Evidence for Equatorial Approach by Diazomethane to the Carbonyl Group of 5α-3-Oxosteroids

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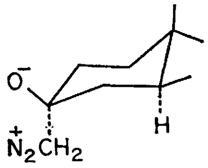
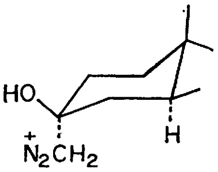
Summary Comparisons of the diazomethane and Tiffeneau–Demjanov ring expansion reactions on 17β-hydroxy-5α-androstan-3-one and its derivatives have indicated equatorial approach of diazomethane to the C-3 carbonyl and have confirmed that for the corresponding addition of cyanide ion under equilibrating conditions the axial cyano-epimer expected to be favoured thermodynamically is the predominant product.

DURING previous investigations on A-homo-steroids prepared by diazomethane ring enlargement of 3-oxosteroids[1] we became interested in ascertaining whether the proportions formed of the two possible A-homo-ketones reflected the direction of attack of diazomethane on the C-3 carbonyl group. Relatively few data[2] are available on the preferred pathways of addition of nucleophiles to carbonyl groups of cyclohexanones and related ring systems. We now present evidence which indicates that diazomethane approaches the carbonyl group equatorially and that, for cyanide ion addition under conditions of thermodynamic control, the axial cyano-product expected from conformational free energy considerations is in fact much preferred.

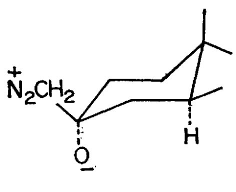
The initial intermediates resulting from such axial or equatorial diazomethane approach would be (**1**) and (**3**) respectively. As there appeared to be no way of examining these or subsequent transient intermediates[3] directly we turned our attention[1] towards the closely related Tiffeneau–Demjanov rearrangement[4] in which the amine precursors of the analogous intermediates (**2**) and (**4**) were isolable and for which it is well established that such epimeric intermediates do give rise to different ratios of ring-expanded products.[5]



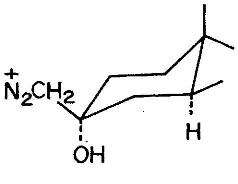
(**1**)



(**2**)

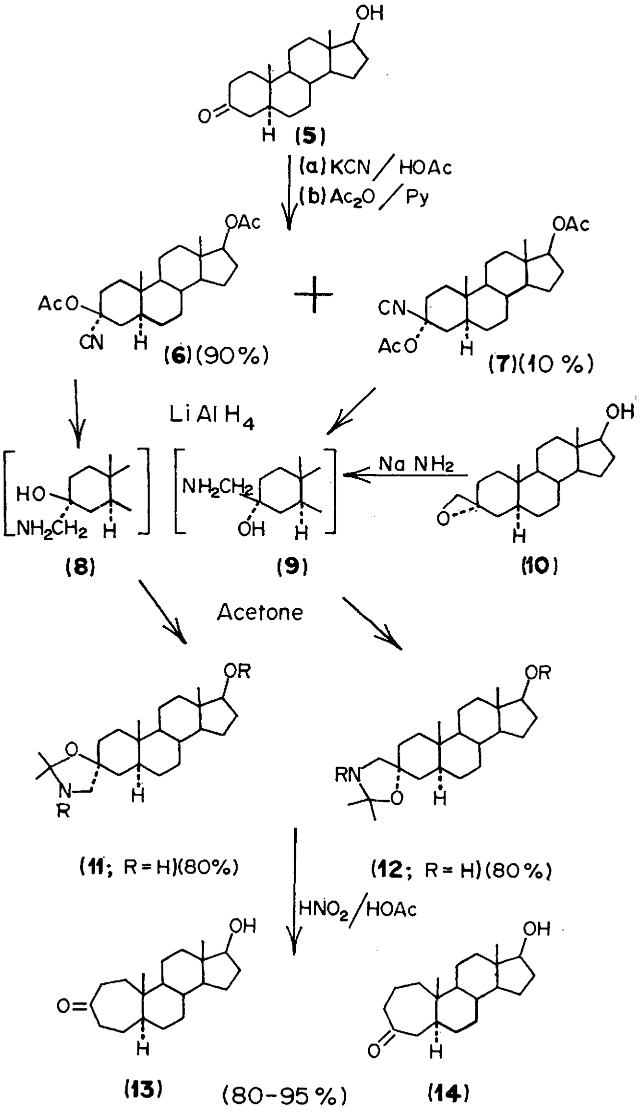


(**3**)



(**4**)

The validity of the approach was evaluated on a representative 3-oxosteroid, 17β-hydroxy-5α-androstan-3-one (**5**) and the sequence of reactions used to prepare the epimeric Tiffeneau–Demjanov intermediates (**8**) and (**9**) are outlined in the Scheme.‡ The two cyanohydrins formed on treatment of (**5**) with potassium cyanide in acetic acid[6] were not isolated but were converted directly into a mixture of the more stable diacetate epimers (**6**) m.p. 207—208° (lit.[6] m.p. 198—200°) and (**7**) m.p. 185—186°§ in the ratio of 9 : 1 respectively. The cyanohydrin diacetates (**6**) and (**7**) were then reduced separately to the corresponding aminomethyl alcohols (**8**) and (**9**) which were isolated[7] as the



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‡ Satisfactory elemental analyses were obtained for all stable new compounds. Spectral data for all compounds were in accord with the structures assigned.

§ Previous workers[6,7] on these and related compounds did not isolate this minor epimer.

acetonides (**11**; R = H) m.p. 165—167° and (**12**; R = H) m.p. 111—113°. The latter compounds were further characterized by acetylation to give (**11**; R = Ac) m.p. 187—188° and (**12**; R = Ac) m.p. 131—132°.

The C-3 stereochemistries of (**6**) and (**7**) were assigned initially from a consideration of the conformational free energy differences of hydroxy (0·7 kcal.mole^{-1}) and cyanide (0·2 kcal.mole^{-1}) groups[8] on the basis of which it would be predicted that in the equilibrium mixture resulting from addition of cyanide ion to the carbonyl group of (**5**), the axial cyano-epimer (**6**) would predominate. The C-3 configurations assigned in this way were confirmed by the unambiguous synthesis of the aminomethyl compound (**9**), by reaction of the epoxide (**10** m.p. 170—172° (lit.[9] m.p. 174—176°) with sodamide in liquid ammonia.[10]

Tiffeneau–Demjanov rearrangement[5,7] of (**11**; R = H) and (**12**; R = H) respectively gave mixtures of the A-homo-ketones (**13**) and (**14**) which were separated from other products by chromatography on alumina. The ratios of (**13**) and (**14**) for each reaction were then established by o.r.d. analysis.[1] The results obtained, together with those of the corresponding diazomethane reaction, are summarized in the Table.

The close agreement between the A-homo-ketone ratios from the diazomethane ring enlargement of (**5**) and from the Tiffeneau–Demjanov intermediate (**9**) provides strong evidence that the diazomethane approached the carbonyl group from the equatorial direction. These data parallel those obtained by Carlson and Behn[5] on *trans*-2-decalone ring expansion reactions and are also consistent with what seems to be a general principle of least hindered approach by diazoalkanes to cycloalkanones.[11]

A-Homo-ketone ratios from ring expansion reactions

Reaction	Ratio (**13**) : (**14**)	A-Homo-ketone yield[a]
(**11**; R = H) + HNO_2	0·87[b]	95%
(**12**; R = H) + HNO_2	1·45[b]	80%
(**5**) + CH_2N_2	1·44[c]	75%

[a] Very little epoxide formation was observed in any reaction.
[b] Average of duplication runs with error $< \pm 3\%$.
[c] From reference 1.

From studies of models there appears to be no reason why either of the two conformers of (**3**) and (**4**), favouring C-3–C-4 or C-2–C-3 bond migrations to (**13**) and (**14**) respectively,[1,2,5,11] should be favoured to any extent and the small (*ca.* 0·25 kcal.mole^{-1}) free energy differences between the two that the A-homo-product ratios reflect confirms this conclusion.

The paper by Carlson and Behn,[5] in which a very similar approach to that described in this communication was followed, appeared while our investigations were in progress and it is a pleasure to acknowledge how much their results, and the helpful comments of Dr. Carlson, facilitated the latter part of our work. Financial support from the National Research Council of Canada and the award (to P.P.) of a Province of Ontario Graduate Fellowship are also gratefully acknowledged.

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