The Influence of Steric Factors in Diazoalkane–Pyranosid-2-ulose Reactions

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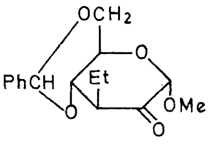
Summary Comparison of the products from reactions of diazomethane and diazoethane with pyranosid-2-uloses provides new information about the importance of steric factors in diazoalkane–cyclic ketone interactions; the reaction of diazoethane with pyranosid-2-uloses is a potentially useful route to higher branched-chain sugars.

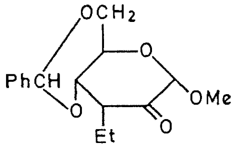
THE importance of steric effects in product control of reactions between diazoalkanes and cyclic ketones is well illustrated by a comparison of the reactions of diazomethane and diazoethane with methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-*arabino*- (**1**) and -*ribo*-hexopyranosid-2-ulose (**2**).[1] Addition of ethereal diazomethane to a solution of (**1**) in methanol afforded the spiro-epoxides (**3**) and (**4**) and the ring-expansion product (**5**). The configurations of the spiro-epoxides were established by lithium aluminium hydride reduction to 2-*C*-methyl derivatives and thence by an unequivocal method.[1] The structure of (**5**) follows from analysis of its n.m.r. parameters (Table) which are consistent with the structure and conformation depicted. This result confirms previous assumptions, based on analogy with other 1,2-nucleophilic displacement reactions, that the migrating centre in diazomethane ring expansions retains its configuration.[2]

The reaction of diazoethane and (**1**), in contrast to the corresponding diazomethane reaction, afforded no spiro-epoxides but only the three seven-membered-ring products (**6**), (**7**), and (**8**), whose structures and conformations follow from their n.m.r. parameters (Table). The following explanation for these differences is offered.[3] The first stage in the reaction between diazoalkanes and cyclic ketones is usually considered to be a nucleophilic addition from the least hindered side of the molecule to form a zwitterionic intermediate. Since equatorial addition of diazomethane to (**1**) is clearly favoured as indicated by the preponderance of the spiro-epoxide (3) and in the absence of evidence to the contrary for diazoethane this common zwitterionic intermediate may be depicted as (**10**,) (**11**), or (**12**). The second stage of the reaction is the nucleophilic displacement of nitrogen by oxygen or by the electrons of a C–C bond. Since displacement of nitrogen requires a *trans*-coplanar transition state, the favoured conformation for the intermediate which leads to (3) must be (**11**; R^1 = R^2 = H) and the intermediate leading to (5) must be (**10**; R^1 = R^2 = H). To explain the gross differences between the diazomethane and diazoethane reactions it is necessary to postulate that the transition state (**11**) when R^1 = Me, R^2 = H or R^1 = H, R^2 = Me is less favourable than the transition states (**10**) and (**12**).

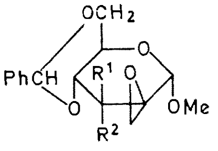
When R^1 = Me there is obviously a strong non-bonded interaction with the C-3 ethyl substituent but why the conformation (**11**) should be less favourable than (**10** or (**12**) when R^2 = Me is less clear. The formation of products (**6**), (**7**), and (**8**) and the absence of (**9**) follows from a consideration of the transition states (**10**) and (**12**). The most unfavourable intermediate is (**10**; R^1 = H, R^2 = Me) where



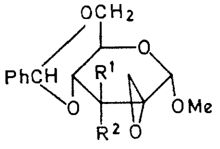
(1)



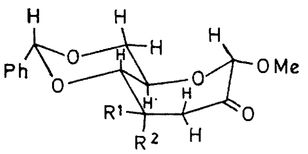
(2)



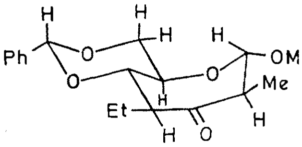
(3) R^1 = Et, R^2 = H. 65%
(13) R^1 = H, R^2 = Et. 27%
m.p. 104–107°



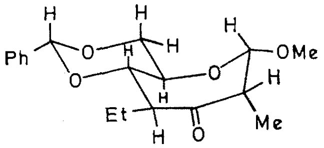
(4) R^1 = Et, R^2 = H. 8%
m.p. 62–64°
(14) R^1 = H R^2 = Et. 41%
m.p. 70°



(5) R^1 = Et, R^2 = H. 18%
m.p. 174°
(15) R^1 = H, R^2 = Et. 16%
m.p. 125–130°



(6) 36%. m.p. 202–203°



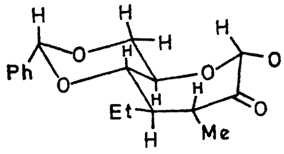
(7) 39% m.p. 75°

TABLE

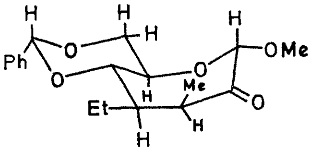
	1-H	2-H	3-H	3′-H	4-H	
(5)	4·76	—	2·42	2·73	1·35	$J_{3,4}$ 2·5, $J_{3',4}$ 11·8, $J_{4,5}$ 9, $J_{5,6}$ 9 Hz
(6)	4·2	3·15	—	—	2·72	$J_{1,2}$ 8, $J_{4,5}$ 9·8 Hz
(7)	4·43	2·85	—	—	2·6	$J_{1,2}$ 1·9, $J_{4,5}$ 9 Hz
(8)	4·78	—	3	—	1·8	$J_{3,4}$ *ca.* 9 Hz

N.m.r. spectra were measured at 100 MHz. Coupling constants are in Hz and chemical shifts are expressed as δ values in p.p.m. Only parameters directly relevant to structural assignments are recorded. It will be noticed that 1-H in (5) and (8) where the carbonyl function is at C-2 resonates at lower field than in (6) and (7) where the C=O group is at C-3. Conversely 4-H is at lower field in (6) and (7) when immediately adjacent to the C=O group than when the C=O is at C-2.

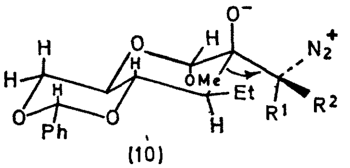
there is a strong non-bonded interaction between the methyl and the C-3 ethyl groups and it is this intermediate which would lead to (**9**). If the initial reaction between (**1**) and diazoethane gave an axial addition product a consideration of the possible transition states suggests (**7**) and (**8**) would be favoured products and that little (**6**) or (**9**) would be formed. The presence of an appreciable quantity of (**6**) as a reaction product is therefore indirect evidence that equatorial addition occurs preponderantly.



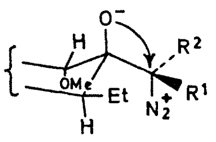
(8) 11% m.p. 143-144°



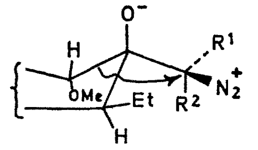
(9) Not detected



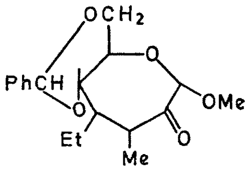
(10)



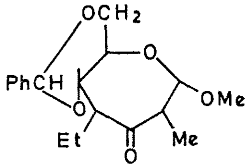
(11)



(12)



(16) 49% m.p. 101-102°
(16a) 5%



(17) 23% m.p. 112-113°

Perhaps most indicative of the importance of steric factors in such reactions is the result that the preponderant products result from nucleophilic attack by the C-1–C-2 bond which carries two oxygen atoms at C-1. This bond is much less nucleophilic than the C-2–C-3 bond and previous evidence had indicated that in cyclic ketones where the 2-position carries electronegative substituents ring expansion is inhibited.[4]

Quite a different pattern was observed for reactions between (**2**) and diazoalkanes. With diazomethane, (**2**) afforded similar yields of the spiro-epoxides (**13**) and (**14**), and some ring expansion product (**15**). From the (**2**)–diazoethane reaction the preponderant product was the 3-*C*-methyl derivative (**16**) ($J_{3,4}$ 2 Hz). Also isolated were (**16a**) ($J_{3,4}$ 4·7 Hz) and the 2-*C*-methyl derivative (**17**) ($J_{1,2}$ 1·5 Hz). The configurations and conformations of this series of compounds are not immediately apparent from the n.m.r. parameters. Assuming both axial and equatorial addition of diazoethane to (**2**), it is obvious from a consideration of possible transition states that the formation of (**16**), (**16a**), (**17**), and the C-2 epimer of (**17**) may be equally favoured sterically and thus that the product ratios will probably depend on the relative nucleophilicity of the C-1–C-2 and C-2–C-3 bonds and on the initial direction of addition of diazoethane to (**2**).

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[1] T. D. Inch and G. J. Lewis, unpublished results.

[2] D. J. Cram in "Steric Effects in Organic Chemistry," ed. M. S. Newman, Wiley, New York, 1956, ch. 5.

[3] Similar explanations of other ring expansion reactions have been published, *e.g.* (a) N. J. Turro and R. B. Gagosian, *Chem. Comm.*, 1969, 949; (b) J. A. Marshall and J. J. Partridge, *J. Org. Chem.*, 1968, **33**, 4090.

[4] C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, 1968, p. 81; G. W. Cowell and A. Ledwith, *Quart. Rev.*, 1970, **24**, 119.