Ring Contraction of Methyl 3-Acetamido-3,6-dideoxy-α-L-glucopyranoside

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Summary Methyl 3-acetamido-3,6-dideoxy-2-*O*-methanesulphonyl-α-L-glucopyranoside, on heating with sodium methoxide in methanol, gives the ring-contracted compound (2) and its (*R*)-diastereoisomer (3).

DURING our work on the partial acylation of methyl 3-acetamido-3,6-dideoxy-α-L- and -D-hexopyranosides[1] we prepared several derivatives with a mesyl group *trans* to the neighbouring acetamido-group. Sugar derivatives of this type furnish[2] products containing epimino- or oxazoline rings upon treatment with sodium methoxide We now report on the reaction of methyl 3-acetamido-3,6-dideoxy-2-*O*-methanesulphonyl-α-L-glucopyranoside[1] (1) with an excess of sodium methoxide in methanol. The mesylate (1) did not react with sodium methoxide at room temperature; after heating under reflux for 6·5 and 8 hrs. the reaction mixture still contained starting material (*ca.* 20 and 7%, respectively) together with compounds (2) {*ca.* 30%, m.p. 114—116°, $[\alpha]_D^{21}$ −63·5 ± 1° ($CHCl_3$)} and (3) {*ca.* 35%, m.p. 141—143°, $[\alpha]_D^{22}$ −56 ± 2° ($CHCl_3$)}, which were separated by chromatography on alumina. The elemental analyses of (2) and (3) were consistent with the formula $C_{10}H_{19}NO_5$, and each contained two methoxy-groups (MeO 26·5%) and an acetamido-group (i.r. spectra). Upon treatment with CH_3I and BaO in dimethylformamide, (2) and (3) furnished, respectively, methyl derivatives (4) (m.p. 115—117°) and (5) (m.p. 104—105°) which were different from methyl 3-acetamido-3,6-dideoxy-2,4-di-*O*-methyl-α-L-glucopyranoside (m.p. 210—211°) or the corresponding mannopyranoside (m.p. 128—130°). With acetic anhydride–pyridine, (2) and (3) afforded, respectively, the acetates (6) (m.p. 76·5—78°) and (7) (m.p. 109—111°). The structure and configuration

of (2) and (3) were assigned on the basis of ^{1}H n.m.r. data. The ^{1}H n.m.r. spectra of compounds (2) and (3) (Tables 1 and 2) confirmed the presence of one acetamido-group and two methoxy-groups. The signals of the amidic protons in both cases formed a broadened doublet with J *ca.* 9·5 Hz. From the elimination of this coupling by means of frequency-swept decoupling experiments, it was possible to find the continuity of vicinal couplings of all protons simultaneously, determining the topology of the C–C bonds. For example, in compound (2) the amidic proton is coupled to the proton of O–CH type (J 9·5 Hz) forming a quartet at 5·05 p.p.m. and exhibiting further coupling (J 6·4 Hz) with a proton forming a triplet of doublets at 2·15 p.p.m. The latter proton must be (according to its chemical shift) bonded to the carbon carrying an oxygen function. It exhibits further couplings with two protons of the O–CH type. One of them formed a doublet at 4·63 p.p.m., the other a multiplet at 3·46 p.p.m. partially coinciding with the signals of the methoxy-groups. On the basis of exchange experiments with deuterioacetic acid, the latter proton was coupled to an OH proton, forming a doublet at 5·00 p.p.m. (J 5·6 Hz) and further to the methine proton of the O–CH–CH$_3$ grouping, forming an octet at 3·75 p.p.m. as shown by tickling experiments. Thus the formal topology of bonds in the compound (2) should be the same as that of a methyl-2,5-dideoxy-2-*C*-(methoxyacetamidomethyl)pentofuranoside. The same conclusion holds for compound (3). From a comparison of the coupling constants of revelant protons of compounds (2) and (3) (Table 2) it follows that the same relative configuration holds for all asymmetric centres on the furanoside ring. Thus the compounds (2) and (3) are C-2 epimers.

This conclusion is in the full agreement with the possible steric course of formation of such ring-contracted products. From the ^{1}H n.m.r. spectra, the glucoside (1) has the favourable 1*C* conformation (J_{12} 3·2, J_{23} 11, J_{34} 9·5, J_{45} 9·6 Hz) with a *trans*-antiparallel relationship between the

TABLE 1.

Proton chemical shifts[a] *of compounds* (2) *and* (3) *and of their acetyl derivatives* (6) *and* (7)

Compound	1-H	2-H	3-H	4-H	5-H	2-H	OH	NH	Ac	OCH_3
(2)[b]	4·63	2·15	3·46	3·75	1·18	5·05	5·00	8·03	1·91	3·21 3·24
(3)[b]	4·70	2·04	3·28	3·71	1·15	4·93	5·01	8·03	1·89	3·17 3·22
(6)[c]	4·87	2·26	4·79	4·21	1·31	5·34	—	7·08	2·01 2·10	3·35 (6H)
(7)[c]	4·94	2·30	4·42	4·18	1·31	5·01	—	6·47	2·07 (6H)	3·36 (6H)

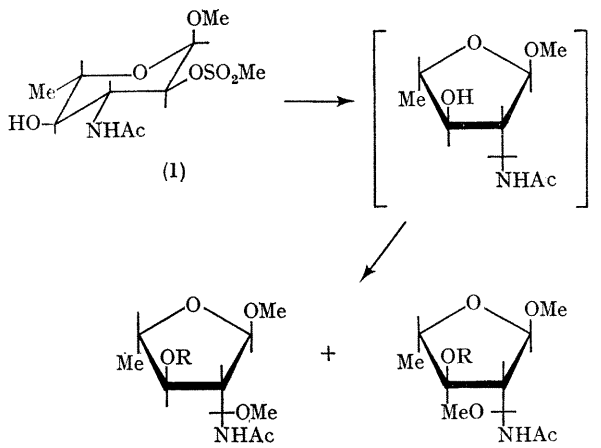
[a] Measured on 100 MHz instrument (Varian HA-100); all shifts as δ (Me_4Si) values from first-order analysis.
[b] In $(CD_3)_2SO$ solution containing a small amount of $CDCl_3$ and using hexamethyldisiloxane (HMDS) as an internal standard; δ (HMDS) = 0·06 p.p.m. relative to Me_4Si.
[c] In $CDCl_3$ solution using Me_4Si as an internal standard.

TABLE 2.

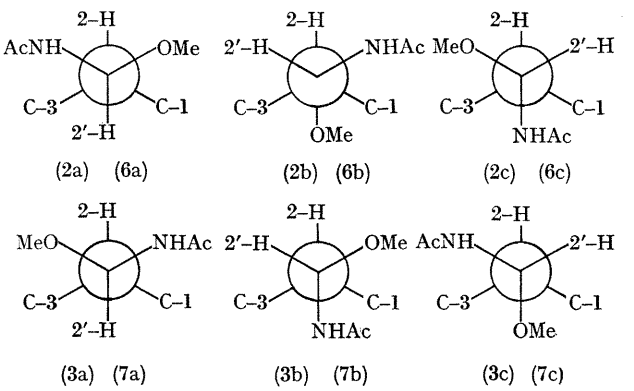
Coupling constants[a] *of protons of compounds* (2) *and* (3) *and of their acetyl derivatives* (6) *and* (7)

Compound	J_{12}	J_{23}	J_{34}	J_{45}	$J_{22'}$	$J_{3'HO}$	$J_{2'NH}$
2	2·5	6·4	7·8	6·1	6·4	5·6	9·5
3	2·2	5·7	7·3	6·2	8·2	5·3	9·5
6	1·3	3·4	6·1	6·4	3·4	—	9·5
7	1·3	2·9	5·3	6·2	9·1	—	9·1

[a] First-order values; *cf.* Table 1.



(2) R=H; (4) R=Me; (6) R=Ac (3) R=H; (5) R=Me; (7) R=Ac



C-2–sulphonate bond and the C-3–C-4 bond. Such a relationship favours an intramolecular displacement of the 2-mesyloxy-group by the C-3–C-4 bond with inversion at C-2.[3] The resulting carbonium ion, of *arabino*-configuration, would react with methoxide ion to give compounds epimeric at C-2, *i.e.* compounds (2) and (3). The alternative *ribo*-configuration can be excluded on the basis of the coupling constant J_{12} of compounds (2) and (3), and (6) and (7), respectively, which indicate a *trans*-disposition of 1-H and 2-H and which are in accordance with n.m.r. data for various arabinofuranosides reported in the literature.[4]

In order to determine the configuration of the new asymmetric centre at C-2′, it is useful to consider the average values of the coupling constants $\langle J_{22'} \rangle$ of all compounds given in Table 2. The average value of $J_{22'}$ is given as $\langle J_{22'} \rangle = \Sigma n_i J_i$, where n_i is the fraction of the staggered rotamers *a*, *b*, and *c*, and J_i the corresponding coupling constant (*trans* or *gauche*[5]). In the case of hydroxy-compounds (2) and (3), the values of $\langle J_{22'} \rangle$ lie in the range of the average value of $\langle {}^3J_{HH} \rangle = 4$—8 Hz predicted by various methods for equal populations of rotamers[6] and it may be only said that the *trans*-form of (3) is more populated than that of (2) in view of the larger value of $\langle J_{22'} \rangle$, 8·2 Hz. After the introduction of the acetyl group into both molecules the situation changes dramatically, and large difference between $\langle J_{22'} \rangle$ values are observed. In the case of compound (6) the small value of $\langle J_{22'} \rangle$ 3·4 Hz indicates a rapid decrease of the population of the *trans*-rotamers, whereas the *trans*-population of (7) is preferred as shown by $\langle J_{22'} \rangle$ 9·1 Hz. Such behaviour allows the assumption that the dipole–dipole repulsion between the acetoxy- and acetamido-groups is dominant. We thus conclude that the rotamers are preferred in which the acetamido-group is twisted as far away as possible from the acetoxy-group in a fixed position at C-3. They are the *gauche*-rotamer (2b) and *trans*-rotamer (3a) or (6b) and (7a), respectively. Thus *S*-configuration is assigned to compounds (2) and (6) and *R*-configuration on at C-2′ in compounds (3) and (7).

Thus, the glucoside (1) gave not the expected epimino- or oxazoline pyranoside derivatives, but methyl 2,5-dideoxy-2-*C*-[(*S*)-methoxyacetamidomethyl]-α-L-arabinofuranoside (2) and its (*R*)-diastereoisomer (3). Similar ring contractions have been reported.[7] It is noteworthy that methyl 6-deoxy-2-*O*-methanesulphonyl-α-D-glucopyranoside, under the basic reaction conditions described above, gave the corresponding 2,3-anhydromannoside.[8] The acetamido-group of (1) probably has an important influence on the stability of the 1*C* conformation, which favours the contraction of the pyranoside ring and which is unfavourable for the displacement of the mesyl group by an acetamido-group.

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