when H_1 is axial (Ic), axial-axial and axial-equatorial couplings (8 and 3 cps, respectively) are observed which result in a quartet[5].



Ia Ib Ic

Measurement of the D_2O solution after 2 hours revealed an increase in the relative intensity of the H_{1a} quartet as compared to the H_{1e} triplet, hence a shift of the equilibrium in favor of the equatorial C_1-OH; this shift is responsible for the mutarotation. This evidence together with the mentioned ee and ea coupling constants[6] are fully consistent with structure Ia.

Hydrolysis of chromomycin A_3 methyl ether, m.p. 185°, with 5% HCl-MeOH gave two anomeric methyl chromosides, $C_8H_{16}O_4$, III, m.p. 92°, $[\alpha]_D^{22°}$ + 122° (c 1.0 in EtOH), and IV, m.p. 152°, $[\alpha]_D^{22°}$ - 36° (c 1.0 in EtOH). Hydrolysis of

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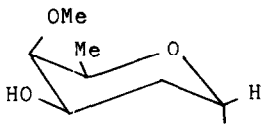
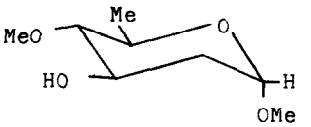
[5]The higher doublet of the quartet was overlaid by the HDO singlet formed by D exchange. However, the quartet was apparent in the spectrum of the corresponding chromoside (IV).

[6]J. A. Pople, W. G. Schneider and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance" 390, McGraw-Hill New York, 1959.

the two chromosides yielded the free chromose A, while methylation of chromose A afforded the two chromosides. The NMR spectra (in $CDCl_3$) of the two chromosides III and IV had, respectively, a triplet at 4.78 (J_{ea}=J_{ee}=3 cps), and a quartet at 4.25 (J_{aa} 9 cps, J_{ae} 3 cps). This was consistent with their anomeric nature and furthermore, since it meant that the C_1-OMe group in III was axial while that in IV was equatorial it follows that the chair forms of III and IV are identical and not inverted. Namely, a 1,3-diaxial interaction of substituents is absent in the III isomer as well as in the IV isomer. Conformational analysis along this line required that III be represented either by IIIa or IIIb.



IIIa



IIIb

The detailed NMR double irradiation experiment described in Fig. 1 gave a coupling constant of 1 cps for H_4-H_5. Accordingly, the chromoside III should be represented by IIIa; furthermore, the other coupling constants fully substantiated the configurations at other optical centers. Consideration of Hudson's rules, Whiffen's calculation[7], and the above-mentioned direction of the anomeric change in chromose A (mutarotation and NMR) showed that the sugar belongs to the D-series. Thus, chromose A can be represented by structure

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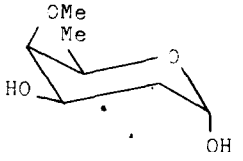
[7] D. H. Whiffen, Chem. and Ind. 964 (1956).

I; the chromoside III is methyl-α-D-chromoside A (structure IIIa), while the anomeric chromoside IV is methyl-β-D-chromoside A.



I α-D-Chromose A

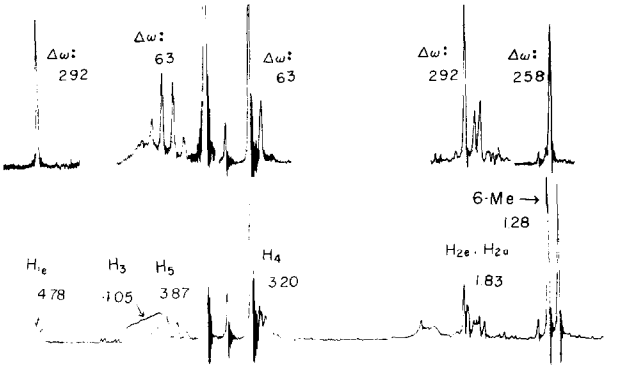


Fig.1. NMR peaks of methyl-α-D-chromoside A (structure (IIIa) (in $CDCl_3$, 100 Mc).

Upper trace: Decoupled signals obtained by irradiation with strong H_2 frequencies having the shown intervals ($\Delta\omega$ in cps).

Lower trace: Ordinary spectrum.

1) The signals around 1.83 are due to C_2 protons. They are only slightly non-equivalent and exhibit a spin coupling of 14 cps. Both these protons are coupled to H_1 (resonating at 4.78) with the same coupling constant of 3 cps. This establishes equatorial configuration for H_1.
2) The two protons at C_2 are also coupled to H_3. The broad resonance around 4.05 is due to this proton. The decoupled trace of the H_2 protons belong to an ABK system similar to that found in 1,2-epoxy-3-butanone[8]. The following coupling constants can be derived: $H_{2a}H_{3a}$ 9 cps; $H_{2e}H_{3a}$ 3-4 cps.
3) H_3 is also spin coupled to H_4 (which resonates at 3.20) with an axial-equatorial coupling of 4 cps. (see decoupled trace). This establishes equatorial configuration for H_4.
4) H_4 is further coupled to the methine proton on C_5. Here the spin coupling is about 1 cps which further confirms the equatorial configuration for H_4.

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[8] C. A. Reilly and J. D. Swalen, J. Chem. Phys. 32, 1382 (1960).