Pergamon

0040–4020(94)00673–3

*Tetrahedron* Vol. 51, No. 20, pp. 5711–5742, 1995
Copyright © 1995 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040–4020/95 $29.00+0.00

# TETRAHEDRON REPORT NUMBER 372

---

# REDUCTION OF 1-OXO-STEROIDS

MARTIN WEISSENBERG* and JACQUES LEVISALLES†
* Department of Chemistry of Natural Products and Pesticides, Agricultural Research Organization,
The Volcani Center, Bet Dagan 50250, Israel
† Laboratoire de Chimie Organique, Université Pierre et Marie Curie, URA 408 du CNRS,
75252 Paris Cedex 05, France

## CONTENTS

## OVERVIEW

On studying the ring A reactions of naturally occurring lupeol derivatives, L. Ruzicka, O. Jeger and co-workers at the ETH (Zurich) investigated the reduction of the 1-oxo-group in steroid and triterpenoid derivatives. In a paper published in 1947 in *Helvetica Chimica Acta*‡, they reported the earliest synthesis of a 1-oxo-$\Delta^2$-compound by allylic oxidation of $\Delta^2$-lupene, and the hydrogenation of the resultant enone over a platinum catalyst to the corresponding saturated alcohol. The ETH team was able to assign the correct 1β-configuration to the hydroxyl group in the reduced product, and to distinguish it from its 1α-isomer obtained independently. This still remains the method of choice for the preparation of steroidal 1β-alcohols. Continuing the trend set up by this early work,

---

‡ See ref. 179.

modern studies on 1-oxo-steroids were initiated by investigations done with naturally occurring 1-hydroxy-steroids (acovenosigenin A, ruscogenin and kitigenin, among others), and 1-oxo-steroids like withanolides. During research undertaken to elucidate the structure of these compounds, some unusual reactions related to the presence of the carbonyl group at C-1 were encountered and that prompted the synthesis of model 1-oxygenated derivatives in more easily available steroidal series such as cholestane, androstane and pregnane. One of the most intriguing reactions of these compounds proved to be the reduction of the 1-keto-group, where a complex interplay of factors including C-1 : C-10 and C-1 : C-11 substituent interactions led to unexpected results. A detailed consideration of this subject is presented herein.

## INTRODUCTION

The oxygenation at position C-3 is the most widely encountered nuclear location in naturally occurring steroids of animal or plant origin.[1] Nonetheless, oxygen functions also have been found in other positions of the steroid nucleus appearing in natural products; as far as rings A/B are concerned, a series of 1-, 2-, 4-, 5-, 6-, and 7-oxygenated derivatives have been isolated from natural sources.[2]

Naturally occurring 1-oxygenated steroids comprise both 1-hydroxy- and 1-oxo-derivatives.* The former are found in plants (as saponins,[6] cardiac glycosides,[1b,7] calcinogenic glycosides,[8] ecdysones[9a] and brassinosteroids[9b]), in marine sponges[10] and also in avian, mammalian and human species (as metabolites[11–14] including vitamin D hormonal derivatives[15]). To the group of 1-oxo-steroids belong ergostane derivatives isolated either from Solanaceae plants including *Acnistus* (*Dunalia*), *Datura*, *Deprea*, *Discopodium*, *Iochroma*, *Jaborosa*, *Lycium*, *Nicandra*, *Physalis*, *Trechonaetes*, *Withania* and *Witheringia* genera (withanolides and physalins),[16,17] or from the stoloniferan Okinawa soft coral, *Clavularia viridis* (stoloniferones).[18] Most of these compounds possess a characteristic epoxy-enone moiety in rings A/B, and some of them are cytotoxic.[16–18] Other C-28 steroidal derivatives originating from modified withanolides and containing a 1-oxo-2-en-4β,5β-dihydroxy-6α-hydroxy- or 6α-chloro-system were isolated from *Tubocapsicum anomalum* plants (Solanaceae).[19] Yet other ergostanoids, petuniasterone O and petunianine A, occur in leaves of *Petunia* species (Solanaceae) and have, respectively, a 1-oxo-2α-acetoxy-[20a] or a 1-oxo-2-en-[20b] 5α-hydroxy-6α,7α-epoxy structure in rings A/B.[20] Likewise, the 1-keto-polyhydroxy-pregnene flavescin, having a 1-oxo-3β-hydroxy-5-ene substitution pattern in rings A/B, has been isolated from *Marsdenia flavescens* plants (Asclepiadaceae).[21] A few 1-oxo-compounds were also found among tetracyclic triterpenoids (which are the biogenetic precursors of steroids[22]), most of them related to the oleanane and nimbin series.[2b] In addition, several 1-oxo-steroidal derivatives occur as metabolites in various tissues of mammals, including humans.[13,23]

Insofar as every carbonyl substituent of the carbon atoms of the steroidal nucleus is sterically and electronically unique compared with each of the others,[24,25] the position 1 in ring A renders its corresponding ketones quite exceptional. This special character is reflected *inter alia* in the inertness or reduced activity of 1-oxo-5α-steroidal derivatives to both carbonyl reactions (formation of a hemi-ketal,[26,27] cyclic ketal,[28,29a] dibenzyl thioketal,[30] oxime,[30] *p*-nitrophenylhydrazone,[31] conjugated nitrile,[32] iminium derivatives[33]), and reactions at the position adjacent to carbonyl (enolisation,[34–38] bromination,[26,30,37] chlorination,[38] oxygenation in basic solution[39,40] and the Zimmermann colour reaction[26,41]). Likewise, 1-oxo-5β-steroidal derivatives were reported to form slowly a thioketal,[42,43] to afford an oxime under forcing conditions,[44] and to lead to a negative Zimmermann colour reaction.[41] Unexpected results have been encountered also in a series of reduction reactions of 1-

---

* A few compounds having 1,2-[3] and 1,11-[4]oxido-bridged structures, or 1,3,5-orthoacetate functional groups,[5] have also been isolated from plants.

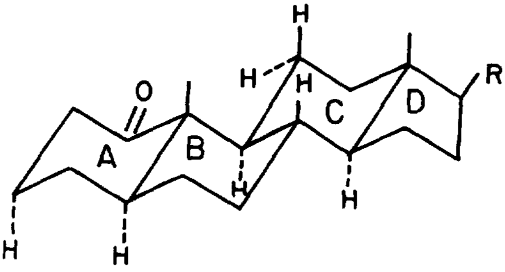


Figure 1. 1-Oxo-5α-steroidal derivative.

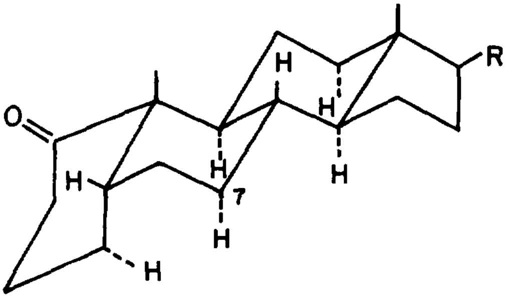


Figure 2. 1-Oxo-5β-steroidal derivative.

oxo-steroidal derivatives to the corresponding secondary alcohols, and/or to methylene derivatives via hydrazone or thioketal intermediates. These reactions, which involve a change in coordination of the trigonal ($sp^2$) carbonyl at C-1 to tetrahedral ($sp^3$) hybridisation, constitute the subject of this survey.

The unusual stability of the 1-oxo group in 5α-1,3-diketones[28,30] was initially attributed to an intramolecular hydrogen bridge between the 11α-hydrogen atom and the carbonyl at C-1,[30,34] or alternatively to a long-range effect of the side chain,[45]* and was found to occur irrespective of the A/B ring juncture.[45] Furthermore, examination of molecular models of 1-oxo-5α-steroids revealed that the proximity of the equatorial 11α-hydrogen to the C-1 carbonyl oxygen (1.9 Å) causes a severe non-bonded interaction, resulting in a steric hindrance[47]† without analogy in other systems. Additional hindrance is seen on the β-side by the adjacent axial angular methyl group at C-10,[30,47–49] along with the equatorially fixed C-9–C-11 bond.[50a] The repulsion between the C-1 and C-11 substituents is relieved in the 5β (A/B *cis*) isomer because the C-11–C-9–C-8 moiety can now assume an axial orientation with respect to ring A,[50b] whereas the bridgehead methyl group at C-10 lies almost in the same plane as the C═O bond, but in an equatorial relationship. This decrease of unfavourable C-1 : C-11 substituent interactions is reflected, *inter alia*, in a directive effect of the 1-oxo-group on enhancing the stability of the A/B-*cis* ring system in 1,4-diones[42] and 1,6-diones,[51] and also in 1-oxo-derivatives obtained following hydrogenation of 4,5-[52,53] and 5,6-[54b,55] double bonds, and peracid epoxidation of 4,5-[56–58] and 5,6-[56–59,60b] double bonds. Based on reactivity towards derivatisation and reduction reactions, the hindrance of the carbonyl at position 1 has variously been evaluated as moderate in the 5α-series,[49,61–63] to substantial in the 5α-series[1e,27,31,32] and in the 5β-series.[34,43,44]

---

* Conceivably, the influence of at least two additional rings is reflected in the chiroptical properties of the carbonyl group in 1-oxo-steroids.[46]

† This seems to be the earliest reference to hindrance of the C-1 carbonyl by the C-H-11α bond.

## 1. REDUCTION OF THE CARBONYL GROUP IN 1-OXO-STEROIDS TO THE METHYLENE GROUP

Two methods, the Wolff–Kishner reduction and the desulphurisation of mercapto-derivatives with Raney nickel, have been used for the reduction of 1-oxo-steroids to the parent deoxo-derivatives. Both procedures involve prior derivatisation of the carbonyl group, however, the hydrazones of the various 1-oxo-steroids submitted to the Wolff–Kishner reaction have never been isolated but rather processed further *in situ*, to give finally the corresponding methylene derivatives (Table 1). The former method has apparently been preferred for preparative and/or structure determination purposes, while the latter has been used often in connection with studies on thioketals.[29b,42]

### 1.1. *Wolff–Kishner*

This procedure, usually performed as modified by Huang–Minlon,[1b] involves formation of the ketone's hydrazone, which is heated rapidly at 200°C in diethylene glycol containing strong alkali. Despite previous statements on C-1 : C-11 steric interaction[32] and on the stereoelectronic contribution of the adjacent angular methyl group[27,30] which have variously been invoked in order to explain the sluggishness of some derivatisation reactions of the 1-oxo-group, especially in the A/B-*trans* series, the 1-hydrazones can apparently be formed in sizable amounts, as inferred from overall yields of 1-deoxo-steroidal derivatives, ranging from 30 to 97% (Table 1). However, while no steroidal 1-hydrazone has so far been isolated and characterised, 5α-1-oxo-steroidal derivatives were reported to react readily with 2,4-dinitrophenylhydrazine[48] and *p*-toluenesulphonylhydrazine,[64] but to remain virtually inactive towards *p*-nitrophenylhydrazine,[31] whereas a 1-oxo-3β-hydroxy-5-ene afforded a phenylhydrazone under usual conditions.[21] Admittedly, the formation rate of the variously substituted 1-hydrazones, and especially of their sterically-overcrowded 1-carbinolamine intermediates, would be affected by steric factors.[24b] Incidentally, in the only attempt reported to date at a Kishner reductive elimination of α,β-epoxy-1-ketones by the Wharton transformation,[65] a 1-oxo-2,3-epoxy-triterpenoid derivative could be converted upon treatment with hydrazine into the allylic alcohol $\Delta^1$-3-ol in 20% yield,[66] through a mechanism believed to involve the corresponding hydrazone as an intermediate.[65c]*

### 1.2. *Desulphurisation of thioketals by Raney nickel*

This technique comprises thioketalisation of the keto-derivatives with thiols or dithiols in the presence of boron trifluoride, followed by treatment of the formed thioketals with freshly prepared Raney nickel in ethyl alcohol. The results listed in Table 1 indicate that in the 5α-series ethylene thioketals are readily formed, indeed more easily than their oxygen-containing analogues which require forcing conditions,[29a] in agreement with early observations.[1d] Longer periods of time and lower yields were reported for thioketalisation of 1-oxo-steroids in the 5β-series, except for a 1-oxo-A-nor-derivative (Table 1, entry 17). Actually, extensive studies of thioketalisation of 5α- and 5β-1,4-dioxo-steroids substantiated further the increased stability of the *cis* A/B rings system in the presence of a carbonyl group at C-1,[42] already referred to in the Introduction. Hence, thioketalisation of 1,4-dioxo-5β-steroids allowed selective preparation of 4-thioketals in the 5β-series which could not otherwise be obtained, since direct thioketalisation of both 5α- and 5β-4-oxo-steroids led to the same 5α-4-dithioketal.[67] Yet, when the hybridisation of C-1 in 5β-1-oxo-4-dithioketal was changed from $sp^2$ to $sp^3$ by thioketalisation or by reduction of the 1-carbonyl group, the *trans* A/B rings system became favoured[42] (see, for example, Table 1, entries 14 and 15, for the complete inversion of configuration at C-5 which occurred upon thioketalisation of the 1-keto group in 1-oxo-4-dithioketal 5β-derivatives). Since the C-S bond distance is 1.82 Å, this minimises the C-1 sulphur : C-11 hydrogen interaction in both 5α- and 5β-series. Besides, in the 5β-series there are two *gauche*

---

* 2α,3α-Epoxy-5α-cholestan-1-one could also be converted into the corresponding $\Delta^1$-3α-ol derivative in approximately 42% yield.[52]

Table 1. Reduction of 1-Oxo-Steroids to Deoxo-Derivatives

| No. | 1-Oxo-steroid substrate | Other substituents | C-5 substituent | Wolff-Kishner | | | Desulphurisation of thioketals | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1-Hydrazone (%) | 1-Deoxo-steroid (%) | Other products | 1-Thioketal (%) | 1-Deoxo-steroid (%) | Other products | |
| 1 | Cholestane | | α-H | a | $49^{b,c}$ | 1α-OH (19%) | | | | 68a |
| 2 | Androstane | 2α,3α-cyclopropane, 17β-OAc | α-H | a | d | | | | | 69 |
| 3 | Androstane | 3α-Me, 17β-OAc | α-H | a | $61^{b}$ | | | | | 69 |
| 4 | Androstane | 3α,5α-epoxy, 17-CO | α-H | a | $97^{b}$ | | | | | 70 |
| 5 | Cholestane | 4-CO | α-H | | | | 94 | 100 | | 42 |
| 6 | Withanolide | 4-CO, $\Delta^{24}$, 24,25-$Me_2$ | α-H | | | | d | 51 | | 43 |
| 7 | Oleanane | 3β-OH, 4,4-$Me_2$, $\Delta^{12}$, 28-COOH | α-H | a | d | | | | | 71 |
| 8 | Cyclolaudane | 3-CO, 4,4-$Me_2$, 9β,19-cyclo | α-H | a | $32^{b}$ | | | | | 72 |
| 9 | Cholestane | 19β-COOMe | α-H | | | | 69 | | $\Delta^{1}(79\%)^{e}$ | 73 |
| 10 | Estrane | 6-CO, 17-CO | α-H | a | $45^{b,f}$ | | | | | 74 |
| 11 | Cholestane | 3α-Me | $\Delta^{5}$ | a | $35^{b}$ | | | | | 75 |
| 12 | Withanolide | $\Delta^{24}$, 24,25-$Me_2$ | β-H | | | | d | 49 | | 43 |
| 13 | Spirostane | (25R) | β-H | | $68^{b}$ | | | | | 76 |
| 14 | Cholestane | 4-ethylene thioketal | β-H | | | | $72^{g}$ | 100 | | 42 |
| 15 | Withanolide | 4-ethylene thioketal, $\Delta^{24}$, 24,25-$Me_2$ | β-H | | | | $52^{g,h}$ | 51 | | 43 |
| 16 | Androstane | 6-CO, 17-CO | β-H | a | d | | | | | 51a |
| 17 | Withanolide | (A-nor), $\Delta^{24}$, 24,25-$Me_2$ | β-H | | | | 94 | d | | 77 |

[a] Further processed to reduction without isolation; [b] total yield, including formation of the carbonyl derivative intermediate; [c] the same reaction has already been reported in an early communication [68b], but the identity and/or purity of the 1-ketone submitted to reduction have been since questioned; [68a,c] [d] yield not quoted; [e] isolated as 19β-$CH_2OH$, following $LiAlH_4$ reduction of the 19β-COOMe group; [f] with partial inversion of configuration at C-5; [g] with complete inversion of configuration at C-5; [h] following separation of unreacted ketone (40%).

interactions C-1 sulphur: C-10 methyl as compared with only one in the 5α-series, whence the increased stability of the 5α-compound. The conventional desulphurisation of thioketals by Raney nickel in ethyl alcohol proceeds smoothly in both 5α- and 5β-series, to give the corresponding methylene derivatives. However, when acetone was used as solvent, the $\Delta^1$-olefin was obtained in high yield (see Table 1, entry 9).

## 2. REDUCTION OF THE CARBONYL GROUP IN 1-OXO-STEROIDS TO HYDROXY-DERIVATIVES

### 2.1. *5α-Series*

The results of reduction of the carbonyl at almost every position on the steroid nucleus have been well documented[1e,24c,78,79] and various theories have been advanced to predict or to rationalise the steric course of this reaction.[24c,79] Earlier concepts were formulated in terms of steric hindrance (D. H. R. Barton),[80] steric approach control and product development control (W. G. Dauben),[81] steric strain control and product stability control (H. C. Brown),[82] and participation of flexible (twist-boat) forms (S. R. Landor).[83] Dauben's treatment, especially the concept of product development control, has been challenged,[84–86] and other interpretations stressing torsional strain,[84] polar effects,[87] steric interference with axial groups,[88,89] eclipsing effects,[90] antiperiplanar attack,[90d] orbital unsymmetric distribution,[91a,b] electrostatic effects,[91c–e] transition state stability control[91f] and nucleophilic/electrophilic character of the reduction agent,[91g] have been suggested.[92]

Regarding the 1-oxo-steroids, disparate and conflicting evaluations and results have been reported for most of the reduction methods employed (see Table 2), partly due to difficulties encountered earlier on in the characterisation of the 1-hydroxy-epimers[49] and concerned with similarities in their melting points and optical rotations,[49] and with discrepancies in their chromatographic mobilities recorded by paper,[93] thin layer[94] and gas chromatography.[49,94]

Obviously, the prospect of predicting the steric course of the reduction of 1-oxo-steroids has attracted certain interest. Dauben, on the basis of his concepts, predicted that reduction of 5α-cholestan-1-one with lithium aluminium hydride should yield the axial 1α-alcohol in a larger amount than obtained by equilibration, and that the use of the bulkier sodium borohydride should increase this preference.[62] Although later work confirmed this prediction (see Table 2), their results were regarded as surprising,[48] largely in view of the steric hindrance expected from the adjacent angular methyl group.[30,48,49] In a further attempt at predicting the preferred direction of nucleophilic attack for a large variety of ketones including nine steroidal derivatives, W. T. Wipke and P. Gund[95] developed an empirical calculation which incorporates the effect of steric congestion—sometimes torsion-corrected—on the stereoselectivity of nucleophilic addition to ketones, in a form amenable to computer analysis of this reaction. The results of reduction of 52 various ketones by small effective steric size nucleophiles (complex hydrides) showed good agreement between experimental and calculated axial/equatorial product ratios. The only one wrongly predicted was 5α-cholestan-1-one, thereby implying its special character. Nevertheless, the reduction of 5α-cholestan-1-one with a large steric size nucleophile ($H_2/Pt/H^+$) exhibits a specificity consistent with that predicted by the calculated congestion ratio.[95] Other empirical methods for quantitative prediction of the stereochemical product ratio in the complex hydrides reduction of cyclic ketones—including steroidal models—have subsequently been outlined,[96,97] but none of them considered the particular case of 1-oxo-steroids. As for the rationalisation of the steric outcome of the 1-oxo-steroids reduction by various reagents, this will be discussed in more detail below.

2.1.1. *Reduction with metal hydrides.* Reduction of a 1-oxo-steroid with a complex metal hydride was first reported by H. B. Henbest and R. A. L. Wilson in 1956.[48] Accordingly, treatment of 5α-cholestan-1-one with lithium aluminium hydride afforded a mixture of alcohols in which the axial isomer predominated (52% of the axial 1α-ol versus 28% of the equatorial 1β-ol),[48] as predicted by Dauben.[62] Nonetheless, this result was regarded at the time as surprising, since both thermodynamic and steric considerations were believed to favour the formation of the presumably more stable equatorial 1$\beta$-ol by attack from the $\alpha$-face of the molecule. Subsequent experiments, however, substantiated the preferential formation of the axial alcohol in even higher amounts, and this trend was observed also when various substituents were present at C-3 or C-4 in the 1-oxo-steroidal derivative (Table 2). The view was expressed[95] that predominance of the axial stereomer is perhaps due to preferential reaction from a less congested twist-boat conformation,[83] notwithstanding an earlier inference that such a conformation is hardly probable in the 5$\alpha$-series, being located at an energy maximum of the potential curve.[98] In fact, in this case it is rather the boat conformation with C-2 and C-5 becoming prow and stern, respectively, which seems to be more stable. At any rate, replacement of lithium aluminium hydride by the more selective lithium tri-*tert*-butoxyaluminium hydride[79] raised the yield of the axial 1$\alpha$-ol to nearly quantitative (Table 2).

Further confirmation of the remarkably accurate prediction of Dauben was adduced by using as reducing agent the sterically more demanding sodium borohydride in methyl alcohol in which the reducing species, being solvated, is of greater size and reactivity[81] and consequently, the preference of the reduction is increased. Indeed, reduction of 5$\alpha$-cholestan-1-one by sodium borohydride was noticed[47b,] and then demonstrated[99] to afford stereospecifically* the axial 1$\alpha$-alcohol. The same result was obtained with other 1-oxo-steroidal derivatives as well (Table 2).

The outcome of such reductions of 1-oxo-steroids was quite different from that of *trans*-8$\alpha$-methyl-1-decalone derivatives,[103] of the related 12-oxo-steroids,[50a] and of the similarly located D-homo-17a-oxo-steroidal derivatives,[104,105] in which the reducing species attacked from the rear to give largely the corresponding $\beta$-oriented equatorial alcohols.† The difference in behaviour of steroidal 1-ones and their quasi-enantiomeric D-homo-17a-one (six-membered D-ring) counterparts was rationalised[49,105,106] by considering the close proximity and the resulting steric interference between C-1 and C-11, already commented upon in the Introduction in connection with other unexpected reactions of 1-oxo-steroids. Severe non-bonded interactions between the C-H-11$\alpha$ bond and equatorial C-1 bonds with hydroxyl,[24c,d,33,37,40,49,93,107–111] methyl[112,113] or amino[33,108,114a,b] groups, have been reported.‡ Interestingly, interaction between a 1$\beta$-cyano group and the C-H-11$\alpha$ bond does not cause ring distortion as reported for the 1$\beta$-methyl group, the 'linear' cyano group presumably exerting less steric interference than the 'tetrahedral' methyl group.[114c] A degree of the steric compression of the equatorial 1$\beta$-hydroxyl group by the C-H-11$\alpha$ bond and/or by weak 1:2 interaction with the axial C-10 methyl group[1f] might actually be seen in its reactivity to oxidation with Cr$^{VI}$, which is remarkable for an equatorial alcohol and comparable to that of its axial

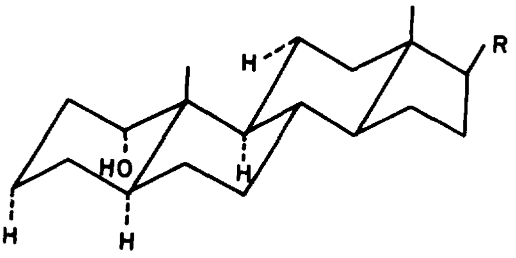


Figure 3. 1$\alpha$-Hydroxy-5$\alpha$-steroidal derivative.

---

* Throughout this survey, the term 'stereospecific' is used in the sense proposed by F. G. Bordwell and P. S. Landis[100] (i.e., denoting nearly complete stereoselectivity). For other views on this matter, see refs 101, 102.

† Although carbonyl reactions in ring D of the normal (five-membered D-ring) steroid series cannot be assessed in axial/equatorial terms,[24c] one should note the exclusive formation of 17$\beta$-alcohols by reduction of 17-ketones with all the usual reagents,[79] as a result of steric hindrance toward front-side attack.

‡ An opposing view, suggesting favourable position of, and distance between the equatorial 1$\beta$-ol and the equatorial C-H-11$\alpha$ bond, has also been expressed.[115a]

Table 2. Reduction of the 1-Oxo-Group in 5α-Steroids

| No. | 1-Oxo-steroid substrate | Other substituents | $H_2$ - Pt | | Na-alcohol | | Li-alcohol | | $AlH_3$ | | $LiAlH_4$ | | $LiAl(t\text{-}BuO)_3H$ | | $NaBH_4$ | | $KB(s\text{-}Bu)_3H$ | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | |
| 1 | Androstane | | | | 50[a] | 50 | | | | | | | 100 | | | | | | 128 |
| 2 | Androstane | | | | | | | | 9 | 91 | | | | | | | | | 49 |
| 3 | Androstane | | | | | | | | | | | | | | | | | 5[b] | 109 |
| 4 | Androstane | $\Delta^{16}$ | | | 53[a] | 28 | | | | | 76 | 13 | | | | | | | 129 |
| 5 | Cholestane | | | 92 | 23[a] | 72 | | | | | | | | | | | | | 68a |
| 6 | Cholestane | | | | 33[c] | 61 | | | | | 52 | 28 | | | | | | | 48 |
| 7 | Cholestane | | | | | 65[c] | | | | | | | | | | | | | 30 |
| 8 | Cholestane | | | | mainly[d] | some | | | | | | | | | | | | | 107 |
| 9 | Cholestane | | | | | | | | | | | | | | 100 | | | | 99 |
| 10 | Cholestane | | | | 62[c] | 38 | 95[c] | 5 | | | | | | | | | | | 111b |
| 11 | Cholestane | | | | 50[e] | 50 | 55[e] | 45 | | | | | | | | | | | 111b |
| 12 | Androstane | 17,17-$Me_2$, (18-nor) | | | 75[f] | 22 | | | | | 96 | 4 | | | only | | | | 33 |
| 13 | Androstane | (D-homo) | | | | | | | | | | | | | only | | | | 106 |
| 14 | Androstane | 17-CO | | | | | | | | | | | | | 94 | | | | 106, 130 |
| 15 | Cholestane | 2α,3α-epoxy | | | | | | | | | | | | | 100 | | | | 121 |
| 16 | Cholestane | 2β,3β-epoxy | | | | | | | | | | | | | 40 | 20 | | | 131 |
| 17 | Cholestane | 2α-Br, 4,4-$Me_2$ | | | | | | | | | | | | | 87 | | | | 37 |
| 18 | Pregnane | 3-CO | | only | | | | | | | | | | | | | | | 126 |
| 19 | Cholestane | 3-ethylene ketal | | | | | | | | | 90 | | | | | | | | 28 |
| 20 | Androstane | 3α-Me, 17β-OH | | | | | | | | | | | only | | | | | | 132 |
| 21 | Androstane | 3α-Me, 17-ethylene ketal | | | | | | | | | only | | | | | | | | 132 |
| 22 | Androstane | 3α,17α-$Me_2$, 17β-OH | | | | | | | | | | | only | | | | | | 132 |
| 23 | Lupane | 3-CO, 4,4-$Me_2$, $\Delta^{29}$ | | | | only[a] | | | | | only | | | | only | | | | 119 |
| 24 | Oleanane | 3β-OH, 4,4-$Me_2$, $\Delta^{12}$, 28-COOH | | | | | | | | | | only | | | | | | | 71 |
| 25 | Cholestane | 4-CO | | | | | | | | | | | | | 100 | | | | 99 |
| 26 | Cholestane | 4,4-$Me_2$ | | | 53[c] | 47 | | | | | 73 | 27 | | | | | | | 37 |
| 27 | Lupane | 4,4-$Me_2$ | | | | 82[f] | | | | | | | | | | | | | 133 |
| 28 | Oleanane | 4,4-$Me_2$, 18α-H, 19β,28-epoxy | | | | | | | | | 59 | 17 | | | | | | | 134 |
| 29 | Withanolide | 5α-OH, 6β-OAc, $\Delta^{24}$, 24,25-$Me_2$ | 85 | | | | | | | | | | | | | | | | 135 |
| 30 | Withanolide | 5α,17α-$(OH)_2$, 6α,7α-epoxy, $\Delta^{24}$ | | | | | | | | | | | | | 84 | | | | 136 |

[a] In propanol-1; [b] most of the ketone was recovered unchanged; [c] in ethanol; [d] in pentanol; [e] in t-butyl alcohol; [f] in propanol-2.

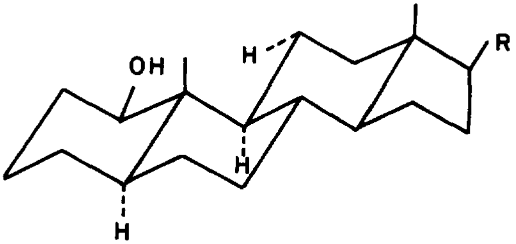


Figure 4. 1$\beta$-Hydroxy-5$\alpha$-steroidal derivative.

isomer.[115b,c] The latter's 1$\alpha$-hydroxyl group, in turn, experiences 1 : 3 diaxial interactions with C-H-3$\alpha$-, C-H-5$\alpha$-, and C-H-9$\alpha$ bonds.[1g, 73]

Since in the chair conformation of ring A in 1-oxo-5$\alpha$-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, or steric-intermediate-controlled, as suggested afterwards.[106] The alternative rear-side attack might be more difficult, owing to the conformational distortion induced in the transition state by interaction between the C-OH-1$\beta$ bond and the C-H-11$\alpha$ bond, the crowding of 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 C-H-5$\alpha$- and C-H-9$\alpha$ bonds.[99] The contrast with the D-homo-17a-ketone, which is not involved in any specific steric interference and hence behaves in an expected fashion upon reduction,[105] bromination[105] and Zimmermann colour reactions,[41] is also apparent in their respective behaviour towards Grignard reactions, albeit in an ambiguous manner. In this case, addition of methyl magnesium halides to both 1-oxo-[116] and D-homo-17a-oxo-[117] steroidal derivatives proceeds with almost exclusive formation of the corresponding equatorial $\beta$-methyl carbinols.* In fact, Henbest and Wilson had called attention at the time to the $\beta$-side approach of the Grignard reagent toward a D-homo-17a-one derivative, paralleling the major route taken by hydride reduction of the 1-ketone in their experiment.[48] Some ambiguity suggested by this view has been subsequently dissipated by the different outcome observed for the hydrides reduction of D-homo-17a-oxo-steroids.[104,105] Summing up, the similar behaviour of 1-ones and D-homo-17a-ones toward Grignard reagents is conceivably due to the general propensity for equatorial methyl attack in the steroid series, leading to extensive formation of products with equatorial methyl and axial hydroxyl groups,[24d] despite the shielding of the $\beta$-face by the axial angular methyl groups adjacent to the carbonyl function.[118] All considered, the case of C-1 remains a particular one.

The presence in ring A of 1-oxo-5$\alpha$-steroidal compounds of other substituents like 2$\alpha$-brom and 4,4-dimethyl,[37] 3-oxo and 4,4-dimethyl,[119] or 4-oxo[99] (see Table 2), does not alter the stereospecificity of the 1-ketone reduction by sodium borohydride. In the case of the 1,4-diketone (Table 2, entry 25), the second keto-group at C-4 is also stereospecifically reduced to the 4$\beta$-ol,[99] as might be expected to occur in a 4-oxo-5$\alpha$-compound.[79] It is noteworthy that no epimerisation of the 5$\alpha$-1,4-diketone (or the 5$\beta$-1,4-diketone for that matter; see Section 2.2) occurred under the reaction conditions, as shown by re-oxidation of the diols to the original diketones.[99]

A case in point is offered by 1-oxo-steroids having vicinal epoxide groups (Table 2, entries 15 and 16). According to an early evaluation,[120] *trans*-epoxy-alcohols were predicted to predominate on hydride reduction of relatively unhindered $\alpha,\beta$-epoxy-ketones, arguably due to electronic factors favouring the kinetic addition of the hydride ion on the same side of the oxiranic oxygen atom. However, the reduction of 2$\alpha$,3$\alpha$-epoxy-5$\alpha$-cholestan-1-one was found to proceed like that of any 1-oxo-5$\alpha$-steroid, affording stereospecifically the *cis*-epoxy-alcohol.[121] In this case the tendency, if

---

* Conversely, a 17-oxo-steroid containing a five-membered ring D yielded mainly a 17$\alpha$-methyl derivative.[117b]

any, for rear-side attack of the reducing agent is counterbalanced by the hindrance due to the epoxide ring.[121] This result prompted a re-examination of the sodium borohydride reduction of various α,β-epoxy-ketones,[121] which stressed the importance of steric factors alongside electronic factors. Accordingly, the main direction of attack of the reducing agent is the same as in the corresponding unsubstituted ketone, whilst the epoxide ring may sterically interfere with this attack, leading to various amounts of the stereoisomeric epoxy-alcohol.[121] Electronic and steric factors should have been anticipated to concur in the reduction of 2β,3β-epoxy-5α-cholestan-1-one, affording mainly the *trans*-epoxy-alcohol. In fact, a 2:1 mixture of *trans*-and *cis*-epoxy-alcohols is obtained, the hindrance exerted by the β-oriented epoxide ring diminishing the propensity for approach of the reducing agent from the 'top' of the molecule (Table 2, entry 16). A re-appraisal of kinetic 1,2-addition of hydride ions to α,β-epoxy-ketones using the torsion angle notation, emphasised the relative importance of controlling factors such as the ability of the epoxide oxygen to chelate the metallic cation of the reducing agent, and the stability of the conformer of lowest energy of the ring, for the steric outcome of the reduction.[122]

While the 1α-alcohol could be obtained stereospecifically by the reduction of the corresponding 1-one with sodium borohydride, an attempt to prepare its equatorial 1β-isomer using potassium tri-*sec*-butyl borohydride ('K-selectride', held to favour selective formation of equatorial alcohols[123]) led to only about 5% of the desired product, most of the starting material being recovered unchanged.[109] The 1β-epimer did arise, however, as a major product (91%), along with the 1α-ol (9%), following reduction of the 1-one with the electrophilic reagent aluminium hydride.[49] Under the same conditions, the D-homo-17a-one afforded again the equatorial 17aβ-ol as the major product (69%), but now accompanied by a slightly higher amount (19%) of its axial counterpart.[49,105] Since the environment around the carbonyl group in both 1-one and D-homo-17a-one is similar, as indicated by their respective optical rotatory dispersion curves[124] and increments in NMR chemical shifts for adjacent angular methyl groups,[105] the product ratios obtained from them by using aluminium hydride could be rationalised by D. N. Kirk and associates in a general way.[49] Accordingly, in both cases the bridgehead methyl groups flanking the carbonyls sterically hinder approach to the β-face and might exert a larger torsional strain than hydrogen in the transition state for this mode of attack. Approach from the α-face is therefore favoured, since torsional interactions are minimised and steric interactions involve only axial C-H bonds.[49] The difference in reactivity between K-selectride and aluminium hydride might be accounted for, assuming the absence of electrophilic assistance by the potassium cation of the former, whereas the latter acts as a strong Lewis acid.[92]

2.1.2. *Catalytic reduction.* It was considered earlier that catalytic hydrogenation of both hindered and unhindered ketones in strongly acid media (fast hydrogenation) affords axial alcohols.[80] The view was expressed that reduction on platinum should involve steric approach control, i.e. adsorption on the catalyst and approach of hydrogen from the less hindered, equatorial side of the carbonyl group, and thus would lead mainly to axial alcohols[125a] (von Auwers–Skita modified hydrogenation rule). On this ground, the reduction of 5α-cholestan-1-one exclusively to the equatorial 1β-ol (Table 2, entry 5) was regarded as an exception to the hydrogenation rule,[125a] or else as an oversimplification of it.[62] Later evaluation inferred that reduction of the 1-one proceeds by equatorial adsorption of the flexible form to give the equatorial 1β-ol, since the axial 10-methyl group prevents equatorial adsorption of chair form which would normally give the axial 1α-ol, and axial adsorption of chair and flexible forms is ruled out owing to the angle of the carbonyl group.[83]* Further examination of this reaction by the steric congestion and/or torsion corrected congestion ratios function[95] offered a satisfactorily consistent prediction of stereospecificity (75:25 1β-ol to 1α-ol) with the experimental product ratios (Table 2, entries 5 and 18, notwithstanding the surprising result at entry 29). At any rate, the exclusive formation of the 1β-ol points to the hydrogenation on platinum as the method of

---

* See Section 2.1.1 for an appraisal of the flexible form stability in the 5α-series.

choice for obtaining equatorial 1β-alcohols from 1-oxo-steroids[126] or 1-oxo-2-en-steroids (see Section 3.1). In contrast, D-homo-17a-oxo-steroids gave by catalytic hydrogenation along with the main product, that is, the equatorial 17aβ-alcohol, a sizeable amount (8–15%)[104a,105] of the axial 17aα-epimer, as compared with that obtained by means of sodium borohydride (about 5%).[104a] Isolation of certain amounts of the axial alcohol was attributed to some steric hindrance of the 17a-keto group toward rearward approach of the reduction reagent.[104a]

2.1.3. *Reduction with alkali metals in alcohols.* Early evaluation of the stereochemistry of this reaction assumed that the thermodynamically more stable equatorial alcohol would be the major product of the reduction with alkali metals in alcohols of steroidal ketones,[80,127] including 1-oxo-steroids.[61] Later work, however, summarised in Table 2, displays conflicting and disparate results for reduction of 1-oxo-steroids with sodium–alcohol systems, and a preponderance of either epimer, as well as roughly equivalent mixtures of both of them, have variously been claimed. The high variance in the reported product composition data originating from many different laboratories might be associated with the various reaction conditions (temperature, time), reagents (nature of metal and alcohol, stoichiometry), and isolation procedures (work up, side reactions, difficulties in characterisation of the epimers,[49] and preparative rather than product analysis purposes) which were used. A recent re-examination of this reaction[111] pointed to preponderant formation of the axial 1α-alcohol, and attributed it both to the steric interaction between C-11 methylene and the hydroxyl destabilising the normal quasi-equatorial arrangement and pushing the oxygen towards the quasi-axial direction, and to the stereoelectronic contribution of the adjacent angular methyl group supporting orbital extension in the equatorial direction. These two combined effects are held to overcome the stereoelectronic stabilisation of orbital extension in the axial direction.[111] Further investigation of the reduction of steroidal 1-, 2-, 3-, 6- and 16-ketones was done with both sodium and lithium in ethyl alcohol or *tert*-butyl alcohol, respectively, in order to assess the relevance of the cation, as well as that of hydride transfer from—and hydrogen bonding by—solvent, which are presumably weaker in *t*-butanol than in ethanol.[111] The results showed that the amount of major product in all cases is decreased in shifting from sodium to lithium in the same solvent, with the exception of the 1-one, wherein strong steric effects are believed to operate[111b] (see Table 2). Contrariwise, the quasi-enantiomeric D-homo-17a-one which is, however, devoid of the strong steric interference present in the 1-one, has been reduced with sodium in ethyl alcohol largely to the expected equatorial 17aβ-alcohol.[105]

### 2.2. *5β-Series*

Inspection of a model of 1-oxo-5β-steroids shows that the hindering effect of the C-10 angular methyl group to frontal attack becomes negligible since ring A is nearly perpendicular to the plane formed by rings B, C, and D, whereas the axial C-H-4α- and C-H-7α bonds may impede approach to ring A from the rear α-side. The carbonyl at C-1 is not assumed to be involved in interaction with the C-H-11α bond, in contrast to its counterpart in the 5α-series; indeed, a 1-oxo-5β-derivative was found to undergo easily bromination and acetoxylation.[137] Although 5α-[28,30,34,35,71,72,126,138–143] and 5β-[13] 1,3-diketones are equally enolised in various solvents,[45] the absorption maximum in UV spectra of 5β-1-ketones is at a shorter wavelength than that of 5α-1-ketones,[144,145] and more like that of D-homo-17a-ones.[105,117b] On the other hand, neither 5α- nor 5β-1-ketones give the Zimmermann colour reaction,[26,41] whilst 17a-ketones display a positive reaction,[41,146] albeit slowly developed.[146] All these data point to the 5β-1-one as being sterically different from both the strained 5α-1-one and the relatively unhindered D-homo-17a-one. Additional information on the steric environment of the keto group in 1-oxo-5β-steroids, as compared with that of 1-oxo-5α- and D-homo-17a-oxo-derivatives, is corroborated from the position[44,105,147–149] and solvent-dependence[42,148,149] of the vicinal angular C-19 and/or C-18 protons signal in NMR spectra, the chemical shift of the carbonyl carbon atom frequency in carbon-13 NMR spectra,[150] carbonyl stretching frequencies[34,45,151,152] and perturbed methylene absorptions[152] in IR spectra, principal bands in UV spectra[34,45,144,145] and

Table 3. Reduction of the 1-Oxo-Group in 5β-Steroids

| No. | 1-Oxo-steroid substrate | Other substituents | $H_2$-Pt | | Na-alcohol | | $LiAlH_4$ | | $NaBH_4$* | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | |
| 1 | Cholestane | | | | | | | | 100 | | 99 |
| 2 | Cholestane | | | | | | | | $100^a$ | | 137 |
| 3 | Androstane | 17β-COOMe | $90^b$ | | $30^{c,d}$ | | | | $90^d$ | | 41 |
| 4 | Cholestane | 2β,3β-epoxy | | | | | | | unreacted | | 121 |
| 5 | Spirostane | 2β,3α-$(OAc)_2$, 5β-OH, (25R) | | | | | $43^e$ | 4 | | | 160 |
| 6 | Cholestane | 3α-OTHP, 4,4-$Me_2$, 5β,6β-ethylidene acetal | | | | | $only^f$ | | | | 161 |
| 7 | Pregnane | 3α,17α-$(OH)_2$, 11-CO | unreacted | | | | unreacted | | unreacted | | 45 |
| 8 | Pregnane | 3α,17α-$(OH)_2$, 20-CO | | | | | | | $major^f$ | minor | 13 |
| 9 | Pregnane | 3α,17α,20α-$(OH)_3$ | | | | | | | only | | 13 |
| 10 | Pregnane | 3-CO, 17α-OH, 20-CO | | | | | | | $major^f$ | minor | 13 |
| 11 | Pregnane | 3α,17α,20β,21-$(OH)_4$, 11-CO | unreacted | | | | unreacted | | unreacted | | 45 |
| 12 | Pregnane | 3α,17α-$(OH)_2$, 20,21-acetonide | | | | | | | $67^b$ | | 45 |
| 13 | Cholestane | 4-CO | | | | | | | 100 | | 99 |
| 14 | Cholestane | 4-ethylene thioketal | | | | | | | 100 | | 42 |
| 15 | Withanolide | 4β-OAc, 5β,6β-epoxy, $\Delta^{24}$, 24,25-$Me_2$ | | | | | | | | $only^f$ | 148 |

* In methanol, unless stated otherwise.
[a] In ether- methanol 3:1; [b] following crystallisation; [c] in propanol-1; [d] following chromatography on alumina; [e] following chromatography on florisil; [f] yield not reported.

ORD data.[45,46,147,153-156] Table 3 shows that reduction of 1-oxo-5β-derivatives by all methods led stereoselectively to the corresponding equatorial 1α-alcohol which, in turn, was produced stereospecifically by using sodium borohydride in methyl alcohol as the reduction agent. This result should have been expected in view of the 'folding back' of ring A,[125b] precluding rear-side α-attack. Still, the formation of the 1α-ol-derivative is noteworthy, this compound providing another case of an equatorial alcohol more prone to conformational distortion than its axial counterpart (see Section 2.1.1 for a similar example in the 5α-series). In fact, a Dreiding display of a 5β-androstane-1α-hydroxy-derivative in the all-chair conformation (Fig. 5) suggested that the distance between the oxygen atom of the equatorial hydroxyl group at C-1 and the 11α-hydrogen atom is very small (*ca* 1.6 Å), the resultant interaction increasing unexpectedly its chromatographic mobility[93] as well as its reactivity to oxidation with $Cr^{VI}$.[115c] Conversely, the axially-oriented 1β-hydroxy-group of its epimer appears to be relatively unhindered, sharing simple 1 : 3 interactions.[93] Incidentally, the result presented in Table 3, entry 15, is not an exception to the general rule of equatorial alcohols formation by sodium borohydride reduction : the reaction product in this case is equatorial too, but has a β-orientation due to distortion of the regular *cis*-A/B rings system by the 5β,6β-epoxide ring, which leads to a spatial arrangement approaching the 5α-steroid-type structure (more on that subject in Section 3.2).

The stereospecificity of the 1-ketone reduction is not influenced by the presence of other substituents in rings A and B of 1-oxo steroids (Table 3). In the case of 1,4-dioxo-5β-cholestane (Table

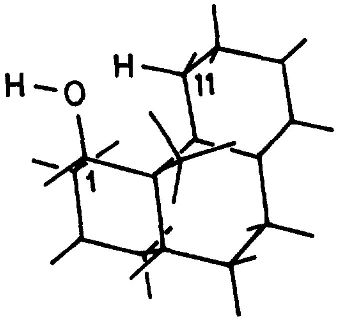


Figure 5. Dreiding model of rings A/B/C of 5β-androstan-1α-ol, photographed from the front (β) face. (From J. J. Schneider,[93] with permission).

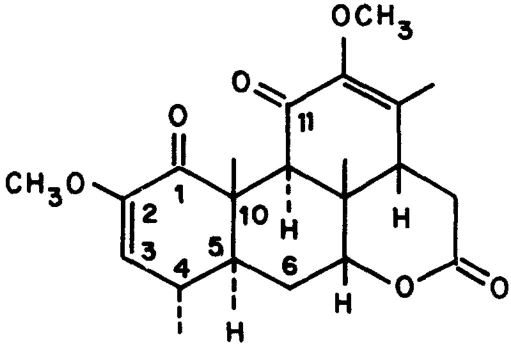


Figure 6. Quassin.

3, entry 13), reduction of the 4-oxo-group proceeds largely by $\beta$-attack to give a 4 : 1 mixture of 1$\alpha$,4$\alpha$- and 1$\alpha$,4$\beta$-dihydroxy derivatives.[99] The formation of the former diol as the major product could be expected, since the equatorial orientation of the angular C-10 methyl group with respect to ring A does not hinder the $\beta$-approach of the anion, and since the folding of the A/B rings hinders the back-side $\alpha$-approach; nonetheless, the fairly substantial amount of the 1$\alpha$,4$\beta$-diol resulting from attack on the 4-oxo-group from the more hindered $\alpha$-side, is remarkable for a ketone in the 5$\beta$-series. Some possible repulsions by either OH group in the R–O–B$<$ form, then, might admittedly be involved in this case. Again, as in the 5$\alpha$-series, re-oxidation of the diols to the original diketone inferred that no epimerisation of the latter at C-5 occurred under the reaction conditions.[99] However, the presence of an additional oxo-group at C-11 suppresses the reduction of the 1-oxo-group, even under vigorous reducing conditions (Table 3, entries 7 and 11); this result is due, presumably, to a reduction in the degree of polarisation of the two closely approaching (2.8 Å)[151] carbonyl groups of that cisoid 1,4-dione, with a consequent reduction in the positive charge on each carbon atom and, admittedly, an adverse effect on metal hydride reduction.[45] In the 5$\alpha$-series, the maximum C-1 : C-11 oxygen–oxygen separations are 2.4 Å for a 1,11-diketone and 2.2 Å for a 2-en-1,11-diketone, as evaluated from Dreiding models, and the interaction effects should be even more severe.[151] While no reduction of such compounds is documented in the literature, attention is called to the reduction of quassin, a naturally occurring quassinoid that is a triterpenoid-degraded compound.[157] Quassin (Fig. 6) displays in its A/B/C rings system a functionality recalling the relevant moieties of a steroidal 5$\alpha$-$\Delta^2$-1,11-dione. In the case of quassin, too, reduction with diisobutylaluminium hydride[158] and sodium borohydride[158,159] under usual conditions leaves both carbonyl groups at C-1 and C-11 unreacted; however, treatment with sodium borohydride under forcing conditions led to the corresponding 1$\alpha$-hydroxy-derivative in 50% yield, the 11-oxo-group still remaining intact.[159]

Another interesting example of inertness towards reduction with sodium borohydride of the C-1 carbonyl group in the 5$\beta$-series is furnished by a 2$\beta$,3$\beta$-epoxy-1-one-derivative (Table 3, entry 4). In this case, front-side approach of the reducing agent is difficult due to hindrance by the epoxide ring, whereas rear-side approach at C-1 is difficult because of the folding of rings A and B. As a result, this compound remained mostly unchanged on attempted reduction under usual conditions,[121] unlike its isomers in the 5$\alpha$-series (Table 2, entries 15 and 16).

### 2.3. $\Delta^4$- *and* $\Delta^5$-*Series*

The presence of a double bond in ring A or B of a 1-oxo-steroid may affect the steric outcome of the hydride reduction, owing to flattening of the rings by the additional trigonal carbon atoms at positions 4 and 5.[125c] Accordingly, as a consequence of the conformation imposed on rings A and

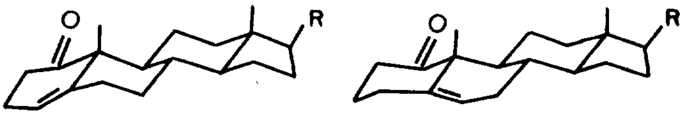


Figure 7. 1-Oxo-$\Delta^4$- and 1-oxo-$\Delta^5$-steroidal derivatives.

B by the unsaturated linkage ($\Delta^4$ or $\Delta^5$),* the 10$\beta$-methyl group projects away from the double bond (Fig. 7), rendering the $\beta$ approach more accessible.[125d] Indeed, some results in Table 4 (entries 2, 4, 5, 9 and 10) point up a predominant formation of the 1$\alpha$-hydroxy-epimer, especially when sodium borohydride was used as the reduction agent. A study conducted with 1-oxo-diosgenin suggested that the percentage of the 1$\alpha$-alcohol decreases with the increase in the bulkiness of the reducing agent, and with the increase of the size of the 3$\beta$-substituent (entries 5 and 6).[163] These results were found to be consistent with the assumption that non-bonded interactions between the equatorial C-OH-1$\beta$ bond and the equatorial C-H-11$\alpha$ bond[93] would cause the 1$\beta$-alcohol to be thermodynamically unfavoured[163] and to display anomalous chromatographic mobility, in spite of the tendency of the 5,6-double bond both to flatten rings A and B and to limit conformational mobility.[93] The characterisation of the products was done conveniently by computer-assisted analysis of their lanthanide-induced NMR shifts, as the equatorial 1$\beta$-alcohol was found to show a much higher ability for complexation with tris-(dipivalomethanato)-europium than its axial 1$\alpha$-hydroxy-epimer.[163] In contrast, parent 1-ketones in the cholestane, androstane and withanolide series (Table 4, entries 7, 8 and 11) display a comparably preferential formation—this time of the 1$\beta$-alcohol—by all hydride-reducing agents save lithium aluminium hydride which affords product ratios around parity (entries 2 and 3). As compounds 5–8 (Table 4) have similar structures with regard to rings A and B, it appears that their different behaviour towards hydrides reduction might be due to a long-range effect of the side chain. The reason for the different behaviour of the withanolides 2–4 as compared with 11 (Table 4) is not apparent. Summing up, even if a certain stereoselectivity could be seen in either the $\alpha$- or $\beta$-direction in the sodium borohydride reduction of various 1-oxo-$\Delta^5$-steroids, the stereospecificity encountered in the similar reduction of 1-oxo-5$\alpha$- and 5$\beta$-steroids is clearly lost in the $\Delta^5$-series.

Turning to the $\Delta^4$-series, it can be seen from Table 4 (entry 1) that reduction of a 1-oxo-derivative with lithium-tri-*tert*-butoxyaluminium hydride gave a mixture of the corresponding 1$\alpha$- and 1$\beta$-alcohols in an approximately 50 : 40 ratio.[164] It is worthwhile mentioning in this connection that in the $\Delta^4$-series too, the equatorial 1$\beta$-hydroxyl group is assumed to be involved in the C-1 : C-11 interaction.[165] Hydrogenation of the same 1-oxo- $\Delta^4$-derivative with palladium as catalyst left the carbonyl unreduced, as expected,† and afforded by hydrogenolysis a 5 : 1 mixture of 1-oxo-$\Delta^5$- and $\Delta^4$-derivatives.[164] By hydrogenation over platinum in acetic acid, the 4,5-double bond was reduced exclusively to the 5$\beta$-isomer, as observed previously with 1-oxo-$\Delta^4$-steroids,[52,53] whereas the 1-carbonyl was reduced stereospecifically to the corresponding equatorial 1$\alpha$-alcohol, in accord with previous results in the 5$\beta$-series[41] (Table 3, entry 3). Partial hydrogenolysis of the 6$\beta$-acetate group occurred too, and finally a 1.3 : 1 mixture of 1$\alpha$-hydroxy-5$\beta$- and 1$\alpha$-hydroxy-6$\beta$-acetoxy-5$\beta$-derivatives was obtained.[164]

## 3. REDUCTION OF CONJUGATED 1-OXO-STEROIDS TO 1-HYDROXY-DERIVATIVES

### 3.1. 5$\alpha$-*Series*

Conjugation of a carbonyl at C-1 with a double bond at C-2–C-3 changes appreciably the steric outcome of its hydride reduction, owing to the flattening of the ring A by both the C=C and the

---

* Actually, some subtle differences between the $\Delta^4$-olefin and its $\Delta^5$-isomer in their half-chair conformation could be envisaged, as the former was suggested to be slightly more 'bent' than the latter at the A/B ring junction.[162]

† Compare with conjugated 2-en-1-oxo-derivatives (Section 3.1, Table 5).

Table 4. Reduction of the 1-Oxo-Group in $\Delta^4$- and $\Delta^5$-Steroids

| No. | 1-Oxo-steroid substrate | Other substituents | Rings A/B juncture | $H_2$ - Pd | | $H_2$ - Pt | | $NaBH_4$ | | $LiAlH_4$ | | $LiAl(t\text{-}BuO)_3H$ | | $Li\text{-}NH_3$ | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | |
| 1 | Withanolide | 6β-OAc, $\Delta^{24}$ | $\Delta^4$ | unreduced[a] | | 66[b] | | | | | | 38 | 30 | | | 164 |
| 2 | Withanolide | $\Delta^{8(14)}$, 20α-OH, (20R,22R), $\Delta^{24}$ | $\Delta^5$ | | | | | 70 | 30 | 50 | 50 | | | | | 59 |
| 3 | Withanolide | $\Delta^{8(14)}$, 17α,20α-$(OH)_2$, (20R,22R), $\Delta^{24}$ | $\Delta^5$ | | | | | | | 50[c] | 50 | | | | | 59 |
| 4 | Withanolide | 13R,14R-seco, 13,14-hemiacetal, (22R) | $\Delta^5$ | | | | | 69 | 31 | | | | | | | 166 |
| 5 | Spirostane | 3β-OH, (25R) | $\Delta^5$ | | | | | 70 | 30 | | | 60 | 40 | | | 163 |
| 6 | Spirostane | 3β-OAc, (25R) | $\Delta^5$ | | | | | | | | | 66 | 34 | | | 163 |
| 7 | Cholestane | 3β-OAc | $\Delta^5$ | | | | | 34[d] | 66 | 40 | 60 | 28 | 72 | | | 167 |
| 8 | Androstane | 3β-OAc, 17-CO | $\Delta^5$ | | | | | 26[e] | 56 | | 55 | | | | | 54 |
| 9 | Cholestane | 3α-Me, $\Delta^7$ | $\Delta^5$ | | | | | 28[g] | | | | | | | | 75 |
| 10 | Cholestane | 3α-Me, $\Delta^7$, 25-OH | $\Delta^5$ | | | | | 13[g] | | | | | | | | 75 |
| 11 | Withanolide | 4-CO, $\Delta^{24}$, 24,25-$Me_2$ | $\Delta^5$ | | | | | 27[f] | 73 | | | | | | | 168 |
| 12 | Cholestane | 7-CO | $\Delta^5$ | | | | | | | | | | | | 89[h] | 55 |

[a] With hydrogenolysis in 60% yield to a 5:1 mixture of the corresponding 1-oxo-$\Delta^5$ - and $\Delta^4$- derivatives; [b] 1.3:1 mixture of 1α-OH- 5β- and 1α-OH, 6β-OAc-5β- derivatives; [c] separated by chromatography on silica gel following periodate oxidation to the related pregnane derivatives; [d] the products ratio for each experiment in entry **7** was estimated from the relative intensities of the 1-OAc and 19-Me signals in the NMR spectra of the mixtures of diacetates obtained by acetylation of the crude reduction products; [e] separated after saponification of 3β-OAc; [f] the 4-oxo-group was stereospecifically reduced to 4α-OH; [g] yield based on the 1-oxo-$\Delta^5$-3α-Me-derivative from which the 5,7-dien-compound originated; [h] with formation of a 1,5α-cyclo bond.

C=O bonds. Examination of Dreiding models revealed that the C-1 carbonyl group projects toward the α (rear) surface of the molecule and away from the C-10 methyl group.[169] Significant and consistent differences were noted in the UV and IR absorption,[169] rotational characteristics[169] and NMR solvent shifts[42] of 1-oxo-$\Delta^2$-derivatives in the 5α-series as compared with their counterparts in the 5β-series, and with 3-oxo-$\Delta^1$-derivatives in both series.[169] The exceptionally large Cotton effect found in CD data of a 2-en-1-one derivative has been ascribed to a positive contribution from the forward-projecting ring C rather than from the vicinal angular methyl group, since the latter's effect is negligible in the analogous D-homo-enone.*[170] Although 1-oxo-$\Delta^2$-5α-steroids had been appraised as hindered,[113] they readily underwent oximation at C-1,[108,134] and base-catalysed oximination at C-2 with a concomitant shift of $\Delta^2$ to $\Delta^3$.[171]

Table 5 shows that early experiments on the reduction with complex metal hydrides of 1-oxo-$\Delta^2$-5α-steroids gave controversial results; a cholestane derivative was reported to afford exclusively the quasi-equatorial 1β-ol (entry 6), a result that was expected from consideration of (a) electronic and steric factors which should favour the addition of the hydride ion on the opposite side of the vicinal C-10 methyl group,[113] with ring A in either the low energy half-chair or 1,2-diplanar forms;[122] and (b) an approach vector analysis,[172a] which suggested a strong influence by substituents at C-5 and C-10 on the stereochemical outcome of the reduction.[172b] However, this reaction seems to be more complex. Although the $\Delta^2$-1β-ol was reportedly[47] obtained in 80% yield after chromatography on alumina (entry 6), it was pointed out later[174] that a related androstane derivative gave, under these conditions, only the quasi-axial 1α-ol (entry 11). According to yet another experiment in the androstane series,[175] the allylic 1β- and 1α-alcohols were obtained in the ratio 9:1 following chromatography on silica; however, their total amount accounted for only 40% of the starting enone (entry 2). The epimerisation on alumina of the usually more stable quasi-equatorial 1β-alcohol (and to a lesser extent of its acetate or benzoate[47,176]) to the quasi-axial 1α-alcohol is interesting in itself and may be attributed to the release of steric compression due to the C-H-11α bond, prevailing in the former isomer.[99] Further evidence on that matter is adduced from a study of acid-catalysed allylic rearrangement of 1-hydroxy-2-enes and 3-hydroxy-1-enes, which showed that the formation ratio of the 1-hydroxy- to 3-hydroxy-derivatives is 5:4, of the 3α- to 3β-hydroxy-derivatives is about 1:1, and of the 1α- to 1β-hydroxy-derivatives is 50:3.[177] The ratios of these products were assessed in terms of the relative stabilities of the C-1 and C-3 carbocations in the intermediates, and of the thermodynamic stability of each allylic alcohol except the 1β-ol, which was suggested to be destabilised by steric repulsion between the C-H-11α- and C-OH-1β bonds.[177] Incidentally, the allylic character of the 1α-hydroxy-$\Delta^2$-system, too, was believed to be distorted because of the proximity of the C-10 methyl group and the C-11 protons,[174] especially since attempts by usual methods to oxidise it with manganese dioxide[174] or dichloro-dicyano-benzoquinone (DDQ),[178] failed. Nevertheless, it is rather the 1α-hydroxy-$\Delta^2$-derivative which is formed by allylic oxidation with selenium dioxide of $\Delta^2$-4,4-dimethyl-5α-compounds[37,179] or by allylic bromination of a similar system in the presence of water.[180]

Re-examination of the reduction of 5α-cholest-2-en-1-one with lithium aluminium hydride as well as with sodium borohydride demonstrated that ca 1 : 1 mixtures of allylic alcohols are obtained, and are easily separated on silica[99] (entry 9). These results disagree with the predictions and the early evaluations;[113,172a,173] admittedly, the significant change in the direction of attack of the reagent may be due to the flattening of ring A in the original enone. The alternative attempt to separate the crude mixture of allylic alcohols on alumina, leads to epimerisation of the $\Delta^2$-1β-alcohol to its 1α-counterpart, for the reasons outlined above.

The reductions with sodium borohydride were usually done in methyl alcohol at room temperature.[99] In one case, when the reaction proceeded in aqueous ethyl alcohol at 0°C, a substantial amount of 1-ketone remained unreduced after one hour (entry 16).[51b]

---

* The ORD-curves for two such model compounds were found to be roughly 'enantiomeric'.[105]

Table 5. Reduction of Conjugated 1-Oxo-Steroids in 5α-Series

| No. | 1-Oxo-$\Delta^2$-steroid substrate | Other substituents | $H_2$ - Pd | | | $H_2$ - Pt | | | Li - $NH_3$ | | $LiAlH_4$ | | $LiAl(t\text{-}BuO)_3H$ | | $NaBH_4$ | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1α-OH (%) | 1β-OH (%) | 1-Oxo (%) | 1α-OH (%) | 1β-OH (%) | 1-Oxo (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1-Oxo (%) | |
| 1 | Androstane | | | | | | $67^a$ | $11^a$ | | | | | | | | | | 128 |
| 2 | Androstane | | | | | | | | | | $4^b$ | 36 | | | | | | 175 |
| 3 | Androstane | $\Delta^{16}$ | | | | | | | | | $34^b$ | 52 | | | | | | 129 |
| 4 | Androstane | (D-homo) | | | | | $38^a$ | $35^a$ | | | | | | | | | | 106 |
| 5 | Cholestane | | | | | | $100^a$ | | | | | | | | | | | 68a |
| 6 | Cholestane | | | | | | | | | | | $80^c$ | | | | | | 47 |
| 7 | Cholestane | | | | | | $28^a$ | $55^a$ | | | | | | | | | | 107 |
| 8 | Cholestane | | | | | | $33^a$ | $66^a$ | | | | | | | | | | 38 |
| 9 | Cholestane | | | | | | | | | | $45^b$ | 55 | | | $55^b$ | 45 | | 99 |
| 10 | Androstane | 17-CO | | | | | $50^a$ | $50^a$ | | | | | | | | | | 130 |
| 11 | Androstane | 17β-OH, 17α-Me | | | | | | | | | only$^c$ | | $63^c$ | | | | | 174 |
| 12 | Cholestane | 3-Me | | | | | $92^a$ | | | | | | | | | | | 185 |
| 13 | Androstane | 3-Ph, 17β-OAc | | $79^a$ | 10 | | | | | | | | | | | | | 140 |
| 14 | Cholestane | 4α,5α-epoxy | | | | | | | | | | | | | $50^a$ | | | 99 |
| 15 | Androstane | 5α,6α-epoxy, 17β-OAc | | | | | | | | | | | | | 100 | | | 99 |
| 16 | Androstane | 6α-OH, 16-CO | | | | | | | | | | | | | | | $58^d$ | 51b |
| 17 | Cholestane | 4,4-$Me_2$ | $9^a$ | $18^a$ | $64^a$ | | | | | | | | | | | | | 37 |
| 18 | Lupane | 4,4-$Me_2$ | | | | | $80^a$ | | | | | | | | | | | 179 |
| 19 | Meliacane | 4,4-$Me_2$, 7α-OH, 14β,15β-epoxy | | | | | | | | $75^{a,e}$ | | | | | | | | 182 |
| 20 | Meliacane | 4,4-$Me_2$, 7-CO, 14β,15β-epoxy | | | | | | | | $63^{a,e}$ | | | | | | | | 182 |
| 21 | Oleanane | 4,4-$Me_2$, 18α-H, 19β,28-epoxy | | | | $45^{a,f}$ | $45^a$ | | | | | | | | | | | 134 |
| 22 | Oleanane | 4,4-$Me_2$, 18α-H, 19β,28-epoxy | | | | $30^{a,g}$ | $60^a$ | | | | | | | | | | | 134 |
| 23 | Oleanane | 4,4-$Me_2$, 18α-H, 19β,28-epoxy | | | | | $63^{a,g,h}$ | | | | $42^c$ | 46 | | | | | | 186 |

[a] With saturation of the conjugated double bond; [b] following chromatography on silica; [c] following chromatography on alumina; [d] in ethanol-water, 1h/0°C; [e] in the presence of methanol; [f] in acetic acid; [g] in ethyl acetate; [h] accompanied by the saturated 1-deoxo-derivative (9%).

Introduction of a 4,5- or a 5,6-epoxy-group in the 2-en-1-one-system affects notably the direction of attack of the reducing agent (more on that in Section 3.2). Indeed, while reduction with sodium borohydride of a 5α,6α-epoxy-4β-acetoxy-2en-1-one led to an inseparable mixture of the allylic 1α- and 1β-alcohols,[99] the same reaction with 4α,5α- and 5α,6α-epoxy-2-en-1-one-derivatives (entries 14 and 15, respectively) takes place by frontal attack as in unconjugated 5α-1-oxo-steroids (see Section 2.1). Besides, the reduction of the former derivative occurs with complete saturation of the double bond, in contrast with other α,β-unsaturated 1-ones in the 5α-series, to yield the saturated axial 1α-alcohol as the only isolable product.[99] The particular behaviour of the 4α,5α-epoxy-2-en-1-one-compound is presumably related to the increased hindrance due to the epoxide ring.[99]

All other methods for reduction of 1-oxo-$\Delta^2$-5α-steroids summarised in Table 5 (catalytic hydrogenation and metal–ammonia reduction) afforded mainly the equatorial 1β-hydroxy-derivatives, with saturation of the double bond. Indeed, the hydrogenation of conjugated 1-ketones in acetic acid over platinum is considered[108,128] to be the best method for preparing the corresponding saturated equatorial 1β-alcohols which are formed in various ratios, according to the reaction conditions, together with the saturated 1-ketones from which they are easily separated by chromatography. In the oleanane series, the saturated axial 1α-alcohol was also formed along with its 1β-counterpart, and in these cases no saturated 1-ketone was isolated (Table 5, entries 21 and 22). The results of the hydrogenation over palladium (entries 13 and 17) are noteworthy, as ketones are generally believed to be inert to this reduction, allowing selective hydrogenation of the conjugated double bond of the α,β-unsaturated carbonyl system.[181] Nonetheless, reduction of the 1-oxo-group was found to occur under these conditions too, leading again to the saturated equatorial 1β-alcohol, accompanied by various amounts of unreacted enones or saturated ketones. In one case, the formation of the saturated axial 1α-alcohol (in a 1 : 2 ratio to its 1β-isomer) was observed as well[37] (entry 17).

Finally, lithium–ammonia reduction of 1-oxo-$\Delta^2$-derivatives in the meliacane series could be stopped at the saturated ketone stage if the latter's enolate salt was quenched with ammonium chloride added at the end of the reaction, while the use of methyl alcohol as proton donor for the enolate salt led directly to the saturated 1β-alcohol,[182] as expected.[183,184]

### 3.2. *5β-Series*

Examination of Dreiding models suggested that the carbonyl group in a A/B-*cis*-$\Delta^2$-1-ketone lies close enough to the angular C-10 methyl group to imply a certain steric hindrance or shielding.[169] This C-1 ketone : C-10 methyl group interaction could account for the positivity of the molecular rotation observed for 1-ketones pertaining to 5β-series, as compared with their counterparts in 5α-series.[169] Other considerations derived from UV, IR, NMR solvent shifts, and rotational characteristics of 1-oxo-$\Delta^2$- and 1,11-dioxo-$\Delta^2$-steroids in both 5α- and 5β-series, and enabling better characterisation and differentiation of them,[169] have already been evaluated herein (see Sections 2.2 and 3.1). Eventually, the cortisone analogue 17,21-dihydroxy-5β-pregn-2-en-1,11,20-trione was expected to be biologically inactive on the ground of the conformational distortion due to C-1 : C-11 carbonyl group interaction, in addition to relocation of the double bond and *cis*-fusion of the A/B ring system which tends to deflect ring A towards the enzymically important α (rear) surface of the molecule.[169]

The results of sodium borohydride reduction of 1-oxo-$\Delta^2$-5β-steroids are displayed in Table 6. In contrast to its isomer in the 5α-series (Table 5, entry 9), reduction of 5β-cholest-2-en-1-one takes place with saturation of the 2,3-double bond to give a mixture of saturated ketone and the equatorial 1α-alcohol, along with ca 15% of unreacted enone[99] (entry 1). In this case, the direction of attack of the hydride is the same as for the saturated 1-ketone (*c.f.* Section 2.2).* However, the presence of

---

* The β-attack of the hydride on such compounds was actually predicted by Toromanoff,[113] except for the saturation of their double bond.

Table 6. Reduction of conjugated 1-Oxo-Steroids in 5β-Series

| No. | 1-Oxo- $\Delta^2$- steroid substrate | Other substituents | NaBH$_4$ | | | | Reference |
|---|---|---|---|---|---|---|---|
| | | | 1α-OH (%) | 1β-OH (%) | 1-Oxo (%) | 1-Oxo-$\Delta^2$ (%) | |
| 1 | Cholestane | | 37[a] | | 13[a] | 15 | 99 |
| 2 | Cholestane | 4-CO | 100[a] | | | | 99 |
| 3 | Cholestane | 4α-OAc, 5β-OH | 53[a] | | 8[a] | | 99 |
| 4 | Cholestane | 4β,5β-epoxy | | 28[a] | 35[a] | | 99 |
| 5 | Androstane | 4β-OAc, 5β,6β-epoxy, 17β-OAc | | 100[a] | | | 99 |
| 6 | Androstane | 5β,6β-epoxy, 17β-OAc | | 100[a] | | | 99 |

[a] With saturation of the conjugated double bond.

unchanged enone and of the saturated ketone in the reaction product is surprising, in view of the complete and stereospecific reduction of 5β-cholestan-1-one (Table 3, entry 1). Since allylic alcohols are not reduced by sodium borohydride to saturated alcohols, the formation of the saturated alcohol and ketone on the enone reduction suggests a 1,4-addition* of the reducing agent. Flattening of ring A in this enone (monoplanar 5β-form[188]) and steric hindrance by the C-10 methyl group† may well account for the more difficult front-side attack at C-1, rather than for attack at the other side of the conjugated system.[99] A similar rationalisation has been attempted[172b] by application of the approach vector analysis[172a] discussed above (see Section 3.1).

5β-Cholest-2-en-1,4-dione yielded by reduction with sodium borohydride an easily separable mixture of saturated 1α,4α- and 1α,4β-diols in roughly the same ratio as obtained from the corresponding saturated dione[99] (*c.f.* Section 2.2). A similar mixture of saturated 4α- and 4β-hydroxy-derivatives was obtained by reduction under the same conditions of 1β-acetoxy-5β-cholest-2-en-4-one.[99] Reduction of the isomeric 5α-derivatives (5α-cholest-2-en-1,4-dione and 1α-acetoxy-5α-cholest-2-en-4-one) afforded inseparable mixtures of allylic alcohols, but not saturated products.[99] The difference in behaviour of the 5β- and 5α-1-acetoxy-2-en-4-one-compounds toward sodium borohydride (1,4- versus 1,2-attack) may be rationalised[99] by considering the greater hindrance of a 4-one in the 5β-series rather than in the 5α-series.[67,189]

Likewise, 4α-acetoxy-5β-hydroxy-cholest-2-en-1-one gave the saturated equatorial 1α-hydroxy-derivative accompanied by the saturated ketone[99] (Table 6, entry 3), whereas reduction of a 4β-acetoxy-5α-hydroxy-$\Delta^2$-1-one-derivative afforded an inseparable mixture of 1α- and 1β-allylic alcohols. Under similar conditions, 5α- and 5β-hydroxy-cholest-2-en-1-one remained unchanged, for reasons which are not apparent.[99]

Introduction of a 4,5- or 5,6-epoxy group in the 2-en-1-one system markedly affects the latter's geometry and implicitly the direction of attack of the reducing agent. Thus, in 5β,6β-epoxy-2-en-1-oxo-steroids and in their 4β-hydroxy-derivatives, ring A is in a boat-like conformation with C-1 and C-4 'upwards'.[99] This conclusion was reached by crystallographic analysis of two naturally occurring steroids: withanolide E,[190] having a 5β,6β-epoxy-2-en-1-one partial structure, and withaferin A,[191] possessing an additional 4β-axial hydroxy-group. According to NMR data, ring A has the same conformation in the corresponding 2,3-dihydro-derivatives.[148] 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 between the two bonds. Since in such

---

* For a comprehensive discussion, see ref. 187.

† In another view, the equatorial orientation with respect to ring A of the C-10 methyl group in a 5β-$\Delta^2$-1-one would not hinder the β-approach of the anion.[113]

5$\beta$,6$\beta$-epoxy-steroids the C-1 carbonyl bond points 'upwards', axial attack from the rear of the molecule implies a reactant-like transition state. In 5$\beta$-cholestan-1-one, also, the carbonyl bond points 'upwards'; however, rear-side attack is difficult owing to the folding of rings A and B. Moreover, in the case of 5$\beta$,6$\beta$-epoxy-2-en-1-ones, the tendency toward rear-side attack is increased further by the hindrance on the $\beta$-side of the molecule due to the epoxide ring. Accordingly, reduction of the 5$\beta$,6$\beta$-epoxy-2-en-1-one derivatives (Table 6, entries 5 and 6) takes place with concomitant saturation of the double bond to give stereospecifically the corresponding equatorial 1$\beta$-alcohols, in contrast with their 5$\alpha$,6$\alpha$-epoxy isomers which afforded the related allylic alcohols, i.e. without involvement of the 2,3-double bond (*c.f.* Section 3.1). The absence of the conjugated double bond does not influence the steric outcome of the reduction of the 1-carbonyl in 5$\beta$,6$\beta$-epoxy-derivatives, as seen previously in the case of 4$\beta$-acetoxy-5$\beta$,6$\beta$-epoxy-1-oxo-with-24-enolide (*c.f.* Section 2.2, Table 3, entry 15). The assignment of configuration to the 1-hydroxy-group in these compounds is based on NMR evidence (broad multiplet for the 1-H signal). As a matter of fact, in 5$\beta$-steroids an equatorial substituent at C-1 should be $\alpha$-oriented. However, the 5$\beta$,6$\beta$-epoxide ring distorts the usual *cis*-A/B ring system to give a spatial arrangement approaching the 5$\alpha$-steroid-type structure, as shown by the 4$\alpha$-H NMR signals (narrow triplets) for 4$\beta$-acetoxy-5$\alpha$,6$\alpha$- and -5$\beta$,6$\beta$-epoxy derivatives.[192] The same pattern is exhibited by the 4-H signals for the reduction products presented in Table 3, entry 15, and Table 6, entry 5, thus indicating the axial orientation of the 4$\beta$-acetoxy-group.[99] Inspection of a model of 4$\beta$,5$\beta$-epoxy-cholest-2-en-1-one shows that the dihedral angle between rings A and B should be similar to that of the isomeric 5$\beta$,6$\beta$-epoxide. Furthermore, the aromatic solvent-induced shifts [$\Delta$($CDCl_3$-$C_6D_6$)] of the C-10 methyl NMR signals in both compounds are of the same sign and magnitude, pointing to the same geometrical relationship between the carbonyl and the methyl groups.[99] The reduction with sodium borohydride of this compound proceeds, therefore, by rear-side attack—as for the isomeric 5$\beta$,6$\beta$-epoxy-derivative—to give a mixture of the saturated axial 1$\beta$-alcohol, and of the corresponding saturated ketone whence only the double bond was reduced (Table 6, entry 4). It should be recalled in this connection that reduction of the isomeric 4$\alpha$,5$\alpha$-epoxy-cholest-2-en-1-one also occurred with complete saturation of the double bond, although by frontal attack as in all 1-oxo-5$\alpha$-steroids, to yield the axial 1$\alpha$-hydroxy-derivative (*c.f.* Section 3.1 and Table 5, entry 14).

According to these results, saturation of the conjugated double bond upon treatment with sodium borohydride seems to be a common reaction of 5$\beta$-steroidal 2-en-1-ones,[99] also observed for 5$\beta$-2-en-4-one-steroidal derivatives.[99,193] The peculiarly similar saturation of double bond in the 4$\alpha$,5$\alpha$-epoxy-2-en-1-one-compound is admittedly associated with the increased hindrance due to the epoxide ring.[99]

### 3.3. *$\Delta^4$- and $\Delta^5$-Series*

Only a few reduction experiments of 2,4- or 2,5-dien-1-ones are recorded in the literature. Thus, 1-oxo-$\Delta^{2,5}$-derivatives in the withanolide series are smoothly reduced with sodium borohydride[194] or diisobutylaluminium hydride[195] to the corresponding allylic alchols, but the stereochemistry at C-1 has not been assessed for either of them. In the case of a 1-oxo-$\Delta^{2,4}$-androstane derivative, reduction with sodium borohydride in methyl alcohol led to formation of the related 1-hydroxy-3$\alpha$,5$\alpha$-ether.[70] Again, no assignment of the 1-hydroxy configuration was attempted, and the reaction was considered another example of the ready 3$\alpha$,5$\alpha$-ether formation shown by this dienone under a variety of conditions.[70] In the hydrocortisone series, treatment with lithium aluminium hydride of a $\Delta^{2,4}$-1,11-dione led to the reduction of both keto-groups, resulting in the formation of the corresponding 1$\beta$-11$\beta$-diol[196] (see Section 2.2 for a comparison with the inertness of 1,11-dioxo-derivatives in the 5$\alpha$- and 5$\beta$-series). The allylic 1$\beta$-hydroxy-group thus produced could be oxidised back to the 1-ketone with DDQ,[196] in contrast to the 1$\alpha$-ol-$\Delta^2$-system in the 5$\alpha$-series, which resists oxidation with this reagent (*c.f.* Section 3.1). Regarding the reduction of the second hindered oxo-group, at C-11, shielding of the β-face by both C-18 and C-19 methyl groups leads to predominant formation of the axial 11β-hydroxy-derivative, in agreement with reported data.[25]

## 4. REDUCTION OF 1-OXO-A-NOR-STEROIDS

Differences in reactivity toward addition reactions of oxo-A-nor-steroids as compared with the corresponding oxo-steroids, originate in ring size and in strains caused by *cis*- and *trans*-fusion of the cyclopentanone ring to adjacent rings.[24c] Much in the same way as cyclopentanone reacts more slowly than cyclohexanone in this type of reaction, a steroidal A-nor-2-ketone reacts more slowly than its 5α-3-ketone analogue,[24b] and 17-oxo-steroids more slowly than ketones in other rings.[125e] Rate differences are presumably associated with a slow step in which the carbonyl carbon hybridisation changes from $sp^2$ to $sp^3$.[24b] In cyclopentanones, due to the near-planar character of the five-membered ring, the appearance of new eclipsing interactions with bonds on adjacent ring carbons (internal or 'I'-strain[197]) interferes with the change of hybridisation,[24c] in contrast to cyclohexanones, in which the substituents are nearly perfectly staggered in the chair conformation.[125e] Hence, the six-membered ring ketone has the carbonyl eclipsed by the equatorial C-H bonds, and the addition reactions are much faster.[125f]

Inasmuch as 1-oxo-A-nor-steroids are analogues of 1-oxo-steroids with respect to the C-10 angular methyl group, they could also be envisaged rather as analogues of 2-oxo-steroids, as far as the juncture position 5 of the A/B rings system is concerned. This duality is reflected in the properties of 1-oxo-A-nor-steroids. Thus, unlike 1-oxo-5α-steroids, they are not involved in C-1 : C-11 interaction, give a positive Zimmermann colour reaction, and do not form a hemi-ketal.[26] However, they do afford an oxime,[30,171] a 2,4-dinitrophenylhydrazone,[198] and, in the 5β-series, a thioketal.[77] They also readily undergo reduction with the usual agents, and some selected results are presented in Table 7. In the 5α-series, the 1-ketone was reduced by all agents to a single alcohol whose configuration was assigned as 1β-ol by comparing the sign of its molecular rotatory contribution with that of the hydroxyl group in the enantiomeric 17α- and 17β-hydroxy-derivatives, and inferring that it should have an equatorial character in the same way as 17β-substituted steroids do.[30] Approximate correspondences in magnitude were not expected, since the rotatory contribution of the 1-keto-group in A-nor-5α-cholestan-1-one is −53°, whereas that of the enantiomeric 17-keto-group in 5α-androstan-17-one is +266°.[30]

In the 5β-series the same trend toward preferential formation of the 1α-ol having equatorial character, is apparent (Table 7, entries 3–5). All the same, a neighbouring effect of the vicinal 2α-hydroxy-group is clearly seen in the reduction by complex hydrides of the corresponding 1-ketone (Table 7, entry 3), whereby significant amounts of the 1β-epimer have also been isolated. Complications arise in the case of enol derivatives such as compounds 6–8 (Table 7) when ketol rearrangements occur as a result of non-bonded interaction between the C-H-1α- or C-OH-1α bonds and the C-H-11α bond in the 2-oxo-A-nor-steroids, which has to be relieved by enolisation of the 2-ketone to $\Delta^1$ or by formation of the ketone at C-1.[199] The following order of stability was observed in these cases:[199]

$$2\alpha\text{-OH,1-CO} > 2\beta\text{-OH,1-CO} > 1\beta\text{-OH,2-CO} > 1\alpha\text{-OH,2-CO}.$$

The difference in stability between the 1-ketones having either a 2α- or a 2β-hydroxy group probably lies in the structural feature of the *cis*-fused A/B rings bending to the α-side, in which protonation of the enol at C-2 from the unhindered β-side should be favoured, leading to the former derivative.[199]

The formation of 5β-derivatives following hydrogenation of $\Delta^{3(5)}$ in compound 8 (Table 7) calls for some comments; the A-nor $\Delta^{3(5)}$-steroid actually adds hydrogen from the top, affording the more stable *cis*-hydrindanone system, a process admittedly influenced by the presence of the carbonyl

Table 7. Reduction of the 1-Oxo-Group in A-Nor-Steroids

| No. | 1-Oxo-A-nor- steroid substrate | Other substituents | C-5 substituent | $H_2$ - Pd | | $H_2$ - Pt | | Na-alcohol | | $LiAlH_4$ | | $NaBH_4$ | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | |
| 1 | Cholestane | | α-H | | | | 80 | | Singly[a] | | 70 | | | 30 |
| 2 | Withanolide | 5β-CHO, 6β-OH | β-CHO | | | | | | | | | Unreduced[b,c] | | 77 |
| 3 | Androstane | 2α,17β-$(OH)_2$ | β-H | | | | | | | 53 | 38 | 84 | 16 | 199 |
| 4 | Androstane | 2β,17β-$(OH)_2$ | β-H | | | | | | | 97 | | | | 199 |
| 5 | Androstane | 2β-OH, 17β-OCOEt | β-H | | | | | | | 89 | | | | 199 |
| 6 | Androstane | $\Delta^2$, 2,17β-$(OH)_2$ | β-H | 40[d] | | | | | | | | 62[e,f] | | 199 |
| 7 | Androstane | $\Delta^2$, 2-OMe, 17β-OH | β-H | | | | | | | 100[g] | | | | 199 |
| 8 | Androstane | 2-CO, 17β-OH | $\Delta^{3(5)}$ | 27[h] | | | | | | | | | | 199 |

[a] Yield not quoted; [b] after 1 h at room temperature; [c] the 5β-formyl group was reduced to the corresponding alcohol in 60% yield; [d] isolated as 1α-OH, 2-CO - derivative, and accompanied by the related 2α-OH,1-CO - compound in 60% yield; [e] isolated as 1α,2α-diol following chromatography on silica; [f] *ca* 14% of the starting ketone did not react; [g] further stabilised as 1α-OH,2-CO - derivative by addition of oxalic acid; [h] formed as 1α-OH,2-CO -5β- compound in an inseparable mixture with 2α-OH,1-CO -5β-compound, following preparative TLC which also produced pure 2α-OH,1-CO -5β- derivative in 43% yield.

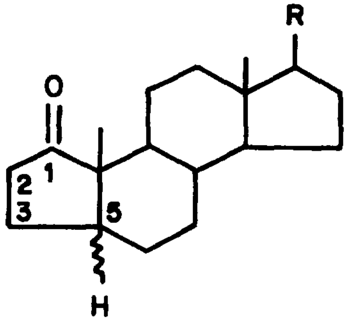
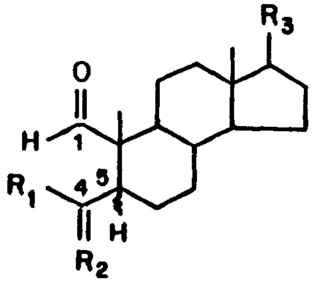
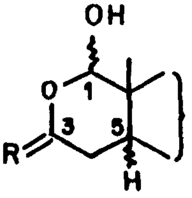


Figure 8. 1-Oxo-A-nor-steroids.



1



2

| | | | |
|---|---|---|---|
| **a** | $R_1 = CH{=}CH_2$, | $R_2 = H_2$, | $R_3 = C_8H_{17}$ |
| **b** | $R_1 = C{\equiv}CH$, | $R_2 = H_2$, | $R_3 = C_8H_{17}$ |
| **c** | $R_1 = C{\equiv}CH$, | $R_2 = CH_2$, | $R_3 = C_8H_{17}$ |
| **d** | $R_1 = CH_2OH$, | $R_2 = H_2$, | $R_3 = \beta{-}OH,\alpha{-}CH_3$ |
| **e** | $R_1 = COOH$, | $R_2 = H_2$, | $R_3 = O$ |
| **f** | $R_1 = COOH$, | $R_2 = H_2$, | $R_3 = \beta{-}OH,\alpha{-}CH_3$ |

**a** $R = H_2$
**b** $R = O$

Figure 9. 1-Oxygenated A-ring *seco*-steroids.

at C-1. A similar tendency has been noted for the hydrogenation of a 1-oxo-A-nor-$\Delta^5$-steroid which also led to the corresponding 5$\beta$-derivative.[77]

## 5. REDUCTION OF 1-OXO-*seco*-STEROIDS

### 5.1. *A-Ring* seco-*steroids*

A wide variety of 1-oxo-1,2-*seco*-steroids has been obtained in 5$\alpha$-, 5$\beta$- and $\Delta^4$-series, and some of them which were submitted to reduction with metal hydrides are represented in Fig. 9. Most of these A-ring *seco*- C-1 aldehydes are very reactive and/or labile : thus, *seco*-aldehydes alcohols (Fig. 9, **1d**) and acids (**1e,f**), once formed, cyclised spontaneously to give hemiacetals **2a**[200] and lactols **2b**,[200,201a] respectively. Yet, the *seco*-aldehyde **1a** failed to yield a 2,4-dinitrophenylhydrazone in acidic methyl alcohol solution, for reasons which could not be ascribed solely to hindrance exerted by the adjacent angular methyl group, and afforded instead a 1,3-dimethoxy-derivative with ring A reclosed.[202] Be that as it may, reduction of either *seco*-C-1 aldehydes or their lactol forms with metal hydrides, proceeds smoothly. Thus, treatment of the former compounds with sodium borohydride (**1b,c**)[203] or lithium aluminium hydride (**1f**)[200] affords the corresponding primary alcohols, whereas reduction with sodium borohydride of the latter derivatives (**2**) leads to lactones, including the pharmacologically important anti-inflammatory and anabolic 2-oxa-3-oxo-$\Delta^4$-steroids.[200,201a,204] Since in the last mentioned case large amounts of undesired saturated lactonic products may also be formed, R. Pappo (at Searle and Co.) devised a reduction procedure that involved a two-phase system consisting of chloroform and an aqueous alkaline solution of sodium borohydride.[201] Accordingly, the lactol is extracted into the aqueous phase and reduced to the corresponding lactone which, in turn, is selectively removed back into the organic phase, and thus protected from further reduction.[201,204a] In other experiments done with a related 4,4-dimethyl lactol in the euphol series, reduction with sodium borohydride in methyl alcohol led to the corresponding lactone as the main product, accompanied by 10% of a hemiacetal (3-hydroxy-2-oxa-derivative).[205] In the presence of one equivalent of potassium hydroxide, the same reduction gave a mixture of 40% lactone and 45% hemiacetal. The lactone itself was reduced quantitatively with sodium borohydride and alkali to the hemiacetal, and with lithium aluminium hydride to a *seco*-A-2-nor-1,3-diol.[205] The treatment of a similar lactol acetate in the 4,4-dimethyl-cholest-5-en-3-one-series with sodium borohydride has been noticed previously.[206] Finally, a hemiacetal having the structure **2a** (Fig. 9) was reduced with potassium borohydride to the corresponding *seco*-A-2-nor-1,3-diol in 60% yield.[200] The preparation by other methods of 1α-lactols,[40,206,207a] 1β-lactols,[207b] or their mixtures,[204] has been summarised.[204a]

### 5.2. *B-Ring* seco-*steroids* (*vitamin D derivatives*)

5.2.1. 5(10),6,8,-*Triene*-1-*one system.* All compounds related to this series (Table 8) are analogues and/or derivatives of the hormonal metabolite 1α,25-dihydroxyvitamin $D_3$ (Fig. 10, **1b**) which induces the formation of calcium-binding protein responsible for the calcium transport and its mobilisation in the body.[15] The requirement for a C-1 hydroxy-group having the α configuration* was established through analogue studies, undertaken to explore the relationship between the ring A hydroxy-groups' stereochemistry, and binding affinity for the intestinal 1α,25-dihydroxyvitamin $D_3$ receptor protein.[208–212] To this end, 1-oxo-vitamin $D_3$ derivatives were needed in order to yield by reduction 1β-hydroxy-analogues (**2**) of the natural metabolite **1b**. Eventually, oxidation of the 1-hydroxyl group in the available 1α-hydroxy-vitamin $D_3$ derivatives was found to afford not the expected 1-oxo-vitamin $D_3$ compounds (**3**) but the corresponding 1-oxo-previtamin $D_3$ (**4**),[208–213] also obtained in higher yield and at a faster rate by oxidation of 1α-hydroxy-previtamin $D_3$.[209] The exclusive formation of the 1-oxo-previtamin $D_3$ in the former case was attributed to an increase in its stability due to the linearly conjugated 5(10),6,8-triene-1-one system.[208,209] Other series of 1-oxo-vitamin D compounds were obtained by oxidation of cyclovitamin D derivatives (**5**)[210,213,214] and of 6,8-PTD (4-phenyl-1,2,4-triazoline-3,5-dione) adducts of previtamin $D_3$ derivatives (**6**).[213,215,216] Following reduction and separation, the pure hydroxy-epimers were finally converted to the corresponding vitamin D compounds by thermal isomerisation (in the case of previtamins),[208–212] by solvolysis and hydrolysis (cyclovitamins),[210,213,214] and by deprotection and subsequent thermal isomerisation (PTD adducts).[213,215,216]

The results of hydride reduction of 1-oxo-vitamin D derivatives are collected in Table 8. Reduction of 1-oxo-previtamin $D_3$ derivatives with sodium borohydride (entries 1,4,9 and 10) led mainly to the 1β-hydroxy-isomer, and with sodium triacetoxyborohydride (entry 11) to the 1α-epimer. With lithium aluminium hydride the 1α-hydroxy-epimer was also formed along with its 1β-counterpart (in a ca 1 : 3 ratio) (entries 1,2,5 and 8), presumably due to coordination of the aluminium atom to the hydroxy-group, yielding a conformationally fixed bidentate ligand which favours hydride attack from the less hindered side of the previtamin $D_3$ A-ring.[209,210] The opposite stereoselectivity was observed, as expected, in the reduction of 1-oxo-*epi*-previtamin $D_3$ derivatives with lithium aluminium hydride (entry 9) and with sodium borohydride (entry 13), and also by

---

*The configuration of the ring A hydroxyl groups in these 9,10-*seco*-steroids corresponds to the 1α,3β-dihydroxy-tetracyclic steroids (Fig. 10). Unless otherwise specified, the configuration of the 3-hydroxy-group remains unchanged from that of the 3β-hydroxyl of the parent tetracyclic steroid, i.e. it is 3*S* if position 1 is unsubstituted, and 3*R* if position 1 carries the α-hydroxyl (1*S*).

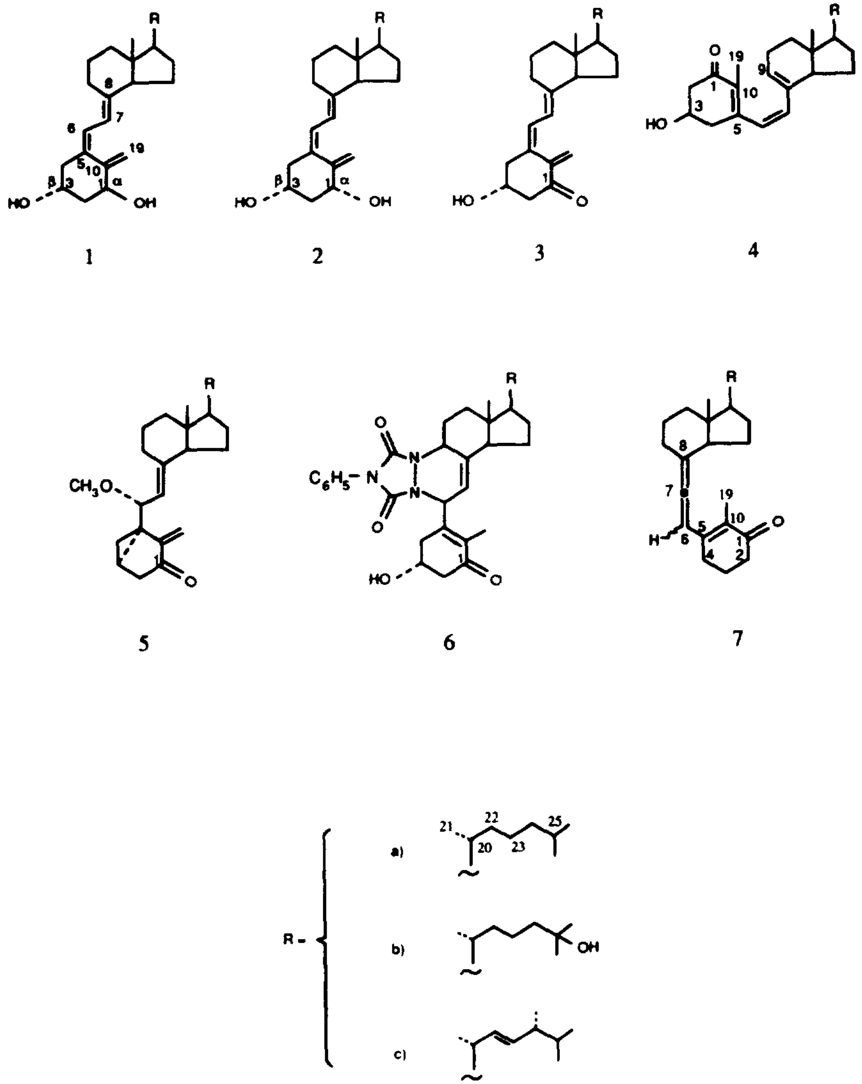


Figure 10. 1-Oxygenated B-ring *seco*-steroids (vitamin D derivatives and analogues).

using aluminium hydride with 1-oxo-previtamin $D_3$ derivatives (entries 3, 6 and 7). The latter results with aluminium hydride were rationalised by considering initial formation of an alkoxy metal hydride complex with the hydroxyl group at C-3 followed by intramolecular hydride transfer to the carbonyl group at C-1.[215] Incidentally, the use of deuteriated or tritiated sodium tri-acetoxyborohydride might be convenient for introducing a deuterium or tritium label at the 1$\beta$-position of the natural metabolite.[212] Yet, reduction with sodium borohydride of 1-oxo-3-deoxy-derivatives (entries 14, 15, and 16) led to about 1 : 1 mixtures of the corresponding 1-hydroxy-epimers.[217,218]

Preliminary investigations of the reduction with lithium aluminium hydride in ether of 1-oxo-3,5-cyclovitamin $D_3$ (Table 8, entry 14) showed that the 1$\beta$- and 1$\alpha$-hydroxy-isomers were formed in a 5 : 1 ratio.[210] In the case of the 1-oxo-*epi*-3,5-cyclovitamin $D_3$ (entry 20), the 1$\beta$-hydroxy-derivative still predominated, but in a lower ratio (2 : 1).[210] In a systematic study on the stereochemistry of the reduction of 1-oxo-3,5-cyclovitamin $D_3$ (Fig. 10, **5a**) and of its vitamin $D_2$ analogue

Table 8. Reduction of the 1-Oxo-Group in Vitamin D Derivatives

| No. | 1-Oxo-vitamin D substrate | Other substituents | $AlH_3$ |  | $LiAlH_4$ |  | $[(CH_3)_2CHCH_2]_2AlH$ |  | $Na[AlH_2(OCH_2CH_2OCH_3)_2]$ |  | $NaBH_4$ |  | $NaBH(OAc)_3$ |  | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) |  |
| 1 | Previtamin $D_3$ |  |  |  | $16^{a}$ | 44 |  |  |  |  |  | $70^{b}$ |  |  | 209 |
| 2 | Previtamin $D_3$ |  |  |  | $20^{a,c}$ | 80 |  |  |  |  |  |  |  |  | 208 |
| 3 | Previtamin $D_3$ |  | 73 | 18 |  |  |  |  |  |  |  |  |  |  | 213 |
| 4 | Previtamin $D_3$ | 3β-OAc |  |  |  |  |  |  |  |  |  | $63^{b}$ |  |  | 209 |
| 5 | Previtamin $D_3$ | 3β-OAc |  |  | $20^{a}$ | 60 |  |  |  |  |  |  |  |  | 210 |
| 6 | Previtamin $D_3$ | 6,8-PTD[d] | 76 | 8 |  |  |  |  |  |  |  |  |  |  | 215 |
| 7 | Previtamin $D_3$ | 6,8-PTD[d], 25-OH | 73 |  |  |  |  |  |  |  |  |  |  |  | 216 |
| 8 | Previtamin $D_3$ | 25-OH |  |  | $25^{a,c}$ | 75 |  |  |  |  |  |  |  |  | 208 |
| 9 | Previtamin $D_3$ | 25-OH |  |  |  |  |  |  |  |  | $3^{b}$ | 97 |  |  | 211 |
| 10 | Previtamin $D_3$ | 25-OH |  |  |  |  |  |  |  |  |  | $69^{b}$ |  |  | 212 |
| 11 | Previtamin $D_3$ | 25-OH |  |  |  |  |  |  |  |  |  |  | $69^{h}$ |  | 212 |
| 12 | Epi-previtamin $D_3$ | 3α-OAc |  |  | $60^{a}$ | 20 |  |  |  |  |  |  |  |  | 210 |
| 13 | Epi-previtamin $D_3$ | 3α-OH, 25-OH |  |  |  |  |  |  |  |  | $69^{b}$ |  |  |  | 212 |
| 14 | Previtamin $D_3$ | 3-Deoxy |  |  |  |  |  |  |  |  | $49^{b}$ | 36 |  |  | 217 |
| 15 | Previtamin $D_3$ | 3-Deoxy |  |  |  |  |  |  |  |  | 29 | 32 |  |  | 218 |
| 16 | cis-Isotachysterol | 3-Deoxy, $\Delta^{8(14)}$ |  |  |  |  |  |  |  |  | 47 | 46 |  |  | 218 |
| 17 | 3,5-Cyclovitamin $D_3$ | 6(R)-OMe |  |  | $1^{a,e}$ | 5 |  |  |  |  |  |  |  |  | 210 |
| 18 | 3,5-Cyclovitamin $D_3$ | 6(R)-OMe |  |  | $13^{a,f}$ | 61 | $1^{a,e,f}$ | 2 |  |  | $1^{e,f,g}$ | 1.8 |  |  | 214 |
| 19 | 3,5-Cyclovitamin $D_3$ | 6(R)-OMe |  |  | $1^{e,f,h}$ | 2.5 | $1^{e,f,h}$ | 1.4 |  |  | $1^{e,f,i}$ | 2.1 |  |  | 214 |
| 20 | 3,5-Cyclovitamin $D_3$ | 6(R)-OMe |  |  | $1^{a,e,j}$ | 4.5 | $1^{a,c,e,f}$ | 1.6 |  |  |  |  |  |  | 214 |
| 21 | 3,5-Cyclovitamin $D_3$ | 6(R)-OMe |  |  | $1^{e,h,j}$ | 2.5 | $1^{c,e,f,h}$ | 1 |  |  |  |  |  |  | 214 |
| 22 | 3,5-Cyclovitamin $D_3$ | 6(R)-OMe |  |  |  |  | $1^{a,c,e,k}$ | 1.5 |  |  |  |  |  |  | 214 |
| 23 | Epi-3,5-Cyclovitamin $D_3$ | 6(S)-OMe |  |  | $1^{a,e}$ | 2 |  |  |  |  |  |  |  |  | 210 |
| 24 | 3,5-Cyclovitamin $D_2$ | 6(R)-OMe |  |  | $11.5^{a,f}$ | 58.5 | $21^{f,h}$ | 24 | $1^{a,e,f}$ | 5 | $1^{e,f,g}$ | 1.7 |  |  | 214 |
| 25 | 3,5-Cyclovitamin $D_2$ | 6(R)-OMe |  |  | $1^{e,f,h}$ | 2.7 | $1^{a,e,f}$ | 1.5 | $1^{e,f,h}$ | 1.4 |  |  |  |  | 214 |
| 26 | 3,5-Cyclovitamin $D_2$ | 6(R)-OMe |  |  |  |  | $1^{a,c,e,f}$ | 1.3 |  |  |  |  |  |  | 214 |
| 27 | 3,5-Cyclovitamin $D_2$ | 6(R)-OMe |  |  |  |  | $1^{c,e,f,h}$ | 1.1 |  |  |  |  |  |  | 214 |

[a] In ether; [b] in methanol; [c] inverse addition; [d] 4-phenyl-1,2,4-triazoline-3,5-dione adduct; [e] epimers ratio, yield not quoted; [f] at room temperature; [g] in ether-ethanol; [h] in tetrahydrofuran; [i] in ether-tetrahydrofuran; [j] at 0°C; [k] at -20°C.

Table 9. Reduction of the 1-Oxo-Group in Vitamin D-Type Vinylallene 1-One Derivatives

| No. | Vinylallene 1-one substrate | $NaBH_4$ [a] | | $LiAl(t\text{-}BuO)_3H$ [b] | | $LiB(s\text{-}Bu)_3H$ *[b] | | 9-BBN **[b] | | PBPH ***[b] | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | 1α-OH (%) | 1β-OH (%) | |
| 1 | (6R)-9,10-Secocholesta-5(10),6,7-triene-1-one | 38.5 | 38.5 | 32.3 | 38.7 | 45.5 | 54.5 | 48.0 | 40.0 | 53.7 | 41.3 | 218 |
| 2 | (6S)-9,10-Secocholesta-5(10),6,7-triene-1-one | 39.2 | 50.8 | 39.3 | 35.7 | 58.3 | 41.7 | 41.4 | 45.6 | 31.7 | 63.3 | 218 |

[a] In ethanol; [b] in tetrahydrofuran.

* L-selectride, lithium tri-*sec*-butylborohydride; ** 9-borabicyclo[3.3.1]nonane; *** lithium perhydro-9b-boraphenalylhydride.

(Fig. 10, **5c**), the previously noted results with lithium aluminium hydride in ether were confirmed, and the effect of reagents, solvents, and temperature on the ratio of the hydroxy-isomers formed, was investigated.[214] Accordingly, the selectivity observed with lithium aluminium hydride in ether was found to decrease when tetrahydrofuran was used as solvent, and the same trend was noted for reduction with sodium dihydrobis(2-methoxyethoxy)aluminate (entries 21 and 22). These results were explained by assuming that coordination of the methoxyl group at C-6 and of the carbonyl group at C-1 in **5a** and **5c** (Fig. 10) to the aluminium atom of the reagent, hinders the approach of the hydride from the α-side.[214] Conversely, tetrahydrofuran might coordinate to the reducing agent, thus rendering chelation between the aluminium atom and the oxygen atoms of ring A in **5a** and **5c** more difficult compared with the reduction in ether, and consequently leading to a lower ratio of the 1*β*- to 1α-hydroxy-isomers.[214] The effect of temperature was not apparent in the reduction selectivity.[214]

Other reducing agents like sodium borohydride and diisobutylaluminium hydride showed no appreciable stereoselectivity, as compared with lithium aluminium hydride. It was inferred that diisobutylaluminium hydride might be too bulky for coordinating with the oxygen atoms of ring A* and, in fact, when tetrahydrofuran was employed as solvent, the isomer ratio was found to be 1 : 1, and hence useful for preparing 1α-hydroxyvitamin $D_2$ and $D_3$, radioisotope-labeled at C-1.[214] No effect of the side-chain on the stereochemistry of reduction of the 1-oxo-group in cyclovitamin $D_3$, as compared with the vitamin $D_2$ analogue (Fig. 10, **3a** and **3c**, respectively), could be observed (Table 8).[214]

5.2.2. 5(10),6,7-*Triene*-1-*one system*. An alternative to the classical linear steroid route for the synthesis of vitamin D analogues is provided by a convergent approach whereby the A ring, and the C/D rings with the proper side chain, are produced separately and then joined to construct the target structure.[218] A key step in this sequence would be the reduction of intermediate vinylallenones having a 5(10),6,7-triene-1-one system (Fig. 10, **7**) to the corresponding vinylallenols, which by thermolysis will rearrange to the related vitamin D derivatives. Accordingly, a study on reduction of vitamin D-type vinylallene 1-one compounds with a variety of reagents was undertaken, but did not point to any significant stereoselectivity (Table 9).[218]

## CONCLUSION

The complex interplay of electronic, steric, and neighbouring group effects operating in the reduction by different methods of unsubstituted and/or variously substituted 1-oxo-steroids was assessed, in an attempt to outline the unique character of the carbonyl group at C-1 in the A/B rings

---

* In another view, the tricoordinated diisobutylaluminium hydride forms a complex with the carbonyl group before the reduction and thus cannot chelate, whereas the methoxy- and carbonyl groups do chelate with the lithium atom of lithium aluminium hydride but not with sodium borohydride/alcohol.[92]

system. The experimental results discussed herein should enable the choice of reducing agents and conditions needed in order to prepare conveniently either C-1 epimeric alcohol in all steroidal series.

*Acknowledgements*—This account was prepared during a sabbatical of M. W. at the Pierre et Marie Curie University, Paris, and the authors thank CNRS for financial support. Special thanks are expressed to Professors A. Nickon, J. Seyden-Penne and A.B. Turner for helpful suggestions and comments. This is contribution No. 3563-E, 1992 series, from the Agricultural Research Organization, The Volcani Center, Bet Dagan, Israel.

## REFERENCES

1. Fieser L. F.; Fieser M. *Steroids*; Reinhold Publishing: New York, 1959; (a) Chapter 1; (b) p. 662; (c) p. 205; (d) p. 309; (e) pp. 268–269; (f) p. 220; (g) p. 219.
2. Devon T. K.; Scott A. I. *Handbook of Naturally Occurring Compounds, Vol. II Terpenes*; Academic Press: New York, 1972; (a) p. 385; (b) p. 281.
3. Enslin P. R.; Naudé T. W.; Potgieter D. J. J.; van Wyk A. J.; *Tetrahedron* **1966,** *22,* 3213.
4. Osborne R.; Pegel K. H. *S. Afr. J. Chem.* **1985,** *38,* 83.
5. (a) Kupchan S. M.; Ognyanov I. *Tetrahedron Lett.* **1969,** 1709; (b) Capon R. J.; MacLeod J. K.; Oelrichs P. B. *Aust. J. Chem.* **1986,** *39,* 1711, and references therein; (c) Wagner H.; Lotter H.; Fischer M. *Helv. Chim. Acta* **1986,** *69,* 359; (d) Yan X.; Lee K.; Yamagishi T. *Shanghai Yike Daxue Xuebao* **1992,** *19,* 206; *Chem. Abstr.* **1992,** *117,* 188260.
6. (a) Patel A. V.; Blunden G.; Crabb T. A.; Sauvaire Y.; Baccou Y. C. *Fitoterapia* **1987,** *58,* 67; (b) Voigt G.; Hiller K. *Sci. Pharm.* **1987,** *55,* 201.
7. (a) Tamm Ch. In *Proc. 1st Int. Pharmacological Meeting*, Stockholm, 1961, *Vol.* 3; Wilbrandt W.; Lingren P. Eds.; Pergamon Press: Oxford, 1961; pp.11–26; (b) Gaignault J. C.; Bidet D. *Fitoterapia* **1988,** *59,* 259.
8. Weissenberg M. In *Toxicants of Plant Origin, Vol* 2 *Glycosides*; Cheeke P. R. Ed.; CRC Press: Boca Raton, Florida, 1989; Chapter 7.
9. (a) Lafont R.; Horn D. H. S. In *Ecdysone*; Koolman J. Ed.; G. Thieme Verlag, Stuttgart, 1989; pp. 39–64; (b) Cutler H. G. In *Natural and Engineered Pest Management Agents*; Hedin P. A.; Menn J. J.; Hollingworth R. M. Eds; American Chemical Society: Washington, 1994; ACS Symposium Series No. 551, Chapter 7.
10. Kerr R. G.; Baker B. J. *Nat. Prod. Rep.* **1991,** *8,* 465.
11. Schneider J. J.; Bhacca N. S. *J. Biol. Chem.* **1966,** *241,* 5313.
12. Townsley J. D.; Brodie H. J. *Biochem. J.* **1966,** *101,* 25c.
13. Edwards R. W. H.; Trafford D. J. H. *Biochem J.* **1968,** *108,* 185.
14. (a) Almé B.; Bremmelgaard A.; Sjövall J.; Thomassen P. *J. Lipid Res.* **1977,** *18,* 339; (b) Honour J. W.; Tourniaire J.; Biglieri E. G.; Shackleton C. H. L. *J. Steroid Biochem.* **1978,** *9,* 495; (c) Obinata K.; Nittono H.; Yabuta K.; Mahara R.; Tohma M. *J. Pediatr. Gastroenterol. Nutr.* **1992,** *15,* 1.
15. Pike W. J. *Annu. Rev. Nutr.* **1991,** *11,* 189.
16. (a) Glotter E.; Kirson I.; Lavie D.; Abraham A. In *Bioorganic Chemistry, Vol II Substrates Behaviour*; van Tamelen E. E. Ed.; Academic Press: New York, 1978; Chapter 3; (b) Glotter E. *Nat. Prod. Rep.* **1991,** *8,* 415.
17. (a) Christen Ph. *Pharm. Acta Helv.* **1986,** *61,* 242; (b) Christen Ph. *Pharm. Unserer Zeit* **1989,** *18,* 129.
18. Kobayashi M.; Lee N. K.; Son B. W.; Yanagi K.; Kyogoku Y.; Kitawaga I. *Tetrahedron Lett.* **1984,** *25,* 5925.
19. Shingu K.; Marubayashi N.; Ueda I.; Yahara. S.; Nohara T. *Chem. Pharm. Bull.* **1990,** *38,* 1107.
20. (a) Elliger C. A.; Wong R. Y.; Benson M.; Waiss, Jr A. C. *J. Nat. Prod.* **1989,** *52,* 1345; (b) Elliger C. A.; Wong R. Y.; Benson M.; Waiss, Jr A. C. *J. Chem. Soc. Perkin Trans. I* **1992,** 5.
21. Duff A. G.; Gellert E.; Rudzats R. *Phytochemistry* **1973,** *12,* 2943.
22. (a) Ourisson G.; Crabbé P.; Rodig O. *Tetracyclic Triterpenes*; Lederer E. Ed.; Holden-Day: San Francisco, 1964; (b) Ourisson G. *Pure Appl. Chem.* **1989,** *61,* 345.
23. (a) Rougereau A.; Person O.; Rougereau G. *Int. J. Vit. Nutr. Res.* **1987,** *57,* 19; (b) Rougereau A.; Person O.; Rougereau G. *Int. J. Vit. Nutr. Res.* **1987,** *57,* 25.
24. Kirk D. N.; Hartshorn M. P. *Steroid Reaction Mechanisms*; Elsevier: Amsterdam, 1968; (a) p. 2. (b) p. 130; (c) p. 131; (d) p. 268, *c.f.* ref. 107; (e) p. 147.
25. Rasmusson G. H.; Arth G. E. In *Organic Reactions in Steroid Chemistry*; Fried J.; Edwards J. A. Eds; Van Nostrand Reinhold: New York 1972; Vol. I, Chapter 5.
26. Sigg H. P.; Tamm Ch. *Helv. Chim. Acta* **1960,** *43,* 1402.
27. (a) Djerassi C., personal communication to Shoppee C. W.; Roy S. K.; Goodrich B. S. *J. Chem. Soc.* **1961,** 1583; (b) Djerassi C.; Mitscher L. A.; Mitscher B. J. *J. Am. Chem. Soc.* **1959,** *81,* 947.
28. Julia S.; Linarès H.; Simon P. *Bull. Soc. Chim. Fr.* **1963,** 2471.
29. (a) Audier H.; Bottin J.; Diara A.; Fétizon M.; Foy P.; Golfier M.; Vetter W. *Bull. Soc. Chim. Fr.* **1964,** 2292; (b) von Mutzenbecher G.; Pelah Z.; Williams D. H.; Budzikiewicz H.; Djerassi C. *Steroids* **1963,** *2,* 475.
30. Shoppee C. W.; Roy S. K.; Goodrich B. S. *J. Chem. Soc.* **1961,** 1583.
31. Kimura M.; Nishina T.; Sakamoto T. *Chem. Pharm. Bull.* **1967,** *15,* 454.
32. Bose A. K.; Ramar R. M. *Steroids* **1968,** *11,* 27.
33. Hewett C. L.; Gibson S. G.; Redpath J.; Savage D. S. *J. Chem. Soc. Perkin Trans. I* **1974,** 1432.
34. Tamm Ch.; Albrecht R. *Helv. Chim. Acta* **1960,** *43,* 768.
35. Tamm Ch. *Helv. Chim. Acta* **1960,** *43,* 1700.

36. (a) Djerassi C.; Nakano T. *Chem. Ind. (London)* **1960,** 1385; (b) Nakano T.; Hasegawa M.; Djerassi C. *Chem. Pharm. Bull.* **1963,** *11,* 465.
37. François Ph.; Lablache-Combier A.; Levisalles J. *Bull. Soc. Chim. Fr.* **1965,** 2588.
38. Shoppee C. W.; Sharma S. C. *J. Chem. Soc. (C)* **1968,** 245.
39. Talaty E. R.; Russell G. A. *J. Org. Chem.* **1966,** *31,* 3455.
40. Hanna R.; Ourisson G. *Bull. Soc. Chim. Fr.* **1967,** 3742.
41. Schlegel W.; Tamm Ch. *Helv. Chim. Acta* **1957,** *40,* 160.
42. (a) Weissenberg M.; Glotter E.; Lavie D. *Israel J. Chem.* **1968,** *6,* 23; (b) Glotter E.; Weissenberg M.; Lavie D. *Tetrahedron* **1970,** *26,* 3857.
43. Lavie D.; Greenfield S.; Glotter E. *J. Chem. Soc. (C)* **1966,** 1753.
44. Suginome H.; Yagihashi F. *J. Chem. Soc. Perkin Trans. I* **1977,** 2488.
45. Schneider J. J.; Crabbé P.; Bhacca N. S. *J. Org. Chem.* **1968,** *33,* 3118.
46. Kirk D. N. *Tetrahedron* **1986,** *42,* 777.
47. Tamm Ch.; Albrecht R. *Helv. Chim. Acta* **1959,** *42,* 2177.
48. Henbest H. B.; Wilson R. A. L. *J. Chem. Soc.* **1956,** 3289.
49. Ayres D. C.; Kirk D. N.; Sawdaye R. *J. Chem. Soc. (B)* **1970,** 505.
50. (a) Biesemans M.; Van de Woude G.; van Hove L. *Bull. Soc. Chim. Belg.* **1990,** *99,* 29; (b) Johnson F. *Chem. Rev.* **1968,** *68,* 375.
51. (a) Bridgeman J. E.; Cherry P. C.; Cottrell W. R. T.; Jones E. R. H.; Le Quesne P. W.; Meakins G. D. *Chem. Commun.* **1966,** 561; (b) Bell A. M.; Cherry P. C.; Clark I. M.; Denny W. A.; Jones E. R. H.; Meakins G. D.; Woodgate P. D. *J. Chem. Soc. Perkin Trans. I* **1972,** 2081.
52. Weissenberg M. *unpublished results.*
53. Frei J.; Ganter C.; Kägi D.; Kocsis K.; Miljkovic M.; Siewinski A.; Wenger R.; Schaffner K.; Jeger O. *Helv. Chim. Acta* **1966,** *49,* 1049.
54. (a) Dodson R. M.; Goldkamp A. H.; Muir R. D. *J. Am. Chem. Soc.* **1968,** *82,* 3118; (b) *Ibid.,* footnote 7.
55. Christensen J. R.; Reusch W. *J. Org. Chem.* **1983,** *48,* 3741.
56. Weissenberg M.; Glotter E.; Lavie D. *Proc. 42nd Meeting Israel Chemical Soc.* **1972,** 15.
57. Weissenberg M.; Glotter E.; Lavie D. *Tetrahedron Lett.* **1974,** 3063.
58. Weissenberg M.; Lavie D.; Glotter E. *J. Chem. Soc. Perkin Trans. I* **1977,** 795.
59. Glotter E.; Kirson I.; Abraham A.; Lavie D. *Tetrahedron* **1973,** *29,* 1353.
60. (a) Ishiguro M.; Kajikawa A.; Haruyama T.; Morisaki M.; Ikekawa N. *Tetrahedron Lett.* **1974,** 1421; (b) Ishiguro M.; Kajikawa A.; Haruyama T.; Ogura Y.; Okubayashi M.; Morisaki M.; Ikekawa N. *J. Chem. Soc. Perkin Trans. I* **1975,** 2295.
61. Klyne W. *Progress in Stereochemistry*; Klyne W. Ed.; Butterworth: London, 1954; Vol. 1, pp. 36–89.
62. Dauben W. G.; Blanz, Jr E. J.; Jiu J.; Micheli R. A. *J. Am. Chem. Soc.* **1956,** *78,* 3752.
63. Mateos J. L. *J. Org. Chem.* **1959,** *24,* 2034.
64. Huneck S. *Tetrahedron Lett.* **1963,** 1977.
65. (a) Wharton P. S.; Bohlen D. H. *J. Org. Chem.* **1961,** *26,* 3615; (b) Huang-Minlon; Chung-Tungshun *Tetrahedron Lett.* **1961,** 666; (c) Coffen D. L.; Korzan D. G. *J. Org. Chem.* **1971,** *36,* 390.
66. Obasi M. E.; Okogun J. I.; Ekong D. E. U. *J. Chem. Soc. Perkin Trans. I* **1972,** 1943.
67. Stevenson R.; Fieser L. F. *J. Am. Chem. Soc.* **1956,** *78,* 1409.
68. (a) Striebel P.; Tamm Ch. *Helv. Chim. Acta* **1954,** *37,* 1094; (b) Ruzicka L.; Plattner P. A.; Furrer M. *Helv. Chim. Acta* **1944,** *27,* 727; (c) Plattner P. A.; Fürst A.; Els H. *Helv. Chim. Acta* **1954,** *37,* 1399.
69. Evans D. E.; Lewis G. S.; Palmer P. J.; Weyell D. J. *J. Chem. Soc. (C)* **1968,** 1197.
70. Hanson J. R.; Organ T. D. *J. Chem. Soc. (C)* **1970,** 1065.
71. Murakami T.; Nagasawa M.; Itokawa H.; Tachi Y.; Tanaka K. *Tetrahedron Lett.* **1966,** 5137.
72. Khuong-Huu F.; Herlem D.; Benechie M. *Bull. Soc. Chim. Fr.* **1970,** 2702.
73. Shoppee C. W.; Coll J. C.; Lack R. E. *J. Chem. Soc. (C)* **1970,** 1893.
74. Chambers V. E. M.; Denny W. A.; Jones E. R. H.; Meakins G. D.; Miners J. O.; Pinhey J. T.; Wilkins A. L. *J. Chem. Soc. Perkin Trans. I* **1975,** 1359.
75. Okamura W. H.; Mitra M. N.; Pirio M. R.; Mouriño A.; Carey S. C.; Norman A. W. *J. Org. Chem.* **1978,** *43,* 574.
76. Morita K. *Bull. Chem. Soc. Jpn.* **1959,** *32,* 791.
77. Lavie D.; Kashman Y.; Glotter E.; Danieli N. *J. Chem. Soc. (C)* **1966,** 1757.
78. Neustadter P. J. In *Steroid Reactions*; Djerassi C. Ed.; Holden–Day: San Francisco, 1963; pp. 135–147, and references therein.
79. Wheeler D. M. S.; Wheeler M. M. In *Organic Reactions in Steroid Chemistry*; Fried J.; Edwards J. A. Eds; Van Nostrand Reinhold: New York, 1972; Vol. I, Chapter 2, and references therein.
80. Barton D. H. R. *J. Chem. Soc.* **1953,** 1027.
81. Dauben W. G.; Fonken G. J.; Noyce D. S. *J. Am. Chem. Soc.* **1956,** *78,* 2579.
82. Brown H. C.; Deck H. R. *J. Am. Chem. Soc.* **1965,** *87,* 5620.
83. Landor S. R.; Reagan J. R. *J. Chem. Soc. (C)* **1967,** 1159.
84. Chérest M.; Felkin H.; Prudent N. *Tetrahedron Lett.* **1968,** 2199.
85. Kirk D. N. *Tetrahedron Lett.* **1969,** 1727.
86. Eliel E. L.; Senda Y. *Tetrahedron* **1970,** *26,* 2411.
87. Kamernitzky A. V.; Akhrem A. A. *Tetrahedron* **1962,** *18,* 705.
88. (a) Richer J. C. *J. Org. Chem.* **1965,** *30,* 324; (b) Marshall J. A.; Caroll R. D. *J. Org. Chem.* **1965,** *30,* 2748; (c) Wigfield D. C.; Gowland F. W. *J. Org. Chem.* **1977,** *42,* 1108.

89. Jacquesy; J. C.; Jacquesy R.; Levisalles J. *Bull. Soc. Chim. Fr.* **1967,** 1649.
90. (a) Chérest M.; Felkin H. *Tetrahedron Lett.* **1968,** 2205; (b) Chérest M.; Felkin H.; Frajerman C. *Tetrahedron Lett.* **1971,** 379; (c) Chérest M.; Felkin H. *Tetrahedron Lett.* **1971,** 383; (d) Anh N. T.; Eisenstein O. *Nouv J. Chim.* **1977,** *1,* 61.
91. (a) Klein J. *Tetrahedron Lett.* **1973,** 4307; (b) Liotta C. *Tetrahedron Lett.* **1975,** 519; (c) Royer J. *Tetrahedron Lett.* **1978,** 1343; (d) Wu Y.-D.; Tucker J. A.; Houk K. N. *J. Am. Chem. Soc.* **1991,** *113,* 5018; (e) Shi Z.; Boyd R. J. *J. Am. Chem. Soc.* **1993,** *115,* 9614; (f) Cieplak A. S. *J. Am. Chem. Soc.* **1981,** *103,* 4540; (g) Midland M. M.; Kwon Y. C. *J. Am. Chem. Soc.* **1983,** *105,* 3725.
92. Seyden-Penne J. *Réductions par les Alumino et Borohydrures en Synthèse Organique*; Technique et Documentation: Paris, 1988.
93. Schneider J. J. *J. Chromatogr.* **1968,** *37,* 89.
94. (a) Herz J. E.; González E. *J. Chromatogr.* **1968,** *37,* 251; (b) Herz J. E.; Márquez L. A. *J. Chem. Soc.* (*C*) **1969,** 2243.
95. Wipke W. T.; Gund, P. *J. Am. Chem. Soc.* **1976,** *98,* 8107.
96. Wigfield D. C. *Canad. J. Chem.* **1977,** *55,* 646.
97. (a) Rei M.-H. *J. Org. Chem.* **1979,** *44,* 2760; (b) Murugan R. *Canad. J. Chem.* **1980,** *58,* 1993.
98. Levisalles J.; Ma J. C. N. *Bull. Soc. Chim. Fr.* **1962,** 1597.
99. Weissenberg M.; Glotter E. *J. Chem. Soc. Perkin Trans. I* **1977,** 988.
100. Bordwell F. G.; Landis P. S. *J. Am. Chem. Soc.* **1958,** *80,* 6383, footnote 7.
101. Zimmerman H. E.; Singer L.; Thyagarajan B. S. *J. Am. Chem. Soc.* **1959,** *81,* 108, footnote 16.
102. Eliel E. L. *Stereochemistry of Carbon Compounds*; McGraw–Hill: New York, 1962; p. 436.
103. (a) Church R. F.; Ireland R. E.; Marshall J. A. *J. Org. Chem.* **1962,** *27,* 1118; (b) Schmidt C. *Canad. J. Chem.* **1973,** *51,* 3989; (c) Yamakawa K.; Tominaga T.; Nishitani K. *Tetrahedron Lett.* **1975,** 4137.
104. (a) Clinton R. O.; Christiansen R. G.; Neumann H. C.; Laskowski S. C. *J. Am. Chem. Soc.* **1957,** *79,* 6475; (b) Hirshmann H.; Hirshmann F. B.; Zala A. P. *J. Org. Chem.* **1966,** *31,* 375.
105. Kirk D. N.; Klyne W.; Peach C. M.; Wilson M. A. *J. Chem. Soc.* (*C*) **1970,** 1454.
106. Contreras L. E.; Evans J. M.; de Marcano D.; Marquez L.; Molina M.; Tempestini L. *J. Org. Chem.* **1974,** *39,* 1550.
107. Shoppee C. W.; Lack R. E.; Sharma S. C.; Smith L. R. *J. Chem. Soc.* (*C*) **1967,** 1155.
108. Marazano C.; Longevialle P. *Bull. Soc. Chim. Fr.* **1975,** 1307.
109. Eggert H.; Van Antwerp C. L.; Bhacca N. S.; Djerassi C. *J. Org. Chem.* **1976,** *41,* 71.
110. Schwenzer G. M. *J. Org. Chem.* **1978,** *43,* 1079.
111. (a) Pradhan S. K. *Tetrahedron* **1986,** *42,* 6351; (b) *Ibid.*, ref. 78, personal communication of Sankaran R. to Pradhan S. K.
112. (a) Mori H., *Chem. Pharm. Bull.* **1962,** *10,* 386; (b) Bertin D.; Perronnet J. *Bull. Soc. Chim. Fr.* **1964,** 2782; (c) Wechter W. J.; Slomp G.; McKellar F. A.; Wiechert R.; Kerb U. *Tetrahedron* **1965,** *21,* 1625.
113. Toromanoff E. *Topics Stereochem.* **1967,** *2,* 157.
114. (a) Djerassi C.; Lund E.; Akhrem A. A. *J. Am. Chem. Soc.* **1962,** *84,* 1249; (b) Allaudin M.; Martin-Smith M. *J. Org. Chem.* **1963,** *28,* 886; (c) Glen A. T.; Lawrie W.; McLean J. *J. Chem. Soc.* (*C*) **1966,** 661.
115. (a) Stefanović M.; Gašić M.; Lorenc Lj.; Mihailović M. Lj. *Tetrahedron* **1964,** *20,* 2289; (b) Schreiber J.; Eschenmoser A. *Helv. Chim. Acta* **1955,** *38,* 1529; (c) Grimmer G. *Liebigs Ann. Chem.* **1960,** *636,* 42.
116. (a) Wiechert R.; *Z. Naturforsch.* **1964,** *19b,* 944; (b) Romeo A.; Tortorello V.; Vetuschi C. *Farmaco, Ed. Sci.* **1968,** *23,* 227; (c) Klimstra P. D. U.S. Patent 3,471,526, **1969;** *Chem. Abstr.* **1970,** *72,* 3646.
117. (a) Ruzicka L.; Wahba N.; Herzig P. T.; Heusser H. *Chem. Ber.* **1952,** *85,* 491; (b) Heusser H.; Wahba N.; Winternitz F. *Helv. Chim. Acta* **1954,** *37,* 1052; (c) Clinton R. O.; Christiansen R. G.; Neumann H. C.; Laskowski S. C. *J. Am. Chem. Soc.* **1958,** *80,* 3389.
118. Toromanoff E. *Bull. Soc. Chim. Fr.* **1960,** 888.
119. Ganguly A. K.; Govindachari T. R.; Mohamed P. A.; Rahimtulla A. D.; Viswanathan N. *Tetrahedron* **1966,** *22,* 1513.
120. Toromanoff E. *Bull. Soc. Chim. Fr.* **1968,** 2457.
121. Weissenberg M.; Glotter E. *J. Chem. Soc. Perkin Trans. I* **1978,** 568.
122. Toromanoff E. *Tetrahedron* **1980,** *36,* 2809.
123. Brown H. C.; Krishnamurthy S. *J. Am. Chem. Soc.* **1972,** *94,* 7159.
124. Djerassi C.; Closson W.; Lippman A. E. *J. Am. Chem. Soc.* **1956,** *78,* 3163.
125. Eliel E. L.; Allinger N. L.; Angyal S. G.; Morrison G. A. *Conformational Analysis*; Interscience/John Wiley: New York, 1965; (a) p. 119; (b) p. 285; (c) p. 283; (d) p. 284.
126. Longevialle P. *Tetrahedron* **1969,** *25,* 3075.
127. House H. O. *Modern Synthetic Reactions, 2nd edition*; Benjamin W. A.: Menlo Park, California, 1972; Chapter 3.
128. von Mutzenbecher G.; Cross A. D. *Steroids* **1965,** *5,* 429.
129. Ohloff G.; Maurer B.; Winter B.; Giersch W. *Helv. Chim. Acta* **1983,** *66,* 192.
130. Evans J. M.; Marcano D.; Marquez L. *Acta Cient. Venez.* **1972,** *23,* 172.
131. Glotter E.; Krinsky P. *J. Chem. Soc. Perkin Trans. I* **1978,** 413.
132. Klimstra P. D. U.S. Patent 3,391,166, **1968;** *Chem. Abstr.* **1968,** *69,* 96989.
133. McGinnis E. L.; Meakins G. D.; Price J. E.; Styles M. C. *J. Chem. Soc.* **1965,** *4379.*
134. Huneck S. *Chem. Ber.* **1965,** *98,* 2291.
135. Tschesche R.; Annen K.; Welzel P. *Chem. Ber.* **1971,** *104,* 3556.
136. Kirson I.; Glotter E.; Lavie D.; Abraham A. *J. Chem. Soc.* (*C*) **1971,** *2032.*
137. Satoh J. Y.; Misawa K.; Takahashi T. T.; Hirose M.; Horiuchi C. A.; Tsujii, S.; Hagitani A. *Bull. Chem. Soc. Jpn.* **1973,** *46,* 3155.
138. Schering A.-G., Belgian Patent 620,548, **1963;** *Chem. Abstr.* **1963,** *59,* 10183.

139. Mechoulam R.; Luchter K.; Goldblum A. *Synthesis* **1974,** 363.
140. Kaufmann H.; Fuhrer H.; Kalvoda J. *Tetrahedron* **1981,** *37* (Suppl. 1), 225.
141. Mühle H.; Tamm Ch. *Helv. Chim. Acta* **1963,** *46,* 268.
142. Barton D. H. R.; Daniels P. J. L.; McGhie J. F.; Palmer P. J. *J. Chem. Soc.* **1963,** 3675.
143. Barton D. H. R.; Lier E. F.; McGhie J. F. *J. Chem. Soc.* (*C*) **1968,** 1031.
144. Sallmann F.; Tamm Ch. *Helv. Chim. Acta* **1956,** *39,* 1340.
145. Sasaki K. *Chem. Pharm. Bull.* **1961,** *9,* 693.
146. Kirk D. N.; Klyne W.; Mudd A. *J. Chem. Soc.* (*C*) **1968,** 2269.
147. Kimura M.; Tohma M.; Yoshizawa I. *Chem. Pharm. Bull.* **1967,** *15,* 1204.
148. Glotter E.; Lavie D. *J. Chem. Soc.* (*C*) **1967,** 2298.
149. Bridgeman J. E.; Cherry P. C.; Clegg A. S.; Evans J. M.; Jones E. R. H.; Kasal A.; Kumar V.; Meakins G. D.; Morisawa Y.; Richards E. E.; Woodgate P. D. *J. Chem. Soc.* (*C*) **1970,** 250.
150. Eggert H.; Djerassi C. *J. Org. Chem.* **1973,** *38,* 3788.
151. Jones R. N.; DiGiorgio J. B. *Canad. J. Chem.* **1965,** *43,* 182.
152. Boul A. D.; Blunt J. W.; Browne J. W.; Kumar V.; Meakins G. D.; Pinhey J. T.; Thomas W. E. M. *J. Chem. Soc.* (*C*) **1971,** 1130.
153. Djerassi C.; Halpern O.; Halpern V.; Schindler O.; Tamm Ch. *Helv. Chim. Acta* **1958,** *41,* 250.
154. (a) Crabbé P. *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*; Holden–Day: San Francisco, 1965; (b) Crabbé P. *L'Ingénieur Chimiste* **1967,** *48,* 33.
155. Kirk D. N.; Klyne W.; Wallis S. R. *J. Chem. Soc.* (*C*) **1970,** 350.
156. Tohma M.; Fujino A.; Yamazaki K.; Kimura M. *Chem. Pharm. Bull.* **1972,** *20,* 2240.
157. Polonsky J. *Fortschr. Naturst.* **1973,** *30,* 101.
158. Murae T.; Takahashi T. *Bull. Chem. Soc. Jpn.* **1981,** *54,* 941.
159. Ceccherelli P.; Curini M.; Diamantini M.; Marcotullio M. C.; Grandolini G. *Tetrahedron* **1987,** *43,* 243.
160. Takeda K.; Okanishi T.; Akahori A.; Yasuda F. *Chem. Pharm. Bull.* **1968,** *16,* 421.
161. Okuno T.; Matsumoto T. *Tetrahedron Lett.* **1969,** 4077.
162. Kirk D. N.; Shaw P. M. *J. Chem. Soc.* (*C*) **1971,** 3979.
163. Noam M.; Tamir I.; Breuer E.; Mechoulam R. *Tetrahedron* **1981,** *37,* 597.
164. Annen K.; Tschesche R.; Welzel P. *Chem. Ber.* **1973,** *106,* 576.
165. Schwarz V.; Ulrich M.; Syhora K. *Steroids* **1964,** *4,* 645.
166. Kirson I.; Zaretskii V. I.; Glotter E. *J. Chem. Soc. Perkin Trans. I* **1976,** 1244.
167. Mihailović M. Lj.; Lorenc Lj.; Pavlović V.; Kalvoda J. *Tetrahedron* **1977,** *33,* 441.
168. Greenfield S. *Ph.D. Thesis,* The Weizmann Institute of Science, Rehovot, Israel, **1967.**
169. Schneider J. J. *J. Chem. Soc. Perkin Trans. I* **1973,** 1361.
170. Burnett R. D.; Kirk D. N. *J. Chem. Soc. Perkin Trans. I* **1981,** 1460.
171. Cava M. P.; Vogt B. R. *J. Org. Chem.* **1965,** *30,* 3775.
172. (a) Baldwin J. E. *J. Chem. Soc., Chem. Commun.* **1976,** 738; (b) Marples B. A. In *Terpenoids and Steroids* (*Specialist Periodical Reports*); Hanson J. R. Ed.; The Chemical Society: London, 1978; Vol. 8, p. 239.
173. Wu Y.-D.; Houk K. N.; Florez J.; Trost B. M. *J. Org. Chem.* **1991,** *56,* 3656.
174. Klimstra P. D.; Counsell R. E. *J. Med. Chem.* **1965,** *8,* 48.
175. Clark I. M.; Clegg A. S.; Denny W. A.; Jones E. R. H.; Meakins G. D.; Pendlebury A. *J. Chem. Soc. Perkin Trans. I* **1972,** 499.
176. Mühle H.; Orosz E.; Tamm Ch. *Helv. Chim. Acta* **1966,** *49,* 939.
177. Yamakawa K.; Nishitani K.; Mashiko T. *Chem. Pharm. Bull.* **1984,** *32,* 3263.
178. Djerassi C.; Williams D. H.; Berkoz B. *J. Org. Chem.* **1962,** *27,* 2205.
179. Jeger O.; Montavon M.; Nowak R.; Ruzicka L. *Helv. Chim. Acta* **1947,** *30,* 1869; The sequence of reactions leading to 2-lupene-1-one has since been revisited,[133] and the intermediates' identity confirmed by spectroscopic methods: Narayanan C. R.; Pachapurkar R. V.; Sawant B. M.; Wadia M. S. *Indian J. Chem.* **1969,** *7,* 187.
180. Lablache-Combier A.; Levisalles J. *Bull. Soc. Chim. Fr.* **1964,** 2236.
181. Augustine R. L. In *Organic Reactions in Steroid Chemistry*; Fried J.; Edwards J. A. Eds; Van Nostrand Reinhold: New York, 1972; Vol. I, Chapter 3.
182. Adesogan E. K.; Okorie D. A.; Taylor D. A. H. *J. Chem. Soc.* (*C*) **1970,** 205.
183. Starr J. E. In *Steroid Reactions*; Djerassi C. Ed.; Holden–Day: San Francisco, 1963; pp. 299–325.
184. Dryden Jr H. L. In *Organic Reactions in Steroid Chemistry*; Fried J.; Edwards J. A. Eds; Van Nostrand Reinhold: New York, 1972; Vol. I, Chapter 1.
185. Cocton B.; Crastes de Paulet A. *Bull. Soc. Chim. Fr.* **1966,** 2947.
186. Waisser K.; Vystrčil A. *Collect. Czech. Chem. Commun.* **1966,** *31,* 3182.
187. (a) Johnson M. R.; Rickborn B. *J. Org. Chem.* **1970,** *35,* 1041; (b) Dilling W. L.; Plepys R. A. *J. Org. Chem.* **1970,** *35,* 2971.
188. Bucourt R. *Bull. Soc. Chim. Fr.* **1964,** 2080.
189. de Marcano D.; Rojas H. *Acta Cient. Venez.* **1974,** *25,* 195; *Chem. Abstr.* **1976,** *84,* 135,930.
190. Lavie D.; Kirson I.; Glotter E.; Rabinovich D.; Shakked Z. *J. Chem. Soc., Chem. Commun.* **1972,** 877.
191. McPhail A. T.; Sim G. A. *J. Chem. Soc.* (*B*) **1968,** 196.
192. Lavie D.; Kashman Y.; Glotter E. *Tetrahedron* **1966,** *22,* 1103.
193. Weissenberg M. *Alembic* (*21*) **1981,** 1; *Chem. Abstr.* **1981,** *95,* 43448.
194. Adam G.; Hesse M. *Tetrahedron* **1972,** *28,* 3527.

195. Sinha S. C.; Kundu S.; Maurya R.; Ray A. B. *Tetrahedron* **1989,** *45,* 2165.
196. Bowers A.; Knox L. H. U.S. Patent 3,138,619, **1964;** *Chem. Abstr.* **1964,** *61,* 8379.
197. Brown H. C.; Fletcher R. S.; Johannesen R. B. *J. Am. Chem. Soc.* **1951,** *73,* 212.
198. Fuchs B.; Loewenthal H. J. E. *Tetrahedron* **1960,** *11,* 199.
199. Yoshida K.; Kubota T. *Tetrahedron* **1965,** *21,* 759.
200. Kocór M.; Kurek A.; Dabrowski J. *Tetrahedron* **1969,** *25,* 4257.
201. (a) Pappo R.; Jung C. J. *Tetrahedron Lett.* **1962,** 365; (b) Pappo R. U.S. Patent 3,101,350, **1963;** *Chem. Abstr.* **1964,** *60,* 596; (c) Pappo R. U.S. Patent 3,155,684, **1964;** *Chem. Abstr.* **1965,** *62,* 1717; (d) Chorvat R. J.; Pappo R.; Scaros M. G. U.S. Patent 3,644,342, **1972;** *Chem. Abstr.* **1972,** *76,* 154012.
202. Clayton R. B.; Henbest H. B.; Smith M. *J. Chem. Soc.* **1957,** 1982.
203. Weissenberg M.; Lavie D.; Glotter E. *Tetrahedron* **1973,** *29,* 353.
204. (a) Frimer A. A.; Hameiri-Buch J.; Ripshtos S.; Gilinsky-Sharon P. *Tetrahedron* **1986,** *42,* 5693; (b) Frimer A. A.; Ripshtos S.; Marks V.; Aljadeff G.; Hameiri-Buch J.; Gilinsky-Sharon P. *Tetrahedron* **1991,** *47,* 8361.
205. Lavie D.; Glotter E.; Shvo Y. *Tetrahedron* **1963,** *19,* 1377.
206. Hanna R.; Ourisson G. *Bull. Soc. Chim. Fr.* **1961,** 1945.
207. (a) Shibata K.; Takegawa S.; Koizumi N.; Yamakoshi N.; Shimazawa E. *Chem. Pharm. Bull.* **1992,** *40,* 935; (b) Alvarez E.; Francisco C. G.; Freire R.; Hernández R.; Salazar J. A.; Suárez E.; Betancor C. *J. Chem. Soc. Perkin Trans. I* **1986,** 1523.
208. Paaren H. E.; Schnoes H. K.; DeLuca H. F. *J. Chem. Soc., Chem. Commun.* **1977,** 890.
209. Sheves M.; Friedman N.; Mazur Y. *J. Org. Chem.* **1977,** *42,* 3597.
210. Paaren H. E.; Mellon W. S.; Schnoes H. K.; DeLuca H. F. *Bioorg. Chem.* **1985,** *13,* 62.
211. Holick S. A.; Holick M. F.; MacLaughlin J. A. *Biochem. Biophys. Res. Commun.* **1980,** *97,* 1031.
212. Muralidharan K. R.; de Lera A. R.; Isaeff S. D.; Norman A. W.; Okamura W. H. *J. Org. Chem.* **1993,** *58,* 1895.
213. Vanmaele L. J.; De Clercq P. J.; Vandewalle M.; Halkes S. J.; Overbeek W. R. M. *Tetrahedron* **1984,** *40,* 1179.
214. Tachibana Y. *Bull. Chem. Soc. Jpn.* **1989,** *62,* 2090.
215. Vanmaele L. J.; De Clerq P. J.; Vandewalle M. *Tetrahedron Lett.* **1982,** *23,* 995.
216. Vanmaele L.; De Clerq P. J.; Vandewalle M. *Tetrahedron* **1985,** *41,* 141.
217. Okamura W. H.; Hoeger C. A.; Miller K. J.; Reischl W. *J. Am. Chem. Soc.* **1988,** *110,* 973.
218. Condran, Jr P.; Hammond M. L.; Mouriño A.; Okamura W. H. *J. Am. Chem. Soc.* **1980,** *102,* 6259.

(*Received* 28 *June* 1993)