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CONFORMATIONAL ASPECTS OF SOME 3-DEOXY-3-*C*-METHYL GLYCALS

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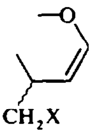
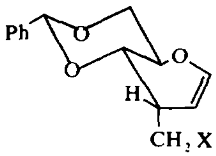
Abstract - The epimeric 3-deoxy-3-C-iodomethyl glycals **2** and **3** present an interesting contrast in their NMR parameters. In both, the methylene protons and the adjacent H-3 comprise an ABX sub-system. However in **2**, the methylene protons H-7 and H'-7 are the BX portion, separated by 0·64 ppm while in **3** they are the AB portion, separated by 0·10 ppm. By careful study of the parameters from the 220 MHz spectra, it is possible to determine that in **2** one of the methylene-protons (H'-7) in the iodomethyl group lies within the shielding zone of the double bond and anti to H-3, while the other (H-7) bisects the H-3 - C-3- C-2 angle. In **3** both H-7 and H'-7 are gauche H-3 and are not affected by the double bond.

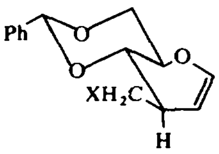
BRANCHED-CHAIN sugars are constituents of several biologically important substances[1] and consequently their chemistry has attracted considerable attention.[2] We have been interested in this laboratory in the synthesis of intermediates which are capable of extensive and varied structural modification. The partial structure **1** illustrates this approach. The unsaturation is characteristic of the glycal family and should therefore be capable of considerable modification along lines already well developed for this specific class of vinyl ethers.[3] Alternatively and/or additionally the molecule possesses potential for modification at the branch via nucleophilic substitution, elimination or oxidation. The latter two cases are particularly noteworthy in view of the synthetic possibilities that may be imagined for the diene and β,γ-unsaturated aldehyde that would be obtained. Indeed such a diene has already been shown to be a key intermediate in a synthetic sequence.[4]



1

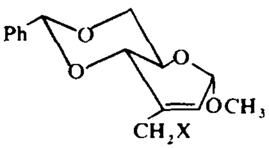


2: X = I
4: X = H



2

3: X = I
5: X = OH
6: X = OTs
9: X = H



7: X = Br
8: X = H

In developing this approach we have described the pair of epimers **2**[5] and **3**[4] which incorporate the functionalities of **1**. Some anomalies encountered in the NMR spectra of these molecules caused us to undertake a detailed comparison of the two systems and we now report on the results of this study.

DISCUSSION

In the chemical characterization of compound **2**, the presence of the iodomethyl substituent was verified by LAH reduction to a substance, **4**, whose NMR spectrum showed the appropriate Me doublet at τ 8·86[5] (Table 1). The axial orientation of the

TABLE 1. NMR PARAMETERS FOR SOME 1.2.3-TRIDEOXY-3-C-METHYL-HEX-1-ENOPYRANOSE DERIVATIVES IN $CDCl_3^\theta$

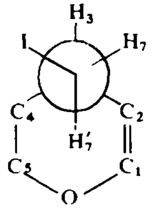
Compound	Chemical shifts from TMS (τ)						Coupling constants* (Hz)						
	H-1	H-2	H-3	H-4	H-7	H'-7	J_{12}	J_{13}	J_{23}	J_{34}	J_{37}	$J_{37'}$	$J^{77'}$
2†	3·65	5·05	7·24	6·00	7·01	6·37	6·3	−1·3	5·2	6·0	11·0	4·0	−9·5
3†	3·55	5·37	7·48	6·20	6·66	6·56	6·1	−2·7	2·0	9·0	6·2	3·5	−10·0
4†	3·73	5·22	7·43	6·02	8·86		6·0	−1·3	6·0	6·0	7·5		n.d.
9‡	3·73	5·53	7·47	n.d.	8·90		6·0	−2·7	2·0	n.d.	7·0		n.d.
5‡	3·73	5·37	7·35	n.d.	6·26		7·0	−2·5	2·0	n.d.	5·0		n.d.
6‡	3·62	5·37	7·27	n.d.	5·82		7·0	−2·5	2·0	n.d.	5·0		n.d.

θ For protons not listed in the Table, see experimental.

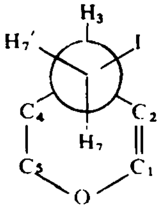
* For **2** and **3** the values are valid coupling constants because of the successful simulations (Fig 2). For the others $J \pm 0{\cdot}2$ read directly from spacings in the spectra interpreted on a first order basis.

† 220 MHz at 500 Hz sweep width.

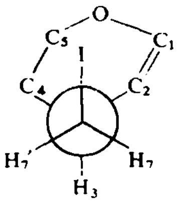
‡ 60 MHz.



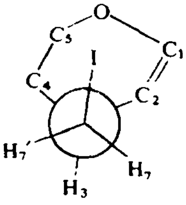
2c



2d



3b



3c

iodomethyl group was demonstrated by methanolysis which led to cyclopropanated glycosides having α-D- and β-D- *allo* configuration.[10] The stereochemistry of **2** is therefore secure and so, by corrolary, must be the epimer (**3**) into which it was transformed.[4]

In the 60 MHz spectrum of **2**, H-3, H-7 and H'-7 were recognized as an ABX sub-system. That the methine proton, H-3 was not the X proton as intuition might dictate, was readily substantiated by double irradiation of the suspected multiplet whereby H-2 becomes a doublet. The signal for H-7 was a quartet but it was not possible to determine which spacing was the vicinal (J_{37}) and which the geminal ($J_{77'}$) because the signal for H'-7 was too obscure and that for H-3 too complex to permit reciprocal analyses.

The 220 MHz spectra of the epimers **2** and **3** are shown partially in Fig 1. By simple comparison of the spacings in the spectra it was possible to make the assignments indicated. The major difference between both spectra is seen to be the appearance of H-3, H-7 and H'-7. Consequently this portion of each spectrum was simulated. Thus the parameters obtained from the 220 MHz spectra (Fig 1) for all protons coupled to H-3 *viz*, H-1, H-2, H-4, H-7 and H'-7 were fed into a computer, and the H-3, H-7 and H'-7 signals were simulated (Fig 2). The good visual comparison between the multiplets in Figs 1 and 2 (particularly in the case of H-3) indicate that the *J*-values read from the spectra and used in the computation are valid coupling

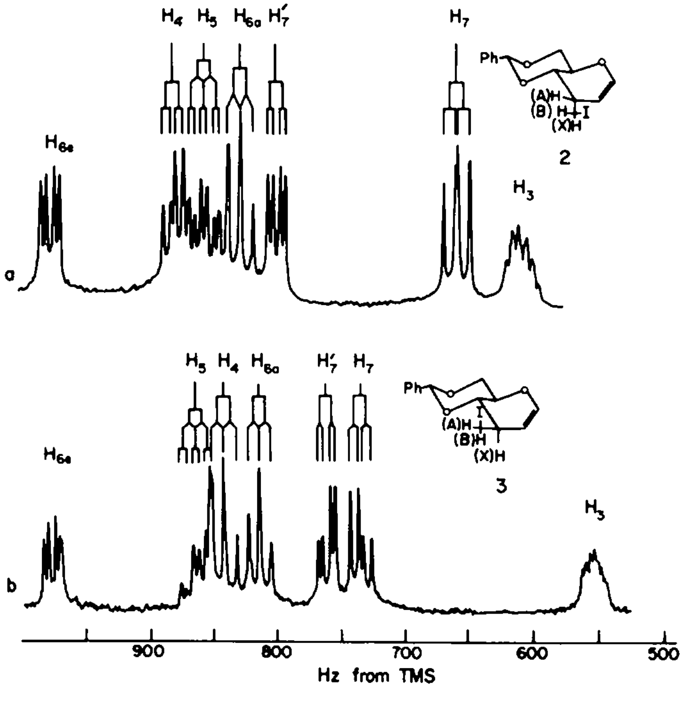


FIG 1. 220 MHz NMR spectra of (a) 4.6-O-benzylidene-3-deoxy-3-C-(iodomethyl)-D-allal,2. and (b) 4.6-O-benzylidene-3-deoxy-3-C-(iodomethyl)-D-glucal,3

constants. Thus for the ABX sub-system in compound **2**, $J_{37'}$ ($\equiv J_{AX}$), $J_{77'}$ ($\equiv J_{BX}$) and J_{37} ($\equiv J_{AB}$) were 4·0, 9·5 and 11·0 Hz respectively. When the latter two values were assigned as J_{37} ($\equiv J_{AB}$) and $J_{77'}$ ($\equiv J_{BX}$) respectively and the spectrum computed, the quartets at τ 6·37 and 7·01 exchanged places.* It is noteworthy that the geminal coupling of $-9{\cdot}5$ Hz agrees well with that observed in methyl iodide.[11]

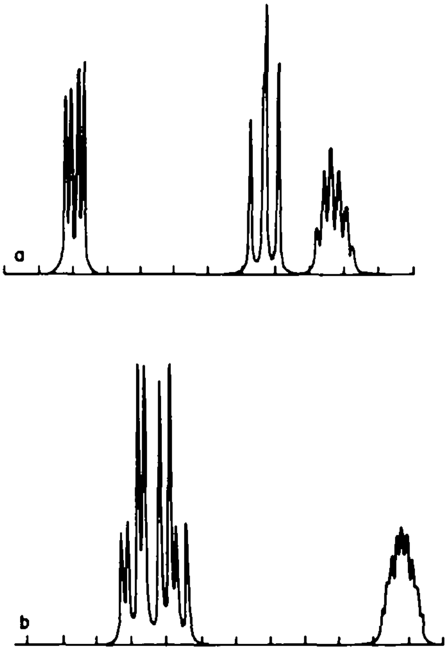


FIG 2. Computer simulated NMR spectra of H-3, H-7 and H'-7 (a) of compound **2**, and (b) of compound **3**

Having established as valid coupling constants all values $J_{1,3}$ listed in Table 1, a closer study was made of the epimeric branching point. Three- and four-bond coupling constants have been advanced as useful criteria for, estimating allylic proton conformations[12] and the validity of this approach is attested by several successful correlations from data in the literature.[7] In the present work the values J_{23} and J_{13} for **2** and **3** as well as for their LAH reduction products, **4** and **9** respectively, agree well with those encountered in analogous cases.[7a, 7b] Thus the 3-bond vinyl–allylic coupling, J_{23}, (Table 1) is smaller for pseudo axial H-3 (**3** and **9**) than for pseudo-equatorial (**2** and **4**). On the other hand the four-bond vinyl–allylic coupling, J_{13}, is smaller for pseudo-equatorial allylic protons than for pseudo axial.

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* The previous assignment[5] made in the hasty supposition that the geminal coupling ought to be larger than the vicinal, is now seen to be incorrect.

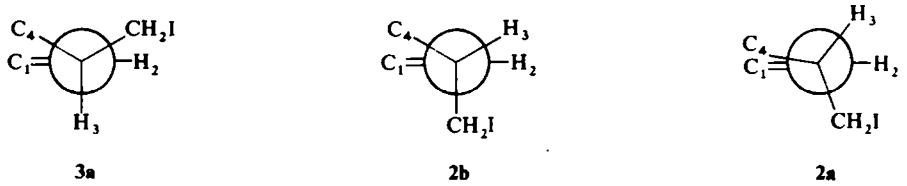
The coupling constants for **2** and **3** were put into the Garbisch equations (1) and (2) for determining the orientation of allylic protons.[12] Solution of the equations gave

$$J_{23}^{est} \simeq 6{\cdot}6\cos^2\phi + 2{\cdot}6\sin^2\phi \,(0^\circ \leqslant \phi \leqslant 90^\circ) \qquad (1)$$

$$J_{13}^{est} \simeq 1{\cdot}3\cos^2\phi - 2{\cdot}6\sin^2\phi \,(0^\circ \leqslant \phi \leqslant 90^\circ) \qquad (2)$$

for **2** $\phi = 44^\circ$ and for **3** $\phi = 90^\circ$. The latter is in excellent agreement with the geometry suggested by inspection of space-filling models and depicted in the Newman projection (Scheme 1) for **3a**.

Scheme I



3a **2b** **2a**

In the case of epimer **2**, the calculation gives a value of 44° for the projected angle between H-2 and H-3. This implies a conformation such as **2a**; however the Garbisch values have a ±15° tolerance, and if the calculated values is taken to its lower limit ($\phi = 29^\circ$), conformation **2b** can be accommodated. In an alternative approach, the Karplus relationship[13] was applied to the coupling constant, J_{34}, and the dihedral angle calculated to be 30·5°. This is more in keeping with conformation **2b** since in **2a**, the projected angle between H-3 and H-4 would be much less than 30°.

With the foregoing stereochemical aspects now clarified, an attempt was made to account for the anomalous contrasts in the spectra of epimers **2** and **3**. Being vicinal to an asymmetric centre, H-7, H′-7 are diastereoptopic and therefore magnetically non-equivalent. However the separation between these protons in compound **2** (0·64 ppm) seemed exceptionally large. Extreme separation between protons at a prochiral centre usually occurs only when that centre is adjacent to a strongly anisotropic moiety such as pyramidal nitrogen.[14] However even in benzyl methyl sulfoxide, the methylene protons are separated by only 0·14 ppm[15] and in benzylsulfinyl chloride they are not chemically shifted in a variety of solvents.[16]

The apparent abnormal situation in the spectrum of **2** was accentuated by comparison with that for the epimer, **3** (Fig 1). In the latter H-3, H-7, and H′-7 also comprize an ABX system, but the methylene protons are the AB portion—a situation intuitively more "normal". Comparison of the data for these protons in **2** and **3** (Table 1) suggests that the "abnormal" features observed in the spectrum of **2** are (i) the shielding of H-7, and (ii) the large value for J_{37}. The latter considered in conjunction with $J_{37'} = 4{\cdot}0$ Hz suggested that in the preferred conformation, the methylene protons have a *trans* and a *gauche* relationship to H-3. Of the two conformations satisfying this condition, **2c** and **2d**, the latter is preferable. Space filling models indicate that in **2c** the iodine atom is brought into severe interaction with the carbon-4 oxygen and indeed cannot rotate past it. Thus in the favoured conformation **2d**, H-7 lies within the shielding zone of the double bond—hence its "abnormal" resonance.

With regard to **3**, the magnitude of the couplings show that H-3 must be *gauche* to both H-7 and H′-7. In conformation **3b** the iodine atom and H-4 interact strongly; however rotation about the C_3–C_7 bond into conformation **3c** relieves the interaction and accounts for the observed difference in J_{37} and $J_{37'}$. In this connection it is interesting to note from the data in the Table that in the alcohol **5** and tosylate **6**, the 7-hydrogens are accidentally equivalent unlike in the related iodide (**3**).

EXPERIMENTAL

Compound **3** was prepared as described in Ref 5. Compounds **2**, **4**, **5** and **6** were prepared as described in Ref 4. The bromoolefin **7**[4] on LAH reduction was converted to **9** via **8** by the reductive rearrangement described elsewhere.[6]

The spectra were determined on a Varian T60, a Varian HA 100 or a Varian HR 220 spectrometer and the parameters reported in the Table were read directly from the spectra.

The existence of the benzylidene ring in compounds **2**–**9** was apparent from the presence of five aromatic protons around τ 2·60 and the methine singlet (Ph C<u>H</u>—) ∽ τ 4·40. The following characteristic features of the 1,3-dioxolane ring embodying H-5, H-6a and H-6e[7a] were clearly identifiable in the 220 MHz spectra of **2**, **3** and **4**: H-5, τ 6·13 ± 0·08 (J_{56a} = 10·0, J_{56e} = 4·5, J_{45} = 9·5). H-6a, τ 6·32 ± 0·08 (J_{6a6e} = −10·5). H-6e: τ 5·54 ± 0·05, Ph C<u>H</u> τ 4·38 ± 0·06. In the 60 MHz spectra of compounds **9**, **5**, and **6**, H-5, H-6a and H-6c were unresolved between τ 5·67–6·70.

The assignment of H-1 (Table 1) in the vinyl ether structures **2** and **3** rests upon a comparison of the observed chemical shifts and spacings with values of well known glycals.[7,8] Double irradiation[9] of H-1 in the 100 MHz spectra then allowed identification of H-2; in a similar way H-3, and thereafter H-4 were identified by double irradiation experiments. The methylene protons H-7 and H′-7 were located by analysis of the 220 MHz spectra (Fig 1). Verification of the assignments followed from successful computer simulation of the pertinent portions of the 220 MHz spectra.

The simulated spectra in Fig 2 were prepared using a modified version of LACOON III run on the IBM 360-75 belonging to the Faculty of Mathematics, University of Waterloo. The line-frequencies and spacings used for the computations and shown below, were read directly from the 220 MHz spectra shown partially in Fig 1.

For **2**: H-1 = 1379·00, H-2 = 1089·00, H-3 = 607·20, H-4 = 1320·00, H-7 = 657·80, H′-7 = 798·60 Hz; J_{12} = 6·3, J_{13} = −1·3, J_{23} = 5·2, J_{34} = 6·00, J_{37} = 11·0, $J_{37'}$ = 4·0, $J_{77'}$ = −9·5; all other couplings were set to zero.

For **3**: H-1 = 1419·00, H-2 = 1018·60, H-3 = 554·40, H-4 = 1364·00, H-7 = 734·80, H-7′ = 756·80; J_{12} = 6·10, J_{13} = −2·7, J_{23} = 2·0; J_{34} = 9·0, J_{37} = 6·25, $J_{37'}$ = 3·5, $J_{77'}$ = −10·0; all other couplings were set to zero.

The ABX sub-systems containing the branching point in both epimers were simulated and the resulting spectra are shown in Fig 2. Assignment of NMR parameters for the alcohol **5** and *p*-toluenesulfonate **6** followed from comparisons with the related iodide **3**. For compounds **4** and **9**, the hydrogenolysis products of **2** and **3** respectively, the assignments followed from similarities with the parent iodides. In addition, double irradiation of the Me doublet of **4** and **9** revealed that the positions of H-3 were, as expected, close to those of the parent iodides.

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REFERENCES

[1] For a recent review see A. Rosenthal, *Advan. Carbohydr. Chem.* **23**, 59 (1968)

[2] See for example: R. D. Guthrie, R. J. Ferrier, T. D. Inch and P. J. Somers, *Carbohydrate Chemistry, Specialist Periodical Reports*, Chap 15, Vol. 3; The Chemical Society, London (1969)

[3] R. J. Ferrier, *Advan. Carbohydr. Chem.* **20**, 67 (1965); *Ibid.* **24**, 199 (1969)

[4] B. Fraser-Reid and B. Radatus, *Chem. Commun.* 779 (1970)

[5] B. Fraser-Reid and B. Radatus, *Canad. J. Chem.* **47**, 4095 (1969)
[6] B. Fraser-Reid and B. Radatus, *J. Am. Chem. Soc.* **92**, 6661 (1970)
[7] [a] R. U. Lemieux, E. Fraga and K. A. Watanabe, *Canad. J. Chem.* **46**, 61 (1968);
[b] M. Sharma and R. K. Brown, *Ibid.* **44**, 2825 (1966);
[c] R. J. Ferrier and N. Prasad, *J. Chem. Soc.* 570, 575, 581 (1969)
[8] L. D. Hall and L. F. Johnson, *Tetrahedron* **20**, 883 (1964)
[9] L. D. Hall, *Advan. Carbohydr. Chem.* **19**, 51 (1964)
[10] B. Fraser-Reid and B. Radatus, *Canad. J. Chem.* **48**, 2146 (1970)
[11] F. A. Bovey, *Nuclear Magnetic Resonance Spectroscopy*, p. 134, Academic Press, New York (1969)
[12] E. W. Garbisch, *J. Am. Chem. Soc.* **86**, 5561 (1964)
[13] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959)
[14] J. R. Fletcher and I. O. Sutherland, *Chem. Commun.* 706 (1969); J. E. Anderson, D. L. Griffith and J. D. Roberts, *J. Am. Chem. Soc.* **91**, 6371 (1969)
[15] A. Rauk, E. Buncel, R. Y. Moir and S. Wolfe, *Ibid.* **87**, 5498 (1965)
[16] G. Canalini, G. Maccagnani and F. Tadder, *Tetrahedron Letters* 3035 (1971)