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4-DEOXY URONIC ACIDS

I. A PMR AND CHEMICAL PROOF OF METHYL 4-DEOXY-β-L-ARABINO-HEXOPYRANOSIDE URONIC ACID METHYLESTER

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In an earlier communication from this laboratory a method for the preparation of an unsaturated galacturonic acid derivative, methyl (α-methyl- $\Delta^{4,5}$-D-galactopyranoside) uronate (I), has been described (1). This compound has been supposed to be a useful intermediate for the synthesis of 4-deoxy sugars, especially of hitherto unknown 4-deoxy uronic acids. Up to now the preparation of only two 4-deoxy hexoses, 4-deoxy-D-glucose and 4-deoxy-D-altrose, and some of its derivatives has been published (2-6).

Catalytic hydrogenation of I yielded a syrup consisting of two compounds in a ratio of about 4:1 (densitometric evaluation of thin layer chromatograms). Since hydrogenation should introduce a new asymmetric center at C-5 these compounds are expected to have D-xylo and L-arabino conformation.

Fractionation of the sirup on a silicagel column afforded the two compounds (II and III) in cristalline form. The main product (II) was obtained as colourless prisms, m.p. 82-83° (corr.) and $[\alpha]_D^{26}$ = + 110.8° (C, 1.299 in abs. MeOH) [Found: C, 46.65; H, 6.65. Calc. for $C_8H_{14}O_6$: C, 46.60; H, 6.84 %].

First order analysis of PMR-spectra *) revealed this substance to be the methyl ester of methyl 4-deoxy-β-L-arabino hexuronide (II). The clearly resolved spectrum 2 resulted from spectrum 1 upon acidification with a trace of trifluoro acetic acid (TFE) to remove spin coupling between hydroxyl groups (7) and neighbouring protons. The assignments of the resonance peaks to the protons in the molecule was thus straightforward:

The doublet at lowest field (δ = 4.76 ppm; 1 H) arises from the most electron deficient proton, e.g. H-1 (8). Because of the α-position to an ester grouping in addition to the electron attracting ring oxygen the proton at C-5 was expected to be more deshielded and hence to appear at lower field than the other ring protons. The triplet (1 H) at δ = 4.41 ppm was accordingly assignet to H-5.

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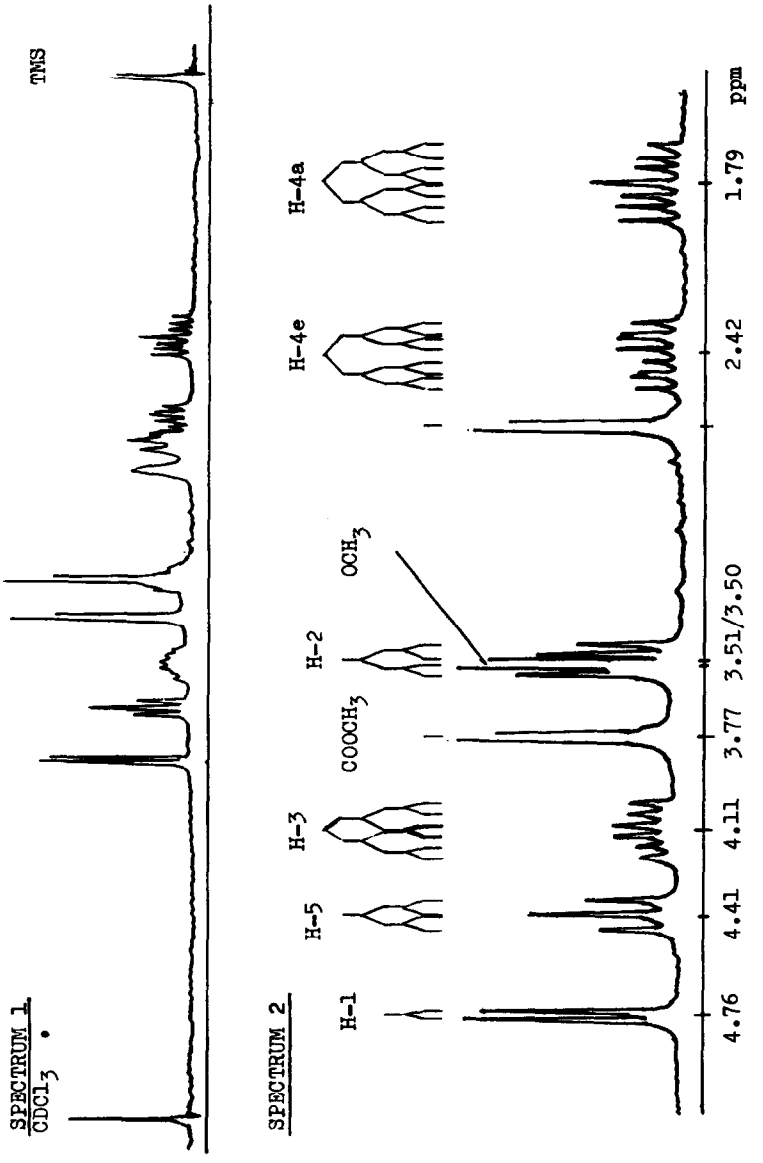
*) The spectra were recorded with a VARIAN-HR-100 Mc NMR-spectrograph in $CDCl_3$ with tetramethyl silane as an internal standard. Calibration was achieved using the side-band method with a HEWLETT-PACKARD frequency counter model 5243 L.


SPECTRUM 1
$CDCl_3$
TMS
SPECTRUM 2
H-1
H-5
H-3
$COOCH_3$
H-2
OCH_3
H-4e
H-4a
4.76
4.41
4.11
3.77
3.51/3.50
2.42
1.79
ppm

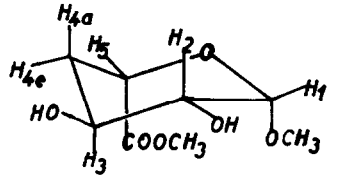
The multiplet (1 H) at δ = 4.11 ppm gave a sixtet (double quartet) upon acidification thus indicating a coupling to a hydroxyl proton. This was equally the case with a multiplet (1 H) overlapped by the resonance peak of the methyl ether protons (δ = 3.51 ppm; 3 H) to give a quartet at δ = 3.50 ppm (1 H). These protons should in consequence be bound to carbon atoms which bear a hydroxyl group, e.g. C-2 and C-3. The two multiplets at δ = 2.42 ppm (1 H) and at δ = 1.79 ppm (1 H) appearing as an octet (double quartet) and as a septet (double quartet) respectively, should arise from the methylene protons at C-4, the axial proton being usually more shielded (8,9). An evaluation of the coupling constants (see table) proved that these assignments were correct and that the sixtet at δ = 4.11 ppm originated from H-3. These findings were finally checked by double irradiation experiments.

Table

Coupling constants	J	cps
1 - 2		3,0
2 - 3		7,2
3 - 4e		4,0
3 - 4a		8,0
4e - 4a		13,3
4e - 5		5,2
4a - 5		5,0

Considering the coupling constants the conformation of II was established as follows. Axial-axial couplings normally show constants in the range of 6-10 cps, axial-equatorial and equatorial-equatorial couplings in the range of 2-4 cps ((8), compare references cited in (10)). Only two typical axial-axial couplings could be observed, e.g. for J_{2-3} and J_{3-4a} indicating H-2 and H-3 to be axially oriented. H-1 must be in an equatorial position. The almost identical values found for the coupling of H-5 to both protons at C-4 are consistent with the view of an equatorial H-5 bisecting the dihedral angle formed by the two C-4/H-4 bonds, although these values are abnormally high for equatorial couplings. However the great difference in the chemical shift between H-2 and H-3 shows that at H-3 an additional deshielding influence is operating which is probably caused by the diamagnetic anisotropy of the ester carbonyl group (9) thus indicating the axial position of the latter. In $CHCl_3$-

FIG



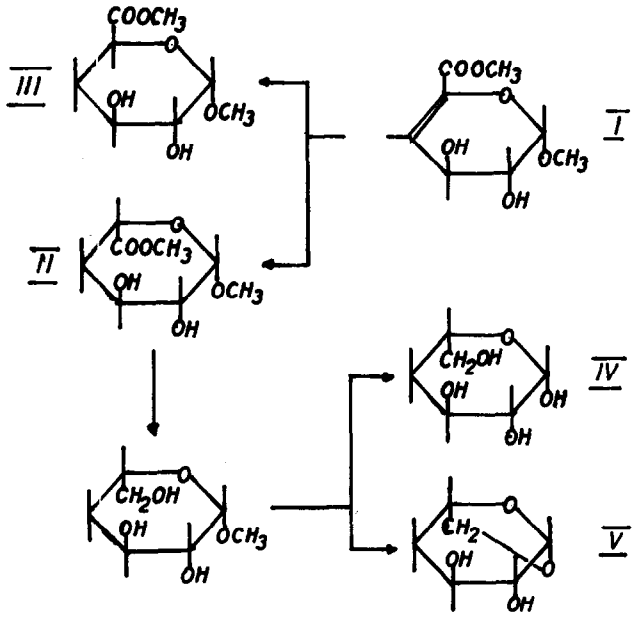
II

solutions this molecule must therefore exist in the C 1 conformation (11) (see Fig.) with the most bulky substituents being in the sterically unfavorable axial position

from a normal point of view (11).

IR-measurements in $CHCl_3$ gave some evidence that this unusual conformation is stabilized by intermolecular hydrogen bonding involving the two equatorial hydroxyl groups, for the broad absorption peak for associated OH in the region of 3200-3400 cm^{-1} showed critical concentration dependence (12).

Chemical evidence for compound II to belong to the L-sugar series was afforded by reduction of the ester grouping by $LiAlH_4$ and subsequent acid hydrolysis.



Paper chromatography of the product (Whatman No.1, n-BuOH/H_2O, descending technique) revealed two main spots, Rf: 0.25 (IV) and 0.45 (V)., V being the main product. These values have been reported for 4-deoxy-D-arabino-hexopyranose (4-deoxy-D-altrose) and the corresponding 1:6-anhydro derivative respectively (4). By fractionation on a cellulose column with the eluant mentioned above V was isolated and cristallised three times from ethyl acetate to give colourless prisms, m.p. 106-107° (corr.); $[\alpha]_D^{23}$= + 163.4° (C, 1.86 in H_2O) [Found: C, 49.03; H, 6.64. Calc. for $C_6H_{10}O_4$: C, 49.32; H.6.90 %]. These data are in agreement with the properties of 1:6-anhydro-4-deoxy-β-D-altrose (4) exhibiting the same degree of optical rotation ($[\alpha]_D^{20}$= -164°; C, 1.4 in H_2O) but in the opposite sense. This indicates that the two compounds are enantiomorphs and consequently V is 1:6-anhydro-4-deoxy-β-L-arabino-hexopyranose (1:6-anhydro-4-deoxy-β-L-altrose or -idose). From this follows compound II to be methyl 4-deoxy-β-L-arabino-hexopyranoside uronic acid methyl ester (or methyl 4-deoxy-β-L-iduronic acid methyl ester), product III consequently is methyl 4-deoxy-α-D-xylo-hexopyranoside uronic acid methyl ester (methyl 4-deoxy-α-D-glucuronic acid methyl ester).

A more detailed description of the reaction sequence outlined above, its products and derivatives will be published elsewhere.

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