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NMR-STUDIES ON SUGARS AND CYCLANOLS - III[1]
ON THE CONFIGURATION OF C-METHYL-BRANCHED SUGARS AND CYCLANOLS AT THE BRANCHING POINT

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The identification of many branched-chain sugars in antibiotics and bacterial cell walls[2, 3], and C-methyl-inositols in mussel muscles and seaweed[4] has been followed by the chemical synthesis of practically all of these natural compounds. Despite this achievement, however, the assignment of the configuration at the branching-point is still difficult although a number of methods have been employed. Configurational information can be deduced from the IR-frequencies of the OH-group[5], kinetics of periodation[6], chromatographic and electrophoretic mobility in solvents containing borate buffer[6, 7] or phenylboronic acid[5], formation of cyclic carbonates[6], degradative studies[3, 9], partially stereospecific synthesis[7-10], formation of bicyclic hemialdals[6, 7, 11] and from the analogous stereochemical course of hydride reduction of an oxosugar and its reaction with Gignard reagents[12].

In view of the recent application of the nitromethane - dialdehyde cyclization[13] to nitroethane which has led to the synthesis of C-methyl-branched aminosugars[14, 15], nucleosides[16] and aminocyclanols[17], a convenient method for ascertaining the configuration at the tertiary carbon-atom was needed, since the methods mentioned above were either too laborious or not applicable. This communication describes the evaluation of the NMR-substituent resonances at the branching point for assignment of configuration.

1. Chemical Shifts of Acetoxy- and Acetamido-Groups in Relation to Their Configuration.

It has been demonstrated by Lemieux et al.[18] and extended by others[1, 19-24] that the NMR-signals of the methyl protons of ring-acetoxy- or ring-acetamido-groups are primarily dependent on the axial or equatorial orientation of these groups. As a first approximation[25] the signals are independent of their relationship to other groups in the molecule. Fig. 1 summarizes the results in deuterochloroform as solvent recorded from the literature[1, 19-24] and from systematic investigations in our laboratory. Despite the undoubtedly more powerful technique of analyzing the coupling-patterns of the ring protons in sugars and cyclanols,

which due to 100 Mc-spectroscopy and spin decoupling now is possible[26], the signal positions of acetoxy- and acetamido-resonances (Fig. 1) offer a convenient and in most cases surprisingly accurate means for configurational and conformational assignments in the field of sugar and cyclanol chemistry.

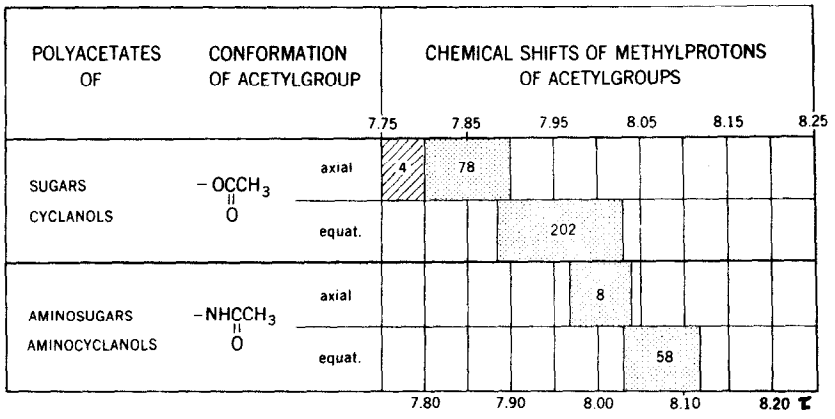


FIG. 1 Relationship between chemical shifts of the methyl resonances of O- and N-acetyl groups and their configuration

2. Chemical Shifts of $C(CH_3)$-Acetoxy Groups.

At the tertiary center of branched-chain sugars and cyclanols an NMR-analysis of coupling patterns is inapplicable for configurational assignments at the branching point. In view of the empirical relationship between the chemical shift of secondary O- and N-acetyl-resonances and their configuration (see Fig. 1), similar relationships would be expected for $C(CH_3)$ OAc- and $C(CH_3)$NHAc-groups, after the influence of the C-methyl group on the chemical shift of the acetyl resonances (as compared with a hydrogen atom) has been taken into account.

From a study of the signal positions of eight C-methyl branched cyclanol acetates in deuterochloroform (Table 1), the equatorial C-methyl protons appeared in the region of 8.53 - 8.63 τ as compared to 8.43-8.57 τ for their epimeric axial counterparts. Though the signals from the latter appeared at slightly higher field, the differences in chemical shift are too small to allow stereochemical conclusions. However, the methyl protons of the acetoxy group at the branching point (Table 2) show differences of about 0.1 p.p.m. between axial (7.93-9.04 τ) and equatorial orientation (8.07-8.12 τ)[27].

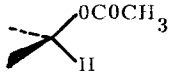
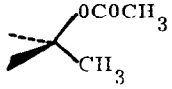
TABLE 1

Chemical Shifts in $CDCl_3$ of tertiary C-Methyl- and Acetoxy Groups.

	t-OAc		t-C-CH_3	
	axial	equat.	axial	equat.
0-Acetyl-trans-1,2-dimethyl-cyclohexanol-1	8.03	-	-	8.53
0-Acetyl-cis-1,2-dimethyl-cyclohexanol-1	-	8.07	8.63	-
Di-0-acetyl-1-C-methyl-trans-cyclohexanediol-1,2	-	8.07	8.56	-
Di-0-acetyl-1-C-methyl-cis-cyclohexanediol-1,2	7.93	-	-	8.53
Tri-0-acetyl-2-C-methyl-trans-cyclohexanetriol-1,2,3	-	8.12	8.58	-
Hexaacetyl-2-C-methyl-epi-inosit	8.04	-	-	8.43
1-Methyl-4-t-butyl-cyclohexanol-1				
trans	-	8.08	8.53	-
cis	8.04	-	-	8.57

These ranges are substantiated by only four examples each, but they suffice to conclude that replacement of a ring hydrogen by a methyl-group causes an upward shift of the acetoxy signal by about 0.1 p.p.m. (Table 2). On the basis of these results, the configuration at the branching point can be deduced from the signal position of the acetoxy group attached to the C-methyl branch of a cyclanol.

TABLE 2

	Conformation of acetoxy group	Absorption range of methyl protons in $CDCl_3$ *)
	axial	7.80 - 7.90 (78)
	equatorial	7.88 - 8.03 (202)
	axial	7.93 - 8.04 (4)
	equatorial	8.07 - 8.12 (4)

*) number of examples in bracketts

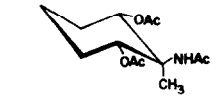
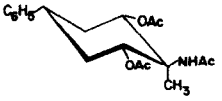
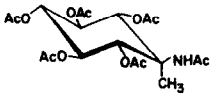
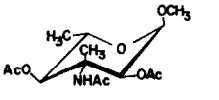
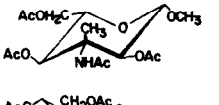
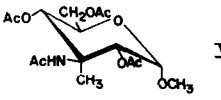
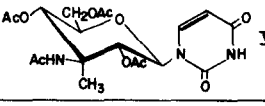
3. Chemical Shifts of C(CH_3)-Acetamido Groups.

A similar study of C-methyl branched aminocyclanols is not possible due to the unavailability of any suitable compounds of known configuration. However, from the results obtained for C(CH_3)-acetoxy groups, a similar upward chemical shift of about 0.1 p.p.m. can be concluded for the methyl protons of acetamido groups, when a methyl-group is substituted for the ring hydrogen. The expected range for axial C-CH_3-acetamido groups would thus be 8.07-8.14τ as compared to 8.13-8.22τ for their equatorial counterparts.

Of the seven C-methyl branched aminocyclanol and aminosugar acetates which have been prepared[14-17] (Table 3), and whose configuration at the branching point had not been assigned,

TABLE 3

CHEMICAL SHIFTS IN $CDCl_3$ OF TERTIARY C-METHYL AND ACETAMIDO GROUPS

COMPOUND	CHEMICAL SHIFTS tert.CH_3	NHAc	CONFORMATION
Di-O-acetyl-2-acetamido-2-C-methyl-cyclohexanediol-1,3 (17)	8.68	8.17	 I
Di-O-acetyl-2-acetamido-2-C-methyl-5-phenyl-cyclohexanediol-1,3 (17)	8.63	8.19	 II
Penta-O-acetyl-1-acetamido-1-C-methyl-1-deoxy-inositol (17)	8.57	8.20	 III
1-O-Methyl di-O-acetyl-3-acetamido-3,6-dideoxy-3-C-methyl- α -L-hexopyranoside (14)	?	8.15	 IV
1-O-Methyl tri-O-acetyl-3-acetamido-3-deoxy-3-C-methyl- α -L-hexopyranoside (15) β-L	8.45	8.17	 V
α-D	8.53	8.17	 VI
1-(Tri-O-acetyl-3'-acetamido-3'-deoxy-3'-C-methyl-β--D-hexopyranosyl)-uracil (16)	8.50	8.15	 VII

the acetamido-signals appear within the very small range of 0.05 p.p.m. This proves their identical stereo-chemical orientation and, on the basis of their chemical shifts (8.15-8.20 τ) strongly indicates an equatorial acetamido group in each case, allowing the configurational assignments at the branching point for compounds I-VII as indicated in Table 3.

Since all compounds (I-VII) were prepared by cyclization of a dialdehyde with nitroethane[14-17], it can be concluded that the stereochemical course of the nitroethane cyclization proceeds in an analogous fashion to the dialdehyde-nitromethane cyclization, the nitro group preferentially if not exclusively attaining the equatorial position in the cyclization step.

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25. A detailed discussion of the data of Fig. 1 in view of the scope and limitations for deducing configurations will be published elsewhere.

26. See i.e. R.U. Lemieux and J.D. Stevens, Canad. J. Chem. 44, 249 (1966); G.E. McCasland, S. Furuta, L.F. Johnson and J.N. Shoolery, J. Org. Chem. 29, 2354 (1964).

27. In the case of two C-methyl branched sugars tertiary acetoxy resonances were found at 7.89 and 8.01 τ (12). These values however cannot be compared with the data in Table 1 due to the presence of large vicinal substituents other than OAc or NHAc (benzamido groups).