Reduction of 1-Oxo-steroids by Sodium Borohydride

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Reduction with sodium borohydride of steroidal 1-ones in the 5α-series affords the corresponding axial 1α-hydroxy-derivatives, whereas the isomeric ketones in the 5β-series give the equatorial 1α-hydroxy-derivatives. Conversely, reduction of 4β,5β- and of 5β,6β-epoxy-1-oxo-steroids takes place by rear-side attack to give the corresponding 1β-hydroxy-derivatives. All these reactions are stereospecific. The reduction of various 2-en-1-ones in the 5α-series proceeds by 1,2-attack to give mixtures of 1α- and 1β-allylic alcohols, in contrast to the reduction of the isomeric enones in the 5β-series which proceeds by 1,4-attack to give the corresponding saturated ketones, in most instances further reduced to the saturated α-oriented alcohols. Similar saturation of the double bond was observed for 5β-2-en-4-one derivatives.

THE experimental results for the reduction by hydrides of oxo-groups at almost every position of the steroid nucleus have been summarised,[1] and various theories have been advanced to rationalise the steric course of this reaction. Earlier concepts were formulated in terms of steric hindrance (Barton [2]), steric approach control and product development control (Dauben [3]), steric strain control and product stability control (Brown [4]), and participation of flexible (twist-boat) forms (Landor [5]). Dauben's treatment, especially the concept of product development control, has been criticised,[6] and alternative interpretations stressing polar effects,[7] steric interference with axial groups,[8] eclipsing effects,[9] and electronic non-equivalence of the two faces of the carbonyl group [10] have been suggested.

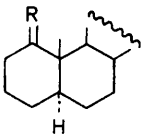
On the basis of his concepts, Dauben predicted [11] that reduction of 5α-cholestan-1-one (1) with lithium aluminium hydride should yield the axial 1α-alcohol in larger amount than obtained by equilibration, and that the use of the bulkier sodium borohydride should increase this preference. Indeed, Henbest and Wilson [12] obtained with lithium aluminium hydride 52% of the axial 1α-ol (2) and 28% of the equatorial 1β-ol (3), whereas Tamm and Albrecht [13] noted that sodium borohydride afforded only the axial alcohol (2). Nevertheless, these results were regarded as surprising,[12,14] largely in view of the steric hindrance expected from the adjacent angular methyl group.[12,15,16] In fact the outcome of such reductions was quite different from that of *trans*-8a-methyl-1-decalone derivatives [17] and of steroidal D-homo-17a-one derivatives,[18] in which the reducing species attacked from the rear to give the corresponding β-oriented alcohols. The difference in behaviour of steroidal 1-ones and 17a-ones was rationalised [19,20] by considering the proximity of the equatorial 11α-H to the C-1 carbonyl oxygen (1.9 Å), resulting in a steric hindrance without analogy in other systems. Severe non-bonded interactions between the 11α-H and equatorial substituents at C-1 have been reported.[14,16,21-23]

Since in the chair conformation of ring A in 1-oxo-5α-steroids the carbonyl bond points 'downwards,' it is likely that equatorial attack from the 'top' of the molecule implies a reactant-like transition state and is steric-approach-controlled, as predicted by Dauben. The alternative rear-side attack might be more difficult owing to the conformational distortion induced in the transition state by interaction between the C-1 β-oxygen and the 11α-H, the crowding at the oxygen atom increasing with the size of the reducing species. Additional steric strain for this mode of attack could be expected from the axial 5α- and 9α-H.

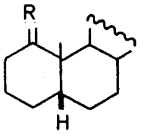
We now present the results of reduction with sodium borohydride in methanol of several 1-oxo-steroids in the

[1] D. M. S. Wheeler and M. M. Wheeler, in 'Organic Reactions in Steroid Chemistry,' eds. J. Fried and J. A. Edwards, Van Nostrand Reinhold, New York, 1972, vol. 1, p. 61.
[2] D. H. R. Barton, *J. Chem. Soc.*, 1953, 1027.
[3] W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, 1956, **78**, 2579.
[4] H. C. Brown and H. R. Deck, *J. Amer. Chem. Soc.*, 1965, **87**, 5620.
[5] S. R. Landor and J. R. Reagan, *J. Chem. Soc.* (*C*), 1967, 1159.
[6] For leading references, see D. N. Kirk, *Tetrahedron Letters*, 1969, 1727; E. L. Eliel and Y. Senda, *Tetrahedron*, 1970, **26**, 2411.
[7] A. V. Kamernitzky and A. A. Akhrem, *Tetrahedron*, 1962, **18**, 705.
[8] J. C. Richer, *J. Org. Chem.*, 1965, **30**, 324; J. A. Marshall and R. D. Caroll, *ibid.*, p. 2748; J. C. Jacquesy, R. Jacquesy, and J. Levisalles, *Bull. Soc. chim. France*, 1967, 1649.
[9] M. Cherest and H. Felkin, *Tetrahedron Letters*, 1968, 2205; 1971, 383.
[10] J. Klein, *Tetrahedron Letters*, 1973, 4307.
[11] W. G. Dauben, E. J. Blanz, jun., J. Jiu, and R. A. Micheli, *J. Amer. Chem. Soc.*, 1956, **78**, 3752.
[12] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1956, 3289.
[13] Ch. Tamm and R. Albrecht, *Helv. Chim. Acta*, 1959, **42**, 2177 (footnote 21).
[14] Ph. Francois, A. Combier-Lablache, and J. Levisalles, *Bull. Soc. chim. France*, 1965, 2588.
[15] C. W. Shoppee, S. K. Roy, and B. S. Goodrich, *J. Chem. Soc.*, 1961, 1583.
[16] D. C. Ayres, D. N. Kirk, and R. Sawdaye, *J. Chem. Soc.* (*B*), 1970, 505.
[17] R. F. Church, R. E. Ireland, and J. A. Marshall, *J. Org. Chem.*, 1962, **27**, 1118; C. Schmidt, *Canad. J. Chem.*, 1973, **51**, 3989; K. Yamakawa, T. Tominaga, and K. Nishitani, *Tetrahedron Letters*, 1975, 4137.
[18] R. O. Clinton, R. G. Christiansen, H. C. Neumann, and S. C. Laskowski, *J. Amer. Chem. Soc.*, 1957, **79**, 6475; H. Hirshmann, F. B. Hirshmann, and A. P. Zala, *J. Org. Chem.*, 1966, **31**, 375.
[19] D. N. Kirk, W. Klyne, C. M. Peach, and M. A. Wilson, *J. Chem. Soc.* (*C*), 1970, 1454.
[20] L. E. Contreras, J. M. Evans, D. de Marcano, L. Marquez, M. Molina, and L. Tempestini, *J. Org. Chem.*, 1974, **39**, 1550.
[21] J. J. Schneider, *J. Chromatog.*, 1968, **37**, 89.
[22] E. Toromanoff, *Topics Stereochem.*, 1967, **2**, 157.
[23] H. Mori, *Chem. and Pharm. Bull.* (*Japan*), 1962, **10**, 386; D. Bertin and J. Perronnet, *Bull. Soc. chim. France*, 1964, 2782; W. J. Wechter, G. Slomp, F. A. McKellar, R. Wiechert, and U. Kerb, *Tetrahedron*, 1965, **21**, 1625.

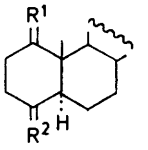
5α- and 5β-series, prepared in our previous works.[24,25] Thus, 5α-cholestan-1-one (1) afforded stereospecifically [26] the axial 1α-hydroxy-derivative (2). The isomeric 5β-cholestan-1-one (4) [24] is stereospecifically reduced to the equatorial 1α-hydroxy-derivative (5), as already reported for a similar system.[27] This result should have been predicted in view of the folding of rings A and B, precluding rear-side α-attack.



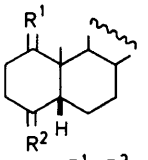
(1) R = O
(2) R = α-OH, β-H
(3) R = β-OH, α-H



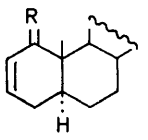
(4) R = O
(5) R = α-OH, β-H



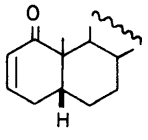
(6) $R^1 = R^2 = O$
(7a) R^1 = α-OH, β-H; R^2 = β-OH, α-H
(7b) R^1 = α-OAc, β-H; R^2 = β-OAc, α-H
(7c) R^1 = α-OAc, β-H; R^2 = β-OH, α-H
(8) R^1 = α-OAc, β-H; R^2 = O



(9) $R^1 = R^2 = O$
(10a) $R^1 = R^2$ = α-OH, β-H
(10b) $R^1 = R^2$ = α-OAc, β-H
(11a) R^1 = α-OH, β-H, R^2 = β-OH, α-H
(11b) R^1 = α-OAc, β-H, R^2 = β-OAc, α-H



(12) R = O
(13) R = β-OH, α-H
(14) R = α-OH, β-H



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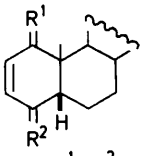
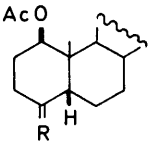
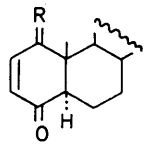


(16) $R^1 = R^2 = O$
(17) R^1 = β-OAc, α-H, R^2 = O



(18a) R = α-OH, β-H
(18b) R = α-OAc, β-H
(19) R = β-OH, α-H
(20) R = O



(21) R = O
(22) R = α-OAc, β-H

Reduction of the carbonyl groups in 5α-cholestane-1,4-dione (6) [24] proceeded stereospecifically to give the 1α,4β-diol (7a), the structure of which was inferred from n.m.r. data and confirmed by reduction of 1α-acetoxy-5α-cholestan-4-one (8),[24] yielding exclusively the corresponding 4β-hydroxy-derivative (7c), which yielded the same diacetate (7b) as did the diol (7a). Under similar conditions, 5β-cholestane-1,4-dione (9) [24] yielded an easily separable 4 : 1 mixture of the 1α,4α- (10a) and the 1α,4β-diol (11a). The structures assigned to these diols are based on n.m.r. data. The orientation of the 1-hydroxy-group in the diols (10a) and (11a) proves that the reduction of the 1-one in (9) proceeds as in the simple 5β-cholestan-1-one (4). No epimerisation of the diketones (6) and (9) occurred under the reaction conditions, as shown by re-oxidation of the diols (7a), (10a), and (11a) giving the original diketones.

The presence of a double bond in ring A or B of a 1-oxo-steroid changes markedly the steric outcome of the hydride reduction, owing to flattening of the rings by both the C=C and the C=O bonds. A case in point is the reduction by sodium borohydride of 3β-acetoxyandrost-5-ene-1,17-dione, giving a 2 : 1 mixture of the 1β- and 1α-alcohols.[28] Analogously, 1,4-dioxowitha-5,24-dienolide [29] gave a 2 : 1 mixture of the 1β,4α- and 1α,4α-diols.[30] Likewise, 5α-cholest-2-en-1-one (12) was reported to give

[24] E. Glotter, M. Weissenberg, and D. Lavie, *Tetrahedron*, 1970, **26**, 3857.
[25] M. Weissenberg, E. Glotter, and D. Lavie, *Tetrahedron Letters*, 1974, 3063.
[26] Throughout this paper, the term 'stereospecific' is used in the sense proposed by F. G. Bordwell and P. S. Landis, *J. Amer. Chem. Soc.*, 1958, **80**, 6383, footnote 7 (*i.e.* denoting nearly-complete stereoselectivity). For other views on this matter see H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *J. Amer. Chem. Soc.*, 1959, **81**, 108, footnote 16; E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 436.
[27] W. Schlegel and Ch. Tamm, *Helv. Chim. Acta*, 1957, **40**, 160.
[28] R. M. Dodson, A. H. Goldkamp, and R. D. Muir, *J. Amer. Chem. Soc.*, 1960, **82**, 4026.
[29] D. Lavie, E. Glotter, and Y. Shvo, *J. Chem. Soc.*, 1965, 7517.
[30] S. Greenfield, Ph.D. Thesis. The Weizmann Institute of Science, Rehovot, 1967.

the quasiequatorial 1β-ol (13) by reduction with lithium aluminium hydride.[13] According to Toromanoff,[22] this result was predictable from electronic and steric factors, which should favour the addition of the hydride ion on the opposite side of the C-10 methyl group. However, this reaction seems to be more complex. Although compound (13) was reportedly [13] obtained in 80% yield after chromatography on alumina, it was pointed out later [31] that a related androstane derivative gave under these conditions only the quasiaxial 1α-ol (14). According to another experiment,[32] in the androstane series the allylic alcohols (13) and (14) were obtained in the ratio 8 : 1 following chromatography on silica; however their total amount accounted for only 40% of the starting enone (12). The epimerisation on alumina of the usually more stable quasiequatorial alcohol (and to a lesser extent of its acetate or benzoate [13]) to the quasiaxial isomer is interesting in itself and may be attributed to the release of steric compression due to the 11α-H prevailing in the former isomer. We repeated the reduction of 5α-cholest-2-en-1-one (12) with lithium aluminium hydride as well as with sodium borohydride, and obtained a *ca.* 1 : 1 mixture of the allylic alcohols (13) and (14), easily separated on silica. These results disagree with the evaluation of Toromanoff; [22] admittedly, the significant change in the direction of attack of the reagent may be due to the flattening of ring A in the enone (12).

In contrast to the enone (12), reduction of the isomeric 5β-cholest-2-en-1-one (15) [24] takes place with saturation of the 2,3-double bond to give a mixture of the saturated ketone (4) and the 1α-alcohol (5), along with *ca.* 15% of unchanged enone (15). In this case, the direction of attack of the hydride ion is the same as for the saturated ketone (4), and as predicted by Toromanoff.[22] However, the presence of unchanged enone (15) and of the saturated ketone (4) in the product is surprising in view of the complete and stereospecific reduction of 5β-cholestan-1-one (4) (see before). Since allylic alcohols are not reduced by sodium borohydride to saturated alcohols, the formation of compounds (4) and (5) in the reduction of the enone (15) suggests a 1,4-addition [33] of the reducing agent. Flattening of ring A in this enone (monoplanar 5β-form [34]) may well account for the more difficult front-side attack at C-1, rather than attack at the other side of the conjugated system.

5β-Cholest-2-ene-1,4-dione (16) [24] yielded under these conditions a mixture of the saturated diols (10a) and (11a) in roughly the same ratio as obtained from the corresponding saturated dione (9). A similar mixture of saturated 4α- and 4β-hydroxy-derivatives (18a) and (19) was obtained from 1β-acetoxy-5β-cholest-2-en-4-one (17).[24] Oxidation of these alcohols afforded the same ketone (20) as obtained by catalytic hydrogenation of the enone (17). The structure of compound (18a), the major product in the above reduction, was confirmed by comparison of the diacetate (18b) with an authentic sample.[24] Reduction of the isomeric 5α-derivatives [5α-cholest-2-ene-1,4-dione (21) and 1α-acetoxy-5α-cholest-2-en-4-one (22) [24]] afforded inseparable mixtures of allylic alcohols, but no saturated products.

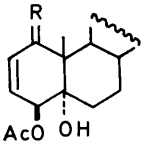
To the best of our knowledge, the only reported hydride reduction of a 4-oxo-5β-steroid is that of 5-hydroxy-5β-cholestan-4-one,[35] giving the corresponding 4α-ol in 75% yield. Although reduction of compounds (9), (16), and (17) proceeds largely by β-attack, as expected in the 5β-series, one should note the high proportion of 4β-hydroxy-derivatives resulting from attack on the more hindered α-side. The difference in behaviour of the enones (17) and (22) towards sodium borohydride (1,4- *versus* 1,2-attack) may be rationalised by considering the greater hindrance of a 4-one in the 5β-series than in the 5α-series.[36,37]

Whereas reduction of 4β,17β-diacetoxy-5-hydroxy-5α-androst-2-en-1-one (23) [25] afforded an inseparable mixture of 1α- and 1β-allylic alcohols (24) which could be reconverted into the starting enone, reduction of 4α-acetoxy-5-hydroxy-5β-cholest-2-en-1-one (25) [25] gave the corresponding saturated 1α-hydroxy-derivative (26a) accompanied by the saturated ketone (27). The latter was also obtained by oxidation of the alcohol (26a). The behaviour of the 4β-acetoxy-5β-hydroxy-1-oxo-system was studied with 4β-acetoxy-5-hydroxy-1-oxo-5β-with-24-enolide (28).[29] As expected, it behaved like a typical 5β-1-one to give the corresponding 1α-hydroxy-derivative (29), reconverted by oxidation into the starting ketone (28).[30] Under similar conditions, 5-hydroxy-5α- and 5-hydroxy-5β-cholest-2-en-1-one [25] remained unchanged for reasons which are not apparent.

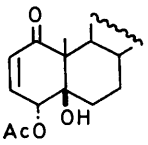
Introduction of a 4,5- or a 5,6-epoxy-group in the 2-en-1-one system markedly affects the direction of attack of the reducing agent. In 5β,6β-epoxy-1-oxo-steroids and in 4β-hydroxy-5β,6β-epoxy-1-oxo-steroids, ring A is in a boat-like conformation with C-1 and C-4 'upwards.' This conclusion was reached by crystallographic analysis of two naturally occurring steroids: withanolide E [38] possessing a 5β,6β-epoxy-2-en-1-one partial structure, and withaferin A [39] possessing an additional 4β-axial hydroxy-group. According to n.m.r. data, ring A has the same conformation in the corresponding 2,3-dihydro-derivatives.[40] Owing to this geometry, the distance between the C-1 carbonyl oxygen and the equatorial 11α-H is 2.9 Å, instead of 1.9 Å as in 5α-cholestan-1-one, thus minimising the interaction

[31] P. D. Klimstra and R. E. Counsell, *J. Medicin. Chem.*, 1965, **8**, 48.
[32] I. M. Clark, A. S. Clegg, W. A. Denny, E. R. H. Jones, G. D. Meakins, and A. Pendlebury, *J.C.S. Perkin I*, 1972, 499.
[33] For a comprehensive discussion, see M. R. Johnson and B. Rickborn, *J. Org. Chem.*, 1970, **35**, 1041; W. L. Dilling and R. A. Plepys, *ibid.*, p. 2971.
[34] R. Bucourt, *Bull. Soc. chim. France*, 1964, 2080.
[35] M. Lemonnier, G. Linstrumelle, and S. Julia, *Bull. Soc. chim. France*, 1972, 169.
[36] R. Stevenson and L. F. Fieser, *J. Amer. Chem. Soc.*, 1956, **78**, 1409.
[37] D. de Marcano and H. Rojas, *Acta Cient. Venez.*, 1974, **25**, 195 (*Chem. Abs.*, 1976, **84**, 135,930).
[38] D. Lavie, I. Kirson, E. Glotter, D. Rabinovich, and Z. Shakked, *J.C.S. Chem. Comm.*, 1972, 877.
[39] A. T. McPhail and G. A. Sim, *J. Chem. Soc.* (*B*), 1968, 196.
[40] E. Glotter and D. Lavie, *J. Chem. Soc.* (*C*), 1967, 2298.

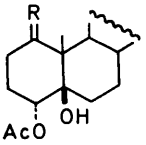
between these two atoms. Since in such 5β,6β-epoxy-steroids, the C-1 carbonyl bond points 'upwards,' axial attack from the rear of the molecule implies a reactant-like transition state. In 5β-cholestan-1-one also the carbonyl bond points 'upwards'; however rear-side attack is difficult owing to the folding of rings A and B. In view of these structural data, one might assume that reduction with sodium borohydride of the above epoxy-1-oxo-steroids would preferentially afford 1β-alcohols. The tendency towards rear-side attack is further increased by the hindrance on the β-side of the molecule due to the epoxide ring.



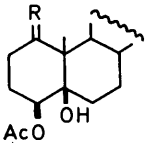
(23) R = O
(24) R = H,OH



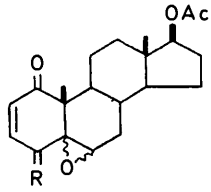
(25)



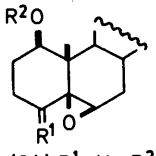
(26a) R = α-OH, β-H
(26b) R = α-OAc, β-H
(27) R = O



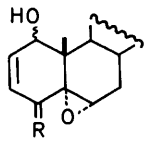
(28) R = O
(29) R = α-OH, β-H



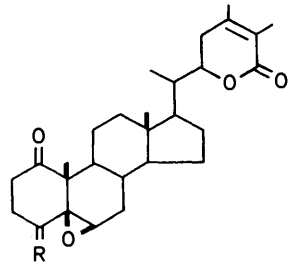
(30) R = H_2; 5β,6β-epoxy
(31) R = H_2; 5α,6α-epoxy
(32) R = α-H, β-OAc; 5β,6β-epoxy
(33) R = α-H, β-OAc; 5α,6α-epoxy



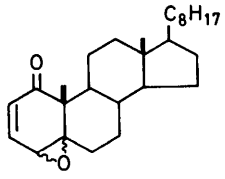
(34) R^1 = H_2, R^2 = H
(35) R^1 = α-H, β-OAc, R^2 = H
(36a) R^1 = α-H, β-OH, R^2 = H
(36b) R^1 = α-H, β-OAc, R^2 = Ac
(36c) R^1 = α-H, β-OAc, R^2 = H



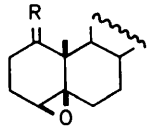
(37) R = H_2, 1α-OH
(38) R = α-H, β-OAc



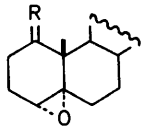
(39a) R = α-H, β-OH
(39b) R = α-H, β-OAc



(40) 4β,5β-epoxy
(41) 4α,5α-epoxy



(42) R = O
(43) R = α-H, β-OH



(44) R = β-H, α-OH
(45) R = O

Reduction of 17β-acetoxy-5,6β-epoxy-5β-androst-2-en-1-one (30) [25] afforded stereospecifically the corresponding 2,3-dihydro-1β-hydroxy-derivative (34). Under similar conditions, the isomeric 5α,6α-epoxide (31) [25] afforded the allylic alcohol (37), in which the quasiaxial orientation of the 1α-hydroxy-group was ascertained by the similarity between its n.m.r. spectrum and that of 1α-hydroxy-5α-cholest-2-ene (14). Re-oxidation of the allylic alcohol (37) gave the starting enone (31).

The reduction of 4β,17β-diacetoxy-5,6β-epoxy-5β-androst-2-en-1-one (32) [25] took place with concomitant saturation of the double bond to give the 1β-hydroxy-4β-acetoxy-derivative (35). The reduction of the isomeric 5α,6α-epoxide (33) proceeded without involvement of the 2,3-double bond, to give a mixture of the 1α- and 1β-alcohols (38). The absence of the 2,3-double bond does not influence the steric outcome of the reduction of the carbonyl group in such compounds. Thus, reduction of 4β-hydroxy-5,6β-epoxy-1-oxo-5β-with-24-enolide (39a) [29] afforded the 1β,4β-dihydroxy-derivative (36a); [30] similarly, reduction of the corresponding acetate (39b) gave the 1β-hydroxy-4β-acetoxy-derivative (36c). Acetylation of the reduction products (36a and c) gave the same diacetate (36b).[30]

The assignment of configuration to the 1-hydroxy-group in compounds (34), (35), and (36c) is based on n.m.r. evidence (broad multiplet for the 1-H signal). In 5β-steroids, an equatorial substituent at C-1 should be α-oriented. However, the 5β,6β-epoxide ring distorts the usual *cis*-AB ring system to give a spatial arrangement approaching the 5α-steroid-type structure, as shown by the 4α-H n.m.r. signals (narrow triplets) for 4β-acetoxy-5α,6α- and -5β,6β-epoxy-derivatives.[41] The same pattern is exhibited by the 4-H signals for compounds (35) and

[41] D. Lavie, Y. Kashman, and E. Glotter, *Tetrahedron*, 1966, **22**, 1103.

(36c), indicating the axial orientation of the 4β-acetoxy-group and implicitly the β-orientation of the equatorial 1-hydroxy-group.

A model of 4β,5-epoxy-5β-cholest-2-en-1-one (40) [25] shows that the dihedral angle between rings A and B should be similar to that of the isomeric 5β,6β-epoxide (30). Furthermore, the aromatic solvent-induced shifts [$\Delta(CDCl_3 - C_6D_6)$] of the C-10 methyl signals in both compounds are of the same sign and magnitude [−5 Hz in (40) and −4 Hz in (30)], pointing to the same geometrical relationship between the carbonyl and the methyl group. The reduction with sodium borohydride of compound (40) should therefore proceed by rear-side attack, as with compound (30). Indeed, two compounds were obtained by this reaction: 4β,5-epoxy-5β-cholestan-1-one (42), in which only the double bond was reduced, and the corresponding axial 1β-hydroxy-derivative (43). Re-oxidation of the alcohol (43) afforded the epoxy-ketone (42).

Reduction of the isomeric 4α,5-epoxy-5α-cholest-2-en-1-one (41) [25] takes place by frontal attack as in all 5α-1-oxo-steroids investigated so far. In contrast with other αβ-unsaturated 1-ones of the 5α-series, this reduction occurs with complete saturation of the double bond to yield the axial 1α-hydroxy-derivative (44) as the only isolable product. Oxidation of the latter afforded the saturated epoxy-ketone (45). Compounds (43) and (44) do not undergo acetylation under mild conditions (acetic anhydride–pyridine at room temperature); this supports the above configurational assignments.

According to these results, saturation of the conjugated double bond on treatment with sodium borohydride seems to be a common reaction of 5β-steroidal 2-en-1-ones. The behaviour of the 4α,5α-epoxy-derivative (41) is presumably related to the increased hindrance due to the epoxide ring.

EXPERIMENTAL

M.p.s were taken with a Fisher–Johns apparatus. Optical rotations were recorded with an automatic Perkin-Elmer 141 polarimeter and refer to solutions in chloroform. N.m.r. spectra were determined with a Varian A-60 instrument for *ca.* 5% solutions in deuteriochloroform containing tetramethylsilane as internal standard (only signals relevant to rings A and B are reported). T.l.c. was carried out on plates of silica gel G (Merck) and spots were developed with iodine vapour. Column chromatography was performed on silica gel 60 (Merck). Mass spectra were taken under the direction of Dr. Z. Zaretskii with an Atlas CH4 instrument. Analyses were performed in the microanalytical laboratory of the Weizmann Institute, under the direction of Mr. R. Heller.

General Procedure for Reduction of Steroidal Ketones with Sodium Borohydride.—To a solution of the oxo-steroid (100 mg) in methanol (15—25 ml), sodium borohydride (100 mg) was added over a few min. The solution was stirred for 2 h at room temperature, then neutralised with dilute hydrochloric acid, and most of the solvent was removed under reduced pressure; water was added and the product was filtered off or extracted with ether, washed, and dried. Further purification as required was carried out by crystallisation or by column chromatography.

5α-Cholestan-1-one (1) [42] (100 mg) afforded 5α-cholestan-1α-ol (2) [12,42a,43] (98 mg), m.p. and mixed m.p. 103—105°.

5β-*Cholestan*-1-*one* (4) [24] (100 mg) gave 5β-cholestan-1α-ol (5) (97 mg), which could not be induced to crystallise; it was identical with an independently synthesised sample.[24]

5α-*Cholestane*-1,4-*dione* (6) [24] (100 mg) gave 5α-*cholestane*-1α,4β-*diol* (7a) (95 mg), which was crystallised twice from methanol; m.p. 194—196°, $[\alpha]_D$ +40.5 (*c* 0.3); δ 3.77 (1- and 4-H, overlapped narrow multiplets) and 1.02 (19-H, s) (Found: C, 80.3; H, 12.1. $C_{27}H_{48}O_2$ requires C, 80.15; H, 11.95%). The *diacetate* (7b) was obtained by treatment with acetic anhydride–pyridine for 48 h at room temperature; m.p. 171—173° (from methanol), $[\alpha]_D$ +48° (*c* 0.3); δ 5.0 (4-H, m, $W_{\frac{1}{2}}$ 6 Hz), 4.87 (1-H, m, $W_{\frac{1}{2}}$ 6 Hz), 2.07 and 2.03 (OAc), and 1.07 (19-H, s) (Found: C, 76.05; H, 10.65. $C_{31}H_{52}O_4$ requires C, 76.15; H, 10.7%). Oxidation of (7a) with Jones reagent in acetone at 10—15 °C afforded quantitatively the diketone (6).

1α-Acetoxy-5α-cholestan-4-one (8) [24] (200 mg) gave 5α-*cholestane*-1α,4β-*diol* 1-*acetate* (7c) (195 mg), m.p. 131—133° (from hexane), $[\alpha]_D$ +51° (*c* 0.4); δ 4.87 (1-H, m, $W_{\frac{1}{2}}$ 6 Hz), 3.86 (4-H, m, $W_{\frac{1}{2}}$ 6 Hz), 2.06 (OAc), and 1.10 (19-H, s) (Found: C, 78.1; H, 11.35. $C_{29}H_{50}O_3$ requires C, 77.95; H, 11.35%). Acetylation of (7c) with acetic anhydride–pyridine overnight at room temperature afforded a diacetate identical with (7b), m.p. and mixed m.p. 171—173°.

5β-Cholestane-1,4-dione (9) [24] (125 mg) gave a crude product showing two spots on t.l.c. Chromatography (elution with hexane–ether, 1 : 1) gave 5β-*cholestane*-1α,4α-*diol* (10a) (90 mg), m.p. 137—138° (from methanol), $[\alpha]_D$ +36° (*c* 0.4); δ 3.95 (4-H, m, $W_{\frac{1}{2}}$ 7 Hz), 3.61 (1-H, m, $W_{\frac{1}{2}}$ 12 Hz), and 1.03 (19-H, s) (Found: C, 80.1; H, 12.0. $C_{27}H_{48}O_2$ requires C, 80.15; H, 11.95%). The *diacetate* (10b) had m.p. 111—112° (from methanol), $[\alpha]_D$ −22.5° (*c* 0.3); δ 5.09 (4-H, m, $W_{\frac{1}{2}}$ 7 Hz), 4.63 (1-H, dd, *J* 9 and 3 Hz), 2.09 and 2.07 (OAc), and 1.02 (19-H, s) (Found: C, 76.2; H, 10.5. $C_{31}H_{52}O_4$ requires C, 76.15; H, 10.7%). Further elution with hexane–ether (3 : 7) afforded 5β-*cholestane*-1α,4β-*diol* (11a) (23 mg), m.p. 142—144° (from ethanol), $[\alpha]_D$ +29° (*c* 0.3); δ 3.97 (4-H, m, $W_{\frac{1}{2}}$ 20 Hz), 3.41 (1-H, m, $W_{\frac{1}{2}}$ 18 Hz), and 1.16 (19-H, s) (Found: C, 80.2; H, 11.9. $C_{27}H_{48}O_2$ requires C, 80.15; H, 11.95%). The *diacetate* (11b) had m.p. 120—122° (from methanol), $[\alpha]_D$ −24.5° (*c* 0.3); δ 5.30 (4-H, m, $W_{\frac{1}{2}}$ *ca.* 20 Hz), 4.63 (1-H, m, $W_{\frac{1}{2}}$ *ca.* 18 Hz), 2.04 (OAc), and 1.03 (19-H, s) (Found: C, 76.3; H, 10.6. $C_{31}H_{52}O_4$ requires C, 76.15; H, 10.7%). The diols (10a) and (11a) were re-converted into the original diketone (9) by oxidation with Jones reagent in acetone solution at 10—15 °C.

5α-Cholest-2-en-1-one (12) [42] (190 mg) gave the allylic alcohols (13) and (14) in the ratio 4.5 : 5.5 (by integration of n.m.r. signals). Chromatography (elution with hexane–ether, 9.7 : 0.3) gave 5α-cholest-2-en-1β-ol (13),[13] m.p. and mixed m.p. 82° (from acetone); further elution gave mixtures, followed by pure 5α-cholest-2-en-1α-ol (14),[42] m.p. and mixed m.p. 103—104° (from acetone) (lit.,[42] double m.p. 90—92 and 103—104°). Reduction of compound (12) with lithium aluminium hydride in ether gave a

[42] (*a*) C. Djerassi, D. H. Williams, and B. Berkoz, *J. Org. Chem.*, 1962, **27**, 2205; (*b*) M. P. Cava and B. R. Vogt, *ibid.*, 1965, **30**, 3775.

[43] P. Striebel and Ch. Tamm, *Helv. Chim. Acta*, 1954, **37**, 1094.

mixture of the above alcohols in the ratio 5.5 : 4.5 (experiment by Miss P. KRINSKY).

5β-Cholest-2-en-1-one (15) [24] (115 mg) gave a crude product showing three spots on a chromatoplate. Chromatography (elution with hexane–ether, 9.5 : 0.5) gave 5β-cholestan-1-one (4) [24] (15 mg), followed by compound (15) (17 mg), and finally 5β-cholestan-1α-ol (5) [24] (42 mg), identical with the product obtained by reduction of (4).

5β-Cholest-2-ene-1,4-dione (16) [24] (110 mg) gave a crude product which was chromatographed. Elution with hexane–ether (4 : 6) gave 5β-cholestane-1α,4α-diol (10a) (70 mg); further elution with hexane–ether (3 : 7) yielded 5β-cholestane-1α,4β-diol (11a) (15 mg). These diols and the corresponding acetates were identical with the compounds obtained by reduction of the dione (9).

1β-Acetoxy-5β-cholest-2-en-4-one (17) [24] (200 mg) gave a product showing two spots on t.l.c. Chromatography (elution with hexane–ether, 9 : 1) afforded 5β-*cholestane*-1β,4α-*diol* 1-*acetate* (18a) (60 mg), which could not be crystallised; δ 5.17 (1-H, m, $W_{\frac{1}{2}}$ 7 Hz), 4.05 (4-H, m, $W_{\frac{1}{2}}$ 8 Hz), 2.04 (OAc), and 0.92 (19-H, s) (Found: C, 78.2; H, 11.3. $C_{29}H_{50}O_3$ requires C, 77.95; H, 11.35%). The diacetate (18b) was identical with an authentic sample,[24] m.p. and mixed m.p. 103—105° (from methanol). Further elution with hexane–ether (1 : 1) gave 5β-cholestane-1β,4β-diol 1-acetate (19) (26 mg), m.p. 118—120° (from ethanol), $[\alpha]_D$ *ca.* 0° (*c* 0.2); δ 5.03 (1-H, m, $W_{\frac{1}{2}}$ 5 Hz), 4.01 (4-H, m. $W_{\frac{1}{2}}$ 18 Hz), 2.06 (OAc), and 0.97 (19-H, s), M^+ 446. Oxidation with Jones reagent of the crude mixture of alcohols (18a) and (19) afforded quantitatively 1β-*acetoxy*-5β-*cholestan*-4-*one* (20), m.p. 101.5—102° (from methanol), $[\alpha]_D$ −24.5° (*c* 0.3); δ 5.20 (1-H, m, $W_{\frac{1}{2}}$ 5 Hz), 2.11 (OAc), and 1.08 (19-H, s) (Found: C, 78.55; H, 10.65%; M^+, 444. $C_{29}H_{48}O_3$ requires C, 78.3; H, 10.9%; *M*, 444.6). Alternatively, compound (20) was obtained by hydrogenation of (17) over 5% Pd–C in cyclohexane.

4α-Acetoxy-5-hydroxy-5β-cholest-2-en-1-one (25) [25] (185 mg) gave a crude product which was separated by chromatography into two components. Elution with hexane–ether (1 : 1) gave 4α-acetoxy-5-hydroxy-5β-cholestan-1-one (27) (14 mg), identical with a sample prepared [25] by catalytic hydrogenation of (25), m.p. and mixed m.p. 180—182° (from methanol). Further elution afforded 5β-*cholestane*-1α,4α,5-*triol* 4-*acetate* (26a) (95 mg), m.p. 198—200° (from methanol), $[\alpha]_D$ −16.5° (*c* 0.2); δ 4.85 (4-H, m, $W_{\frac{1}{2}}$ 6 Hz), 4.00 (1-H, m, $W_{\frac{1}{2}}$ 16 Hz), 2.11 (OAc), and 1.17 (19-H, s) (Found: C, 75.4; H, 11.05. $C_{29}H_{50}O_4$ requires C, 75.3; H, 10.9%). The *diacetate* (26b) had m.p. 143—144° (from methanol), $[\alpha]_D$ −20° (*c* 0.2); δ 5.19 (1-H, m, $W_{\frac{1}{2}}$ 16 Hz), 4.88 (4-H, m, $W_{\frac{1}{2}}$ 6 Hz), 2.11 and 2.13 (OAc), and 1.04 (19-H, s) (Found: C, 73.95; H, 10.6. $C_{31}H_{52}O_5$ requires C, 73.75; H, 10.4%). Oxidation of (26a) with Jones reagent in acetone at 10—15 °C gave the ketone (27).

Reduction of 4β,17β-diacetoxy-5-hydroxy-5α-androst-2-en-1-one (23) [25] gave an inseparable mixture of allylic alcohols (24). Attempted reduction of 5α- and of 5β-hydroxycholest-2-en-1-one [25] under similar conditions left the two compounds mostly unchanged (t.l.c. and n.m.r. evidence).

17β-Acetoxy-5,6β-epoxy-5β-androst-2-en-1-one (30) [25] (185 mg) gave 5,6β-*epoxy*-5β-*androstane*-1β,17β-*diol* 17-*acetate* (34) (185 mg), m.p. 193—195° (from aqueous methanol), $[\alpha]_D$ −32° (*c* 0.3); δ 3.53 (1-H, m, $W_{\frac{1}{2}}$ 15 Hz), 3.03 (6-H, d, *J* 2.5 Hz), and 1.04 (19-H, s) (Found: C, 72.5; H, 9.15. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.2%).

17β-Acetoxy-5,6α-epoxy-5α-androst-2-en-1-one (31) [25] (200 mg) gave 5,6α-*epoxy*-5α-*androst*-2-*ene*-1α,17β-*diol* 17-*acetate* (37) (195 mg), m.p. 177—178° (from acetone–hexane), $[\alpha]_D$ +17° (*c* 0.4); δ 5.88br (2- and 3-H, m), 3.82 (1-H, m, $W_{\frac{1}{2}}$ 9 Hz), 2.90 (6-H, d, *J* 4.5 Hz), and 1.04 (19-H, s) (Found: C, 72.85; H, 8.5. $C_{21}H_{30}O_4$ requires C, 72.9; H, 8.65%).

4β,17β-Diacetoxy-5,6β-epoxy-5β-androst-2-en-1-one (32) [25] (135 mg) gave 5,6β-*epoxy*-5β-*androstane*-1β,4β,17β-*triol* 4,17-*diacetate* (35) (130 mg), m.p. 195—197° (from methanol), $[\alpha]_D$ −12° (*c* 0.4); δ 4.45 (4-H, m, $W_{\frac{1}{2}}$ 6 Hz), 3.63 (1-H, m, $W_{\frac{1}{2}}$ 15 Hz), 3.13 (6-H, d, *J* 2.5 Hz), 2.09 (OAc, s), and 1.10 (19-H, s) (Found: C, 68.2; H, 8.1. $C_{23}H_{34}O_6$ requires C, 68.0; H, 8.35%). Under similar conditions, 4β-acetoxy-5,6α-epoxy-5α-cholest-2-en-1-one (33) [25] led to an inseparable mixture of allylic alcohols (38).

4β,5-Epoxy-5β-cholest-2-en-1-one (40) [25] (200 mg) gave a crude product which showed two spots on a chromatoplate. Chromatography (elution with hexane–ether, 9.15 : 0.85) gave 4β,5-*epoxy*-5β-*cholestan*-1-*one* (42) (65 mg), needles from methanol, m.p. 111—112°, $[\alpha]_D$ −72.5° (*c* 0.37); δ 3.10 (4-H, m, $W_{\frac{1}{2}}$ 4 Hz) and 1.21 (19-H, s) (Found: C, 81.0; H, 11.05. $C_{27}H_{44}O_2$ requires C, 80.95; H, 11.05%). Further elution with the same solvent gave mixtures of (42) and (43) followed by pure 4β,5-*epoxy*-5β-*cholestan*-1β-*ol* (43) (56 mg), plates from methanol, m.p. 100—101°, $[\alpha]_D$ −10.5 (*c* 0.3); δ 3.64 (1-H, m, $W_{\frac{1}{2}}$ 6 Hz), 3.04 (4-H, d, *J* 3.5 Hz), and 1.25 (19-H, s) (Found: C, 80.5; H, 11.5. $C_{27}H_{46}O_2$ requires C, 80.55; H, 11.5%). Compound (43) remained unchanged on attempted acetylation with acetic anhydride–pyridine, overnight at room temperature. Oxidation with Jones reagent in acetone at 15 °C afforded the ketone (42), m.p. and mixed m.p. 110—112°.

4α,5-Epoxy-5α-cholest-2-en-1-one (41) [25] (145 mg) gave a crude product which was chromatographed. The major component (65 mg), obtained by elution with hexane–ether (4 : 1), was identified as 4α,5-*epoxy*-5α-*cholestan*-1α-*ol* (44), m.p. 112—113°, $[\alpha]_D$ +64.5° (*c* 0.7); δ 3.56 (1-H, m, $W_{\frac{1}{2}}$ 4 Hz), 3.06 (4-H, d, *J* 3.5 Hz), and 1.00 (19-H, s) (Found: C, 80.3; H, 11.35. $C_{27}H_{46}O_2$ requires C, 80.55; H, 11.5%). Compound (44) could not be acetylated with acetic anhydride–pyridine, overnight at room temperature. Mild oxidation with Jones reagent afforded 4α,5-epoxy-5α-cholestan-1-one (45), which could not be induced to crystallise; δ 3.06 (4-H, narrow m) and 1.10 (19-H, s), M^+ 400.

[6/1621 *Received*, 20*th August*, 1976]