

163. *Favoured Ring Forms in Acetals of the Polyhydric Alcohols.*

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Published data concerning the condensations of polyhydric alcohols with acetaldehyde, benzaldehyde, and formaldehyde are reviewed, and rules are presented which enable the products resulting from such condensations to be predicted. The graded hydrolysis and acetolysis of acetals are discussed in the light of these rules. A comment is made on the epimerisation of dimethylene acetals of saccharic acids.

WE have recently reviewed published data on the synthesis and structural analysis of cyclic acetals and ketals derived from the polyhydric alcohols, and, on the basis of the information thus collected, we now present certain "rules," which enable the pattern of condensation between a given carbonyl compound and a given polyhydric alcohol to be predicted. It has long been known that the course of such a reaction is determined both by the relative configurations of the hydroxyl groups in the polyhydric alcohol (cf. the methylene derivatives of sorbitol, dulcitol, and mannitol) and by the structure of the carbonyl component (cf. the methylene and isopropylidene derivatives of mannitol).

In order to simplify the presentation and discussion of these rules, a code system will be introduced, whereby the position and size of an acetal ring can be indicated precisely. The Greek letters, α , β , and γ , will signify the relative positions, along the carbon chain of the polyhydric alcohol, of the two hydroxyl groups engaged in the cyclisation, and C and T will indicate whether these two groups are disposed *cis* or *trans* in the usual Fischer projection formula; C and T will be required only when *both* alcohol groups are secondary. Thus, a system in which an alkylidene residue spans two secondary hydroxyl groups, located on adjacent carbon atoms and having a *trans*-orientation, contains an α T-ring, whereas a β -ring is present when one of the alcohol groups concerned is primary and the other is situated on the β -carbon atom.

A study of the methylene acetals of proven structure derived from dulcitol, mannitol, sorbitol, and ribitol enabled Hann and Hudson (*J. Amer. Chem. Soc.*, 1944, **66**, 1909) to reach certain conclusions, which, when expressed in terms of our code, were as follows: (a) a β C-ring is favoured, but a β T-ring is not; (b) a β -ring is favoured; (c) a β C-ring is preferred to a β -ring; (d) a γ T-ring is favoured, but a γ C-ring is not; (e) an α -ring may be formed when a β -ring is not permissible. Later, Ness, Hann, and Hudson (*J. Amer. Chem. Soc.*, 1948, **70**, 765) added a rider to the effect that a γ T-ring (previously believed, from considerations of the behaviour of methylene acetals during acetolysis, to be highly favoured) may not be formed when β - and β C-rings also are permissible. The American workers observed, too, that these rules were compatible with the data then available for benzylidene acetals of the polyhydric alcohols. The Hann-Hudson rules have long been recognised as being an outstanding contribution in this field, and have been of great value in the interpretation of the problems of acetal formation and in the prediction of the structures of acetals of the polyhydric alcohols; their applications are far too well known to require enumeration here.

In the light of all the relevant information concerning the acetals of the tetrityls and their higher homologues which has been garnered since the introduction of the above rules, it is now possible to extend them to cover virtually all known cases of the formation of benzylidene, ethylidene, and methylene derivatives of the polyhydric alcohols. The extended rules are: (1) the first preference is for a β C-ring; (2) the second for a β -ring; (3) the third for an α -, α T-, β T-, or γ T-ring; (4) in methylenation, a β T-ring takes precedence over an α T- or a γ T-ring; (5) in benzylidenation and ethylidenation, an α T-ring takes precedence over a β T- or a γ T-ring; (6) rules (4) and (5) may not apply when one (or both) of the carbon atoms carrying the hydroxyl groups concerned is already part of a ring system.

Rule (5) is to be regarded as tentative because of the small number of examples upon which it can be based. We know of no case in which the condensation of an aldehyde with a polyhydric alcohol affords a γ -, α C-, or γ C-ring. It should be noted that the participation of two alcohol groups, possessing a *trans*-orientation, in acetal formation is made possible by free rotation within the carbon skeleton of the polyhydric alcohol, a situation which is not encountered when the carbon atoms carrying these hydroxyl groups are already part of a ring system; it is for this reason that it is necessary to include rule (6).

In Table I are listed, with four exceptions, all the benzylidene, ethylidene, and methylene acetals of known structure, derived from the tetrityls and their higher homologues, of which we have a record; every one of these 50 compounds complies with the above modified rules. A decision whether rule (6) should, or should not, be applied is not necessary in any of the cases cited, but the question does arise in the four exceptions, namely, in the syntheses of 1:3-2:5-dimethylene rhamnitol (Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1945, **67**, 1800), 3:5-benzylidene-1:4-anhydrosorbitol (Bashford and Wiggins, *J.*, 1948, 299), 3:5-benzylidene 6-chloro-1:4-anhydro-6-deoxysorbitol (Montgomery and Wiggins, *J.*, 1948, 237), and 3:5-benzylidene 6-bromo-1:4-anhydro-6-deoxysorbitol (Overend, Montgomery, and Wiggins, *J.*, 1948, 2201).

The rules predict that allitol, dulcitol, and iditol should form diacetals, but not triacetals, with the three aldehydes under consideration, and in fact no triacetals have yet been prepared from the first two of these hexitols. However, there were reports in the early literature that iditol affords a tribenzylidene (last reference, *Ann. Chim. Phys.*, 1907, **10**, 450) and a trimethylene derivative (last reference, *Compt. rend.*, 1906, **143**, 352). In view of the failure of Hann and Hudson (*J. Amer. Chem. Soc.*, 1945, **67**, 602) to repeat the preparation of the latter compound, these reports should be discounted until further evidence in support of them is forthcoming.

A second point arising out of Table I concerns the methylene derivatives of talitol. Our rules indicate that talitol should furnish 2:4-methylene, 1:3-2:4-dimethylene, and 1:3-2:4-5:6-trimethylene derivatives, and indeed Hann, Haskins, and Hudson (*ibid.*, 1947, **69**, 624) have prepared the mono- and tri-acetals, but, in place of the predicted diacetal, they obtained two isomers, which they thought to be 2:3:4:5-* and 1:3-4:6-dimethylene talitol. We believe that the former compound (yield, 2%) was really 2:4-3:5-dimethylene allitol and that it arose from a trace of allitol impurity in the syrupy sample of talitol employed in the synthesis. Our reasons are as follows: (1) the direct methylenation of allitol is known to yield the 2:4-3:5-dimethylene derivative (Wolfrom, Lew, and Goepf, *ibid.*, 1946, **68**, 1443); (2) the D-talitol sample used had been prepared from α -D-altropyranose penta-acetate by treatment with sodium methoxide in methanol and subsequent hydrogenation, so epimerisation may well have occurred to a small extent; and (3) the melting point and specific rotation of the "dimethylene talitol," of its diacetate, and of its ditoluene-*p*-sulphonate, agree well with those recorded for the corresponding members of the allitol series (cf. Hann, Haskins, and Hudson, *loc. cit.*; Wolfrom, Lew, and Goepf, *loc. cit.*). Hudson and his colleagues noted that the data upon which they assigned the 1:3-4:6-structure to the second dimethylene hexitol did not exclude the 1:2:4:6- and 1:3:5:6-structures, but all of these possibilities are at variance with the modified rules. Since this compound is, as far as we are aware, the only one which definitely infringes the rules, a more detailed study of its structure would be desirable.

* In this paper the form "2:3:4:5-structure" has been used whenever the evidence available did not serve to distinguish between the 2:3-4:5-, 2:4-3:5-, and 2:5-3:4-structures.

TABLE 1. Syntheses of benzylidene, ethylidene, and methylene acetals which conform with the modified rules.

Parent hydroxy-compound	Types of rings formed	Acetal derivative	Reference
Arabitol	β	1:3-Benzylidene	<i>J. Amer. Chem. Soc.</i> , 1943, 65 , 1663
" , 1:5-dibenzoyl	αT	2:3-Benzylidene	" " "
Ribitol	βC	2:4-Methylene	<i>Ibid.</i> , 1944, 66 , 1906
"	$\beta C, \beta$	1:3-2:4-Dimethylene	" " "
Xylitol	—	1:2:3:4-Dibenzylidene	" 1947, 69 , 1667
" , 2:4-methylene	$\beta C, \beta$	1:3-2:4-Dimethylene	" 1944, 66 , 670
" , 1-deoxy-2:4-methylene	β	1:3-Benzylidene	" 1950, 72 , 561
Allitol	β	3:5-Methylene	" " "
Dulcitol	$\beta C, \beta C$	2:4-3:5-Dimethylene	" 1946, 68 , 1443
"	β, β	1:3-4:6-Dibenzylidene	" 1942, 64 , 132
"	β, β	1:3-4:6-Dimethylene	" 1942, 64 , 986
" , 1:6-dibenzoyl	—	2:3:4:5-Dibenzylidene	" 1942, 64 , 136, 137
" , 1:6-ditryl	—	2:3:4:5-Dibenzylidene	" 1939, 61 , 1827
" , 2:5-dibenzyl	β, β	1:3-4:6-Dimethylene	" 1942, 64 , 986
Iditol	$\beta C, \beta C$	2:4-3:5-Dimethylene	" 1945, 67 , 602
Mannitol	$\beta, \beta, \gamma T$	1:3-2:5-4:6-Triethylidene	<i>J.</i> , 1951, 2708
"	β, β	1:3-4:6-Dimethylene	<i>J. Amer. Chem. Soc.</i> , 1943, 65 , 2215
" , 1:6-dibenzoyl	$\beta, \beta, \gamma T$	1:3-2:5-4:6-Trimethylene	" " "
"	αT	3:4-Benzylidene	<i>Ber.</i> , 1933, 66 , 931
"	—	2:3:4:5-Dibenzylidene	<i>J. Amer. Chem. Soc.</i> , 1943, 65 , 1419
"	$\beta T, \beta T$	2:4-3:5-Dimethylene	<i>J.</i> , 1944, 58, 364
" , 1:2:5:6-tetra-benzoyl	αT	3:4-Benzylidene	<i>Ber.</i> , 1933, 66 , 931
"	αT	3:4-Ethylidene	<i>J.</i> , 1951, 2708
" , 1:6-dibenzoyl 3:4-benzylidene	γT	2:5-Methylene	<i>J. Amer. Chem. Soc.</i> , 1943, 65 , 2215
" , 1:6-dibenzoyl 2:5-methylene	αT	3:4-Benzylidene	" " "
" , 1:6-dibromo-1:6-dideoxy	$\beta T, \beta T$	2:4-3:5-Dimethylene	<i>J.</i> , 1948, 2201
" , 1:6-dichloro-1:6-dideoxy	αT	3:4-Ethylidene	<i>J.</i> , 1946, 384
"	—	2:3:4:5-Diethylidene	" " "
" , 1:6-dideoxy-1:6-di-iodo	$\beta T, \beta T$	2:4-3:5-Dimethylene	<i>J. Amer. Chem. Soc.</i> , 1943, 65 , 67
" , 1:6-dimethyl	$\beta T, \beta T$	2:4-3:5-Dimethylene	<i>J.</i> , 1946, 384
Sorbitol	βC	2:4-Benzylidene	<i>Ber.</i> , 1935, 68 , 1582
"	$\beta C, \beta$	1:3-2:4-Dibenzylidene	<i>J. Amer. Chem. Soc.</i> , 1944, 66 , 837
"	$\beta C, \beta, \alpha$	1:3-2:4-5:6-Tribenzylidene	" " "
"	$\beta C, \beta$	1:3-2:4-Diethylidene	<i>Ibid.</i> , 1947, 69 , 849
"	$\beta C, \beta, \alpha$	1:3-2:4-5:6-Triethylidene	<i>J.</i> , 1948, 1933
"	$\beta C, \beta$	1:3-2:4-Dimethylene	<i>J. Amer. Chem. Soc.</i> , 1944, 66 , 665
"	$\beta C, \beta, \alpha$	1:3-2:4-5:6-Tri-methylene	<i>J.</i> , 1944, 517
" , 1:6-dibenzoyl	$\beta C, \beta T$	2:4-3:5-Dibenzylidene	<i>J.</i> , 1946, 488
" , 1:6-dichloro-1:6-dideoxy	$\beta C, \beta T$	2:4-3:5-Dimethylene	<i>J. Amer. Chem. Soc.</i> , 1944, 66 , 1898
" , 5:6-dimethyl	—	2:3:4:5-Dibenzylidene	<i>J.</i> , 1948, 237
6-Deoxysorbitol	$\beta C, \beta$	1:3-2:4-Dimethylene	<i>J.</i> , 1944, 517
" , 2:4-methylene 1-tosyl	βT	3:5-Methylene	<i>J. Amer. Chem. Soc.</i> , 1944, 66 , 1235
Talitol	βC	2:4-Methylene	<i>Ibid.</i> , 1947, 69 , 624
"	$\beta C, \beta, \alpha$	1:3-2:4-5:6-Tri-methylene	" " "
Gluco-gulo-heptitol	βC	3:5-Benzylidene	<i>Ibid.</i> , 1946, 68 , 1769
"	βC	3:5-Methylene	" " "
Perseitol	β, β	1:3-5:7-Dibenzylidene	<i>Ibid.</i> , 1948, 70 , 765
"	β, β	1:3-5:7-Dimethylene	" " "

It should be mentioned that the benzylidenation of 1:6-dibenzoyl dulcitol (Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 136, 137) and the ethylidenation of 1:6-dichloro-1:6-dideoxymannitol (Wiggins, *J.*, 1946, 384) both afford two isomeric

diacetals, but in neither case is it yet known whether they differ in the position or in the stereoisomerism of the acetal groups.

An alternative way of assessing the relative stabilities of acetal groups of different types is to consider the products resulting when di- and tri-acetals are submitted to partial hydrolysis with aqueous acid. From the list of such cases given in Table 2, it can be seen that the order of stability is: $\beta C > \beta > \alpha$ and γT , which is precisely the order already deduced. (N.B. α - and γT -Rings cannot occur together in any acetal derived from a polyhydric alcohol containing fewer than seven carbon atoms.)

TABLE 2. Graded acidic hydrolysis of benzylidene, ethylidene, and methylene acetals.

Parent compound	Order of ring scission:			Reference
	1st	2nd	3rd	
1 : 3-2 : 4-5 : 6-Tribenzylidene sorbitol	α	β	βC	<i>J. Amer. Chem. Soc.</i> , 1944, 66 , 837
1 : 3-2 : 5-4 : 6-Triethylidene mannitol	γT	β	β	<i>J.</i> , 1951, 2708
1 : 3-2 : 4-Diethylidene sorbitol	β	βC	—	<i>J.</i> , 1948, 1933
2 : 4-3 : 5-Dimethylene allitol	βC	βC	—	<i>J. Amer. Chem. Soc.</i> , 1946, 68 , 1443
1 : 3-2 : 4-5 : 6-Trimethylene sorbitol	α	β	βC	<i>J.</i> , 1944, 517

TABLE 3. Graded acetolysis of methylene acetals.

Parent compound		Positions of acetal groups	Rings broken	Rings retained	References (all in <i>J. Amer. Chem. Soc.</i>)
Alcohol component					
Ribitol		1 : 3-2 : 4	β	βC	1944, 66 , 1906
Xylitol		2 : 4-3 : 5	β	βC	1944, 66 , 670
" , 1-mesyl		2 : 4-3 : 5	β	βC	1950, 72 , 561
" , 1-tosyl		2 : 4-3 : 5	β	βC	" "
2 : 5-Dibenzoyl dulcitol		1 : 3-4 : 6	β, β	None	1943, 65 , 2215
Iditol		2 : 4-3 : 5	None	$\beta C, \beta C$	1945, 67 , 602
Mannitol		1 : 3-2 : 5-4 : 6	β, β	γT	1943, 65 , 2215
" , 6-deoxy		1 : 3-2 : 5	β	γT	1945, 67 , 1800
Sorbitol		1 : 3-2 : 4	β	βC	1944, 66 , 665
"		2 : 4-3 : 5	βT	βC	1944, 66 , 1898
"		1 : 3-2 : 4-5 : 6	α, β	βC	1944, 66 , 665
" , 6-deoxy		1 : 3-2 : 4	β	βC	1944, 66 , 1235
Talitol		1 : 3-2 : 4-5 : 6	α, β	βC	1947, 69 , 624
" , 2 : 5-diacetyl		1 : 3-4 : 6(?)	β, β	None	" "

TABLE 4. Syntheses of isopropylidene derivatives of the polyhydric alcohols.

Parent hydroxy-compound	isoPropylidene deriv.	Reference
Xylitol	3 : 5(?)	<i>Chem. Zvesti</i> , 1949, 3 , 146
"	1 : 2-3 : 5(?)	" "
"	2 : 3 : 4 : 5(?)	<i>J. Amer. Chem. Soc.</i> , 1944, 66 , 73
Dulcitol	2 : 3 : 4 : 5*	<i>Ibid.</i> , 1939, 61 , 611, 2432
"	2 : 3 : 5 : 6*	" "
Mannitol	1 : 2	<i>Ber.</i> , 1933, 66 , 1394
"	1 : 2-5 : 6	<i>J. Amer. Chem. Soc.</i> , 1939, 61 , 2607
"	1 : 2-3 : 4-5 : 6	<i>J.</i> , 1946, 13
" , 1 : 6-dibenzoyl	3 : 4	<i>Ber.</i> , 1932, 65 , 1055
" , 1 : 6-dichloro-1 : 6-dideoxy	3 : 4	<i>J.</i> , 1946, 384
"	2 : 3 : 4 : 5	" "
" , 1 : 2 : 5 : 6-tetrabenzoyl	3 : 4	<i>Ber.</i> , 1933, 66 , 931
Sorbitol	1 : 2	<i>J. Amer. Chem. Soc.</i> , 1950, 72 , 2404
"	1 : 2-5 : 6	" "
"	1 : 2-3 : 4-5 : 6	" "

* Certain experiments reported by Pizzarello and Freudenberg (*J. Amer. Chem. Soc.*, 1939, **61**, 611) still require to be interpreted in the light of these structures.

One might suppose that the limited acetolysis of methylene acetals with an ice-cold mixture of acetic anhydride, acetic acid, and 1—2% sulphuric acid, a reaction which has been used so effectively by Hudson and his colleagues in their studies of the structures of these acetals, might also confirm this order of stability, and, up to a point, this is so, for examples are given in Table 3 of cases in which α -, β -, and βT -rings are broken before

β C-rings; however, the expected scission of a γ T-ring in preference to a β -ring does not occur. As was pointed out by Hudson and his co-workers (references in Table 3), it seems that the major factor governing the rate of acetolysis of a methylene compound is whether or not the methylene group is engaged at a primary position. Two compounds in which this over-riding factor is eliminated provide an interesting contrast, when subjected to acetolysis under identical conditions. Thus, 2 : 4-3 : 5-dimethylene iditol is not attacked (both β C-rings stable), whereas 2 : 4-3 : 5-dimethylene sorbitol suffers scission of the β T-ring, but not of the β C-ring.

The foregoing observations would seem to have a direct bearing on the demonstration by Haworth, Jones, Stacey, and Wiggins (*J.*, 1944, 61, 364) that the 2 : 4-3 : 5-dimethylene derivatives of D-glucosaccharic and D-mannosaccharic acids can both be epimerised to 2 : 4-3 : 5-dimethylene L-idosaccharic acid. In the former case, inversion occurs at $C_{(5)}$ (in the β T-ring), but not at $C_{(2)}$ (in the β C-ring); in the latter case, there is inversion at both $C_{(2)}$ and $C_{(5)}$ (both in β T-rings). The product, which presumably is stable under these conditions, possesses two β C-rings.

Current knowledge regarding favoured ring structures in isopropylidene derivatives of the polyhydric alcohols leaves much to be desired, for the information available is meagre (see Table 4), and, moreover, is contradictory as far as the condensations of xylitol and dulcitol with acetone are concerned. Nevertheless, it is clear that the above rules do not apply, and that there is a marked preference for the formation of five-membered rings. We have no record of a condensation between acetone and a derivative of a polyhydric alcohol yielding a seven-membered ring; six-membered rings are rare but they probably exist in 2 : 3 : 4 : 6-diisopropylidene 1 : 5-anhydro-D-mannitol (*Adv. Carbohydrate Chem.*, 1950, 5, 191) and in the diisopropylidene derivative of 2 : 4-benzylidene D-sorbitol (*Ber.*, 1935, 68, 18, 1377). All that can be said with assurance at present is that α - and α T-rings are permissible, and that, in synthesis, the former takes precedence over the latter. If the graded acidic hydrolysis of 1 : 2-3 : 4-5 : 6-triisopropylidene mannitol (*Ber.*, 1934, 67, 1969; *Helv. Chim. Acta*, 1934, 17, 1574; *J.*, 1946, 13) be any guide, an α -ring is hydrolysed more readily than an α T-ring. The hydrolysis of 1 : 2-3 : 4-5 : 6-tricyclohexylidene D-mannitol follows the same course as that of the isopropylidene analogue (*J.*, 1950, 786).

In conclusion, it may be noted that the carbonyl compounds can be divided, on the basis of the ring types favoured in their condensations with the polyhydric alcohols, into two groups, one including benzaldehyde, acetaldehyde, and formaldehyde, and the other, acetone and cyclohexanone. It is too early to say whether this present sharp division between aldehydes and ketones is purely fortuitous or whether it is likely to be maintained when the condensation products derived from other carbonyl compounds are subjected to structural analysis.

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