STEREOCHEMISTRY OF REDUCTION OF KETONES BY COMPLEX METAL HYDRIDES[1]

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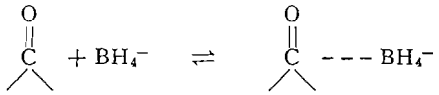
ABSTRACT

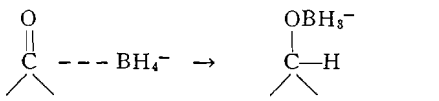
The stereochemistry of the reduction of a number of cyclic ketones with complex metal hydrides has been determined. In the absence of any large steric effect in the ketones, the reduction is essentially stereospecific, giving the more stable alcohol.

INTRODUCTION

The reduction of a carbonyl group by a simple metal hydride must proceed by four successive stages (1), utilizing each of the four available hydrogen atoms. Each stage probably involves two reaction steps, the initial reversible formation of a complex of the hydride ion and the carbon atom of the carbonyl group (I) and the irreversible transfer of hydrogen to this carbon atom (II).



(I)



(II)

In the case of a cyclic ketone there are two possible directions of attack, pseudo equatorial and pseudo axial, giving the axial or equatorial alcohol. Dauben and co-workers (2, 3) have discussed the stereochemistry of reduction of cyclic ketones in terms of "steric approach control" to the attack of the hydride upon the ketone (stage I), and "product development control", determined by the relative thermodynamic stabilities of the two alcohols formed (and governing the relative stabilities of the two possible transition states in stage II). For a complex metal hydride substituted with bulky substituents, approach to the carbon atom of the carbonyl group, in stage I, will take place from the less hindered side. In stage II the large steric size of the reagent will favor the formation of the transition state leading to the more stable of the two products, since a bulky group is more stable in this the equatorial position. Reduction of an unhindered ketone should thus give the equatorial alcohol, whereas a sterically hindered ketone could give either isomer depending on the direction of steric hindrance.

A number of complex metal hydrides have recently been prepared and the simplest is sodium trimethoxyborohydride. However, this undergoes disproportionation in solution (4) and the reduction of 2-methylcyclohexanone with this reagent gives the same ratio of isomers as does sodium borohydride (2). Recently H. C. Brown and McFarlin (5) have developed a simple preparation of lithium tri-*tert*-butoxyaluminum hydride and we have investigated the stereochemistry of the reduction of a number of cyclic ketones (Table I) with this reagent. In all cases this reagent is considerably more stereospecific than either lithium aluminum hydride or sodium borohydride.

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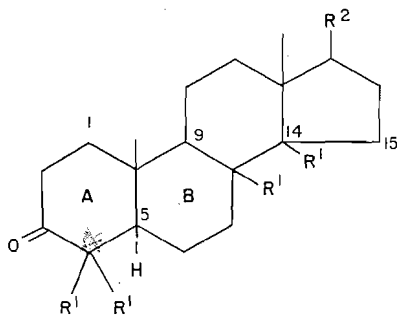
TABLE I
PERCENTAGE OF EQUATORIAL ISOMER*

	$LiAlH_4$	$NaBH_4$	$LiAlH(t\text{-}BuO)_3$‡	$LiAlH_4/AlCl_3$‡
Cholestan-3-one	88†	85‖	98.5	100
Coprostan-3-one	93†	87‖	96.5	94
Cholest-4-en-3-one	74†	95‖	100	—**
Cholest-5-en-3-one	87†	83‖	100	—††
Cholestan-7-one	—	58‖	86	—
Δ^5-Androsten-17-one-3β-acetate	—	—	100	—
Δ^8-Lanostenone	100‡	—	100	—
Camphor	90§	—	25	—
4-Methylcyclohexanone	81§	85¶	84	—

*Percentages normalized to 100%. †Ref. 16. ‡Present work. §Ref. 17. ‖Ref. 6. ¶Ref. 2. **Cholest-4-ene-(80%) + cholestane. ††Cholest-4-en-3-one (83%) + alcohols.

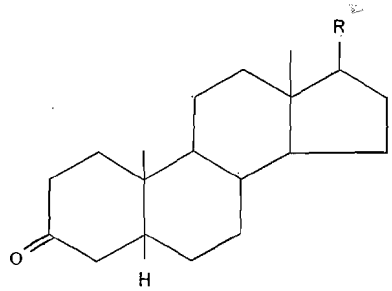
DISCUSSION

The keto group of cholestan-3-one (*IIIa*) is unhindered to attack from either an axial or equatorial direction (3, 6). In the transition state, however, the bulky alkoxide group could not occupy a pseudo-axial position, since it would be sterically hindered by the axial hydrogen atoms on carbon atoms 1 and 5. Moreover in such a position it is also sterically hindered to solvation (7), which would help to stabilize the ion. Thus the preferred transition state will be that with the alkoxy group in a pseudo-equatorial position, and the product observed is essentially that (β-cholestanol) which arises from this. Similarly coprostan-3-one (IV) is not subject to steric hindrance from either direction (6) and the equatorial (α) isomer is largely formed. A double bond at the union of rings A and B as in Δ^4- and Δ^5-cholesten-3-one will lead to a general flattening of the rings. The steric repulsion to a 3-α group will be less, since there is now no α-hydrogen at carbon-5 and the flattening of the rings moves the 3-position away from the 1-α hydrogen atom. However, electronic interaction (6) between the double bond and the pseudo-equatorial alkoxy group will greatly stabilize the transition state for formation of the equatorial alcohol, and this is formed exclusively in both cases.



III a R^1 = H
R^2 = Isohexyl

b R^1 = Me
R^2 = Isohexyl



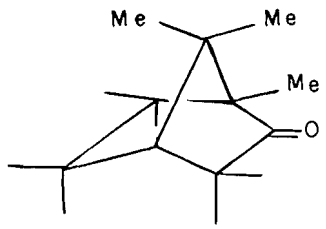
IV R = Isohexyl

The attack on the ketone group of cholestan-7-one from an axial direction will be hindered by the axial hydrogen atoms at C-5, C-9, and C-14. However, approach to the keto group from a pseudo-equatorial direction is highly hindered by the axial methyl groups at C-10 and C-13 and by the eclipsing effect of the 15-α hydrogen atom (6), and cholestan-7α-ol is only formed in 6% yield. This same eclipsing effect will tend to expel the bulky alkoxy transition complex from the 7-β position, and 57% of cholestane is formed (cf. 6).

Approach to the 17-keto steroid group from the topside of the molecule is hindered by the axial methyl group on C-18. However, approach from the underside is free and the resulting pseudo-equatorial transition complex will not be hindered by the methyl group on C-18, since the *trans*-fusion of rings C and D bends the 17-position down away from this group. Thus, Δ^5-androsten-17-one-3β-acetate gives exclusively Δ^5-androsten-3β,17β-diol.

In the case of Δ^8-lanosten-3-one (III*b*) approach to the ketone group from the upper pseudo-equatorial direction is also hindered by the axial methyl group on C-4. However, again approach from the underside is unhindered and the pseudo-equatorial transition complex (stage II) is not very hindered by either methyl group. Accordingly the β-alcohol is the sole product.

The camphor molecule (V) presents an interesting case, since one of the *gem*-dimethyl groups on the bridgehead is placed nearly above the ketone group (8). Approach from the exo (equatorial) direction is hindered and, although there is little hindrance to approach from the *endo* (axial) direction, the resulting pseudo-exo transition complex will be highly hindered. The net result of these opposing factors is that only 25% of the exo product (isoborneol) is formed.



V

In the transition state of reduction of 4-methylcyclohexanone, the methyl group is free to take up either an axial or equatorial position (9), with the large alkoxy group remaining in the preferred equatorial position. Consequently lithium tri-*tert*-butoxy-aluminum hydride gives nearly the same isomer distribution as lithium aluminum hydride and sodium borohydride.

The complex of lithium aluminum hydride and excess aluminum chloride was first used for reduction by B. R. Brown (10). Aluminum hydride is formed as an intermediate (11), but the active reducing species may be AlH_2Cl (12). In the cases of the two saturated ketones, cholestan-3-one and coprostan-3-one, reduction was essentially stereospecific giving predominately the β-alcohols. Cholest-4-en-3-one, however, gave no alcohol. The product, previously reported as Δ^4-cholestene (13), was shown to be a mixture of cholestene with about 10% cholestane. Hydrogenolysis has been observed in the reduction of other compounds by this reagent (14, 15). Cholest-5-en-3-one gave a mixture which contained

cholest-4-en-3-one as well as alcohols. Because of these unfavorable observations and the uncertainty of the nature of the reducing reagent, no further work was carried out with this complex.

EXPERIMENTAL

Tetrahydrofuran and *t*-butanol were dried by refluxing with and distilling from lithium aluminum hydride and sodium, respectively. Lithium aluminum hydride and aluminum chloride were commercial samples which were finely ground. The ketones used were all analytically pure samples.

Reductions with lithium tri-tert-butoxy aluminum hydride.—In a typical experiment *t*-butanol (2 ml) was added slowly to a solution of lithium aluminum hydride (400 mg) in tetrahydrofuran (30 ml) at 0° (5). Cholestanone (1.0 g) in tetrahydrofuran (30 ml) was then added and the mixture allowed to stand at 0° for ½ hour and at room temperature for 1 hour. The mixture was then poured into excess dilute hydrochloric acid and the product extracted in the usual way. In this case the crude product was chromatographed on alumina and eluted with hexane–benzene giving α-cholestanol (14 mg), m.p. 182°–185°, and β-cholestanol (937 mg), m.p. 143°–146°. Both alcohols gave no depression on mixed melting-point determinations with authentic samples.

Coprostanone.—The product from coprostanone (200 mg) gave a precipitate with digitonin (50 mg) from which β-coprostanol (7 mg) was liberated with pyridine. α-Coprostanol (185 mg), m.p. 115°, was recovered by evaporation of the mother liquors (6).

Cholest-4-en-3-one.—Cholest-4-en-3-one (1.0 g) gave a crude product (1.0 g), m.p. 121°, which on chromatography using hexane–benzene as eluent (50 fractions) gave only cholest-4-en-3β-ol, m.p. 127°–131°, recrystallized from ether–methanol to m.p. 132°, $[\alpha]_D^{CHCl_3}$ +44°.

Cholest-5-en-3-one.—Cholest-5-en-3-one (500 mg) gave cholesterol, m.p. and mixed m.p. 148°, $[\alpha]_D^{CHCl_3}$ −42° (lit. $[\alpha]_D$ −39°, m.p. 149° (18)).

Cholestan-7-one.—Cholestan-7-one (500 mg) gave a product separated by chromatography into a fraction (243 mg) eluted with hexane, m.p. 65°–70°, recrystallized from hexane to m.p. 80°, $[\alpha]_D$ +30°. The infrared absorption showed no carbonyl or hydroxyl groups or double bond. Further elution with hexane–benzene gave 7α-cholestanol (27 mg), m.p. 92°–98° (lit. m.p. 94°–97° (19)), and 7β-cholestanol (168 mg), m.p. 103°–109° (lit. m.p. 108°–112° (19)).

Δ⁵-Androsten-17-one-3β-acetate.—Reduction in like manner of Δ⁵-androsten-17-one-3β-acetate gave a product, m.p. 183°–184°, $[\alpha]_D$ −54°. Reported for Δ⁵-3β,17β-androstendiol, m.p. 182°–183°, $[\alpha]_D$ −55° (20).

Δ⁸-Lanosten-3-one.—Δ⁸-Lanosten-3-one (500 mg) gave a product, m.p. 142°–146°, recrystallized to m.p. 146°–148° and undepressed on admixture with lanostenol.

Camphor.—Two grams of this gave a product, m.p. 85°–110°, which could not be separated by chromatography on alumina (cf. 22). The mixture (500 mg) in pyridine (2 ml) was treated with *o*-nitrobenzoyl chloride and allowed to stand overnight. The pyridine was removed in vacuum and the isoborneol (106 mg), m.p. 210° from petroleum ether, separated by steam distillation (23). The residual borneol *o*-nitrobenzoate (618 mg) corresponded to borneol (322 mg).

4-Methylcyclohexanone.—Ten grams of 4-methylcyclohexanone gave a product n_D^{20} 1.4560, d_4^{30} 0.9061, which showed a small infrared ketone peak. After washing with sodium bisulphite solution the values were n_D^{20} 1.4569 and d_4^{30} 0.9063, and the compound showed no infrared carbonyl absorption. *Cis*- and *trans*-4-methylcyclohexanol have

respectively n_D^{20} 1.4614, 1.4561, and d_4^{30} 0.9173 and 0.9040 (24). The isolated product therefore contains 15% (from n_D^{20}) or 17% (from d_4^{30}) of the *cis*-isomer.

Reductions with lithium aluminum hydride – aluminum chloride.—In a typical experiment aluminum chloride (600 mg) was added to lithium aluminum hydride (135 mg) dissolved in ether (50 ml).

Cholestanone.—One gram of this ketone in ether (20 ml) was then added and the mixture allowed to stand at room temperature for at least four hours. The product (m.p. 141°–143°) was isolated by pouring the mixture into dilute hydrochloric acid. Recrystallization from ether–methanol gave β-cholestanol, m.p. 141°–142°, undepressed on admixture with an authentic sample.

Coprostanone.—Coprostanone (200 mg) gave a product from which β-coprostanol (12 mg) was isolated by digitonin separation. α-Coprostanol (180 mg) was isolated from the mother liquors, as before.

Cholest-4-en-3-one.—This gave a product, readily eluted from alumina with hexane, m.p. 65°, $[\alpha]_D^{CHCl_3}$ +56°. This rotation corresponds to Δ^4-cholestene ($[\alpha]_D$ +65°) 78% and cholestane ($[\alpha]_D$ +24°) 22%. Bromine titration showed the presence of about 85% olefin.

Cholest-5-en-3-one.—Five hundred milligrams gave a product (450 mg), which had λ_{max} 240 mμ, ε 15,700 corresponding to cholest-4-en-3-one 87%. Infrared spectra showed the presence of alcohols. No attempt was made to separate the mixture.

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