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Reduction of 12-Keto Steroids. 2[1]

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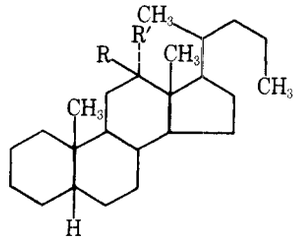
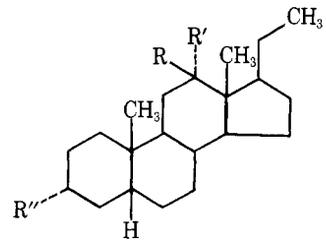
In an effort to explore the steric factors responsible for the course of the lithium–ammonia and sodium borohydride reductions of 12-keto steroids, the reductions of 24-nor-5β-cholan-12-one (**5**), 23,24-dinor-5β-cholan-12-one (**6**), and 5β-pregnan-12-one (**7**) have been studied. Under the conditions used, ketones **5** and **6** give mixtures of 12α- and 12β-ols very similar to those observed previously in the reduction of 5β-cholan-12-one (**1**). Ketone **7** and 3α-hydroxy-5β-pregnan-12-one (**3**) behave markedly differently, giving almost exclusively the 12β-ol on reduction with lithium–ammonia. The synthesis of ketones **5** and **6** is described.

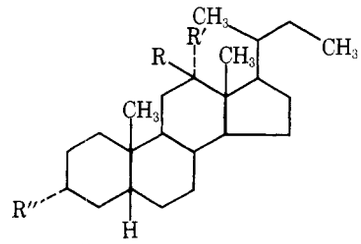
A number of years ago, we observed that dissolving metal (lithium–ammonia or sodium–alcohol) reduction of certain 12-keto steroids proceeded in what at that time was considered to be an anomalous manner.[1a] That is, reduction of compounds related to 5β-cholan-12-one (**1**) gave as the major product the thermodynamically unstable, axial 12α-ol (**2**), while reduction of 3α-hydroxy-5β-pregnan-12-one (**3**) gave the "normal" thermodynamically stable product (**4**). A mechanistic and steric explanation for these data was presented in this earlier paper.[1a] In the years following our original report, revised mechanisms for the dissolving metal reductions of ketones were suggested, some of which do not appear to permit a rationalization of the data reported in our 1964 publication.[2]



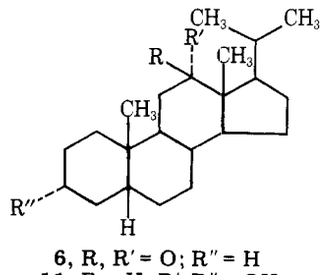
1, R, R′ = O
2, R = H; R′ = OH



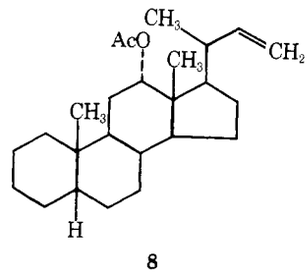
3, R, R′ = O; R″ = OH
4, R, R″ = OH; R′ = H
7, R, R′ = O; R″ = H



5, R, R′ = O; R″ = H
9, R, R″ = H; R′ = OH
10, R = H; R, R″ = OH



6, R, R′ = O; R″ = H
11, R = H; R′, R″ = OH
12, R, R″ = H; R′ = OH



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Also, the detailed nature of the steric parameters in the steroid molecule responsible for the drastically different course of reduction of ketones **1** and **3** was not known with certainty. It appeared probable that the steric effect responsible for the behavior of 12-keto steroids on reduction was shielding of the β face of the steroid molecule by the C-21 methyl group in ketone **1**, while ketone **3** is unshielded and behaves as a normal unhindered cyclohexanone. This is the explanation offered originally for the steric course of these reductions[1a] and seemed to be reinforced by the results obtained by Blickenstaff's group in studies of the rates of acetylation of a series of 12-hydroxy steroids.[3] However, an alternative explanation which seemed to be in somewhat better agreement with the recent mechanistic proposals for dissolving metal reductions[2] involved the shielding of the α face of the steroid molecule by C-24 of ketone **1**. In the case of ketone **3**, the two-carbon chain would be unable to shield the 12-carbonyl and reduction would proceed normally.

In order to ascertain which, if either, of these explanations was correct we sought to prepare 24-nor-5β-cholan-12-one (**5**) and 23,24-dinor-5β-cholan-12-one (**6**) in order to study their behavior on reduction. Also, to exclude the possibility that the 3-hydroxyl group in ketone **3** was affecting the course of the reduction of this compound, the reduction of 5β-pregnan-12-one (**7**) was to be studied.

The synthesis of ketones **5** and **6** was relatively straightforward. Ketone **5** was prepared initially from deoxycholic acid (3α,12α-dihydroxy-5β-cholan-24-oic acid) by following the known route to 12α-acetoxy-5β-cholan-24-oic acid,[4] which on decarboxylation with lead tetraacetate[5] afforded 12α-acetoxy-24-nor-5β-chol-22-ene (**8**).[6] Catalytic reduction of **8** followed by reductive cleavage of the ester gave 24-nor-5β-cholan-12α-ol (**9**). Although this synthesis afforded the precursor to ketone **5**, the overall yield was mediocre and an alternative synthesis from 24-nor-5β-cholane-3α,12α-diol (**10**)[7]

Table I

Ketone	Registry No.	% 12β-ol formed on reduction of the corresponding ketone[a]		
		Lithium–ammonia (A)	Lithium–ammonia (B)	Sodium borohydride
24-Nor-5β-cholan-12-one (5)	63714-52-3	29 (79) 40[c]	81[b] (72)	28 (81) 22 ± 3[d]
23,24-Dinor-5β-cholan-12-one (6)	63714-53-4	27 (48)[e]		23[e] (79) 25 ± 4[d]
5β-Pregnan-12-one (7)	17996-90-6	89[b]	[f]	59 (69)
5β-Cholan-12-one (1)	5916-16-5	25[g]	ca. 90[g]	25[g]
3α-Hydroxy-5β-pregnan-12-one (3)	19316-03-1	84[g]		54[h]

[a] Average of two runs expressed in relative percent, balance of the mixture 12α-ol (% yield of reduction products). Unless noted, analysis by NMR (see text). All product ratios ±5%. [b] The 12β-ol is a new compound. The physical properties and analysis are reported in the Experimental Section. [c] *tert*-Butyl alcohol as a proton source. [d] Analysis by HPLC.[10] [e] One run only, due to lack of material. [f] Gave a mixture containing apparently pinacol plus 12β-ol, which was not investigated further. [g] Reference 1a. [h] M. E. Wall, private communication.

was devised. Selective Oppenauer oxidation of the 3-hydroxyl, followed by Wolff–Kishner reduction, gave alcohol **9**, which was oxidized to ketone **5** with Jones reagent.

The synthesis of ketone **6** was patterned after this more efficient preparation of ketone **5**. 24-Nor-5β-cholan-23-oic acid (nordeoxycholic acid)[8] was decarboxylated and the resulting product was reduced and hydrolyzed to give 23,24-dinor-5β-cholane-3α,12α-diol (**11**). Oppenauer oxidation of diol **11** followed by Wolff–Kishner reduction gave 23,24-dinor-5β-cholan-12α-ol (**12**) which on Jones oxidation afforded the desired 12-ketone (**6**).

The third ketone, 5β-pregnan-12-one (**7**), was a known compound and was prepared essentially according to the published procedure.[9]

The reductions of ketones **5**, **6**, and **7** were carried out by three different methods: lithium in ammonia, with the substrate and a proton source (methanol) added to a solution of excess lithium in ammonia (method A); the addition of lithium in small portions to a suspension of the ketone in ether–ammonia until a blue color persisted, followed by addition of methanol (method B); and reduction with sodium borohydride in methanol. The resulting product mixtures were analyzed by NMR (repeated integration of the carbinol protons) and in two cases by analytical HPLC.[10] The results are summarized in Table I.

It will be noted that ketones **1**, **5**, and **6**, all of which have a tertiary carbon at C-20 and a conformationally mobile side chain, behave similarly under all conditions, while the ketones in the pregnane series (**3** and **7**) in which C-20 is secondary give considerably different results.[11]

The steric factor primarily responsible for the unusual behavior of 12-keto steroids on reduction with dissolving metals is almost certainly the presence of tertiary carbon at C-20, with the expected preferred conformation about the C-17–C-20 bond permitting the C-21 methyl group to shield the β face of the 12-carbonyl. This is the argument presented in our earlier paper[1a] and is that invoked by Blickenstaff's group[3] to explain their acetylation data. From an examination of the data in Table I, it is apparent that neither the length of the alkyl residue attached to C-20 nor the presence of a 3-hydroxyl in the pregnane series greatly affect the course of these reductions. It had earlier been shown that the stereochemistry of the A–B ring fusion also had little effect on the course of these reductions.[1a,12]

Although the data reported in the table are consistent with those reported previously for the reductions of 12-keto steroids, both the lithium–ammonia and borohydride reductions are difficult to rationalize in terms of the currently popular explanations of the courses of these reactions.

The usual explanation for the stereochemistry of sodium borohydride reduction of cycloalkanones involves a consideration of torsional and steric strain in the reactant-like transition states leading to the epimeric alcohols.[13] Examination of models of ketones **1**, **5**, and **6** indicates that in the conformer in which H-17 and H-20 are anti, these arguments lead to the conclusion that the 12β-ol should be the major product, *however, the 12α-ol is the major product (ca. 75%) in all three cases.*[14]

These results can be rationalized, however, in terms of the mechanism suggested recently by Wigfield for the reduction of ketones by sodium borohydride.[15] In this mechanism, the proposed transition state includes one molecule of alcohol, one molecule of alkoxide, a borohydride ion, and the substrate ketone, with the borohydride attacking the carbonyl carbon at an angle of 126°.[15a] This mechanism leads to a transition state for the production of the 12α-ol (β attack) which suffers from interaction of borohydride ion with the angular methyl group (C-18); however, that leading to the 12β-ol (α attack) involves an extreme interaction between the solvent alcohol and C-21.[16] The results of the reductions of 12-pregnanones **3** and **7** in which the C-21 methyl group does not shield the face of the 12-carbonyl and which give considerably less of the 12α-ol are also explicable in terms of Wigfield's mechanism since there will no longer be an interaction between C-21 and the solvent.

Although several groups have proposed mechanisms, all of which are quite similar, for the dissolving metal reduction of ketones,[1a,2] none of the mechanisms proposed to date are entirely consistent with the data for both simple ketones and ketones **1**, **5**, and **6**. In particular it is difficult to rationalize the drastic differences in the course of the reductions of these ketones using different conditions (methods A and B). Any proposed mechanism must also be consistent with the following experimental observations: (1) The reductions of ketones in the absence of a proton source lead to varying amounts of pinacol-type products.[2] (2) The reductions of bicycloheptanones related to camphor give predominantly the endo alcohol, regardless of stability.[2a-c,17] (3) Reductions of simple cyclohexanones give far more of the equatorial alcohol than is present in an equilibrium mixture.[2a] (4) Reductions of highly hindered ketones (e.g., 11-keto steroids) afford almost exclusively the stable alcohol.[18]

A modification of the previous mechanism for these reductions which accounts for these data has as the first two steps the reaction of the active metal with ammonia, followed by a one-electron reduction of the ketone to a radical anion. These two steps are common to all the current mechanisms for these reductions.[2] This initially formed radical anion can then undergo any one of several reactions. In the presence of a proton source (method A, Table I), this intermediate would sequentially be rapidly protonated, reduced, and protonated again to give the product alcohol. This would result in a fast, kinetically controlled reduction to give products, the stereochemistry of which would be governed by roughly the same

considerations as those of the borohydride reductions of the same ketone. This is the case with ketones **1**, **5**, and **6** and has been commented upon previously.[2a] Also, since the reductions of ketones **1**, **5**, and **6** are very sensitive to reaction conditions, the reduction of ketone **5** according to method A was carried out using *tert*-butyl alcohol which is less acidic than methanol as a proton source. This procedure increased the amount of 12β-ol to 40%.

If the reduction is carried out in the absence of a proton donor (method B) the initially formed radical anion will have a finite existence, almost certainly coordinated with a metal ion and/or the ammonia solvent. The course of the reduction will then be governed by either the stereochemistry of this associated species or the site of protonation of the complexed intermediate.[19] Alternatively, the relatively long-lived, complexed, and/or solvated radical anion may dimerize, forming the pinacol, a known reaction under these conditions.

Experimental Section[20]

12α-Acetoxy-24-nor-5β-chol-22-ene (8). A mixture of 1.711 g of 12α-acetoxy-5β-cholan-24-oic acid,[4] 1.983 g of dried lead tetraacetate, 0.056 g of anhydrous cupric acetate, 0.7 mL of pyridine, and 56 mL of benzene was heated at reflux in a nitrogen atmosphere for 9 h. The reaction mixture was filtered through Celite and the filtrate was washed with 10% aqueous hydrochloric acid and water. The benzene solution was concentrated to a small volume and diluted with 150 mL of ether, and this solution was extracted with four portions of 2.5% aqueous potassium hydroxide. Acidification of the base-soluble fraction followed by ether extraction gave 0.719 g (42%) of recovered 12α-acetoxycholanic acid.

The benzene–ether solution of neutral materials was washed with water and brine and dried and the solvent was removed at reduced pressure to give 0.809 g of yellow gum. This material was dissolved in hexane and chromatographed on Camag acid washed alumina. Elution with hexane–benzene (1:1) gave 0.506 g (32%) of olefin **8** as a white solid. Recrystallization from aqueous methanol gave white needles: mp 105–106 °C;[6] IR 5.75 μm; NMR δ 0.71 (s, 3 H, H-19), 0.89 (s, 3 H, H-18), 0.91 (d, J = 7 Hz, H-21), 2.03 (s, 3 H, CH_3CO_2), 4.8 (m, 4 H, H-12, H-23, and H-24).

Anal. Calcd for $C_{25}H_{40}O_2$: C, 80.59; H, 10.82. Found: C, 80.75; H, 11.00.

12α-Acetoxy-24-nor-5β-cholane. A solution of 0.506 g of 12α-acetoxy-24-nor-5β-chol-22-ene (**8**) in 200 mL of ethanol containing 0.200 g of Adam's catalyst hydrogenated at 45 psig and ambient temperature for 8 h. The mixture was filtered through Celite and the solvent was removed in vacuo to give 0.394 g (78%) of white crystals: mp 83–85 °C; IR 5.75 μm; NMR δ 0.70 (s, 3 H, H-19), 0.75 (d, J = 7 Hz, 3 H, H-21), 0.89 (s, 3 H, H-18), 2.05 (s, 3 H, CH_3CO_2), 5.05 (t, J = 4 Hz, 1 H, H-12).

Anal. Calcd for $C_{25}H_{42}O_2$: C, 80.16; H, 11.30. Found: C, 80.42; H, 11.47.

24-Nor-5β-cholan-12α-ol (9). A. A solution of 7.41 g of 24-nor-5β-cholane-3α,12α-diol[7] (**10**), in 200 mL of toluene and 53 mL of cyclohexanone was distilled until the distillate was clear. To the hot solution was then added 5.52 g of aluminum *tert*-butoxide and the mixture was heated at reflux for 2.5 h. The reaction mixture was washed with 10% aqueous hydrochloric acid and the aqueous portion was back extracted with ether. The combined organic layers were washed with water and brine and dried and the solvent was removed in vacuo. The residual syrup was suspended in ca. 500 mL of 1% aqueous sulfuric acid and steam distilled. The residue was isolated by ether extraction to give a yellow gum which although it was essentially homogeneous to TLC and had the spectral properties expected for 12α-hydroxy-24-nor-5β-cholan-3-one could not be induced to crystallize and was reduced without further purification.

The crude hydroxy ketone was dissolved in 150 mL of diethylene glycol, treated with 10 mL of 98% hydrazine, and heated at reflux for 1 h. The mixture was cooled to approximately 100 °C and a solution of 15 g of potassium hydroxide in aqueous diethylene glycol was added. The reaction mixture was slowly distilled until a head temperature in excess of 185 °C was obtained and the mixture was then heated at reflux for 6 h. After cooling, the dark brown solution was poured into water and extracted with three portions of ether. The combined extracts were washed with two portions of water and dried, and the solvent was removed at reduced pressure to give 4.33 g of brown oil which partially crystallized. The crude material was dissolved in benzene and filtered through a short column of Woelm silica gel to give 3.10 g (44%) of 24-nor-5β-cholan-12α-ol as a white solid which was homogeneous to TLC. A small quantity was recrystallized from aqueous methanol: mp 128–129 °C; NMR δ 0.65 (s, 3 H, H-19), 0.88 (s, 3 H, H-18), 0.91 (d, J = 7 Hz, 3 H, H-21), 3.90 (t, J = 4 Hz, 1 H, H-12).

Anal. Calcd for $C_{23}H_{40}O$: C, 83.07; H, 12.12. Found: C, 83.29; H, 12.20.

B. To a solution of 0.265 g of 12α-acetoxy-24-nor-5β-cholane in 10 mL of dry ether was added, with stirring, 0.30 g of lithium aluminum hydride. The reaction mixture was stirred at room temperature for 2 h and the excess hydride was decomposed by the cautious addition of ice water. The ether was decanted from the precipitated salts and dried and the solvent was removed to give 0.175 g of colorless oil which slowly crystallized. Recrystallization once from acetone followed by recrystallization from aqueous methanol gave white crystals, mp 127–129 °C, mixture melting point with material from part A 127–128 °C.

24-Nor-5β-cholan-12-one (5). To a solution of 0.378 g of 24-nor-5β-cholan-12α-ol (**9**) in 15 mL of reagent grade acetone was added dropwise a slight excess of Jones reagent. The reaction mixture was stirred at room temperature for 1 h and quenched with methanol, and the chromic salts were filtered off and washed with methylene chloride. The combined filtrates were concentrated and cooled to give 0.264 g (70%) of ketone as white crystals, mp 176–179 °C. Recrystallization from acetone gave the analytical sample: mp 181–183 °C; IR 5.90 μm; NMR δ 0.98 (d, J = 7 Hz, 3 H, H-21), 1.00 (s, 6 H, H-18, H-19).

Anal. Calcd for $C_{23}H_{38}O$: C, 83.57; H, 11.59. Found: C, 83.52; H, 11.62.

3α,12α-Diacetoxy-23,24-dinor-5β-chol-20-ene. 3α,12α-Diacetoxy-24-nor-5β-cholan-23-oic acid (nordeoxycholic acid diacetate)[8] was subjected to lead tetracetate decarboxylation as described above for the preparation of 12α-acetoxy-24-nor-5β-chol-22-ene. From 14.68 g of acid there was obtained 8.94 g of crude olefin, which was reduced without purification, and 4.91 g of recovered acid. For characterization a small quantity of the crude olefin was recrystallized first from hexane and then from aqueous methanol to give white crystals: mp 143–144 °C; IR 5.80 μm; NMR δ 0.61 (s, 3 H, H-19), 0.90 (s, 3 H, H-18), 1.61 (br s, 3 H, H-21), 1.99, 2.08 (s, 3 H each, CH_3CO_2), 4.75 (m, 4 H, H-3, H-12, H-22).

Anal. Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 75.03; H, 9.72.

3α,12α-Diacetoxy-23,24-dinor-5β-cholane. A solution of 10.10 g of crude 3α,12α-diacetoxy-23,24-dinor-5β-chol-20-ene in 300 mL of methanol was hydrogenated in the usual manner using 0.200 g of platinum oxide. After filtering out the spent catalyst and removing the solvent, the residue was dissolved in hexane–benzene (1:1) and chromatographed on Merck acid-washed alumina. Elution with the same solvent pair gave 2.49 g of diacetate as a white solid. Recrystallization from aqueous methanol gave white needles: mp 115–117 °C; NMR δ 0.71 (s, 3 H, H-19), 0.84 (d, J = 7 Hz, 6 H, H-20, H-21), 0.90 (s, 3 H, H-18), 2.00, 2.09 (s, 3 H each, CH_3CO_2), 4.65 (br m, $W_{1/2}$ = 25 Hz, 1 H, H-3), 5.01 (t, J = 4 Hz, 1 H, H-12).

Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.45; H, 10.04.

23,24-Dinor-5β-cholane-3α,12α-diol (11). 3α,12α-Diacetoxy-23,24-dinor-5β-cholane was reduced with lithium aluminum hydride as described above in the preparation of 24-nor-5β-cholan-12α-ol. From 1.45 g of diacetate there was obtained 0.977 g (84%) of diol as a colorless glass, which formed crystals: mp 92–94 °C from aqueous acetone; NMR δ 0.65 (s, 3 H, H-19), 0.91 (s, 3 H, H-18), 3.58 (br m, $W_{1/2}$ = 25 Hz, H-3), 3.94 (t, J = 4 Hz, 1 H, H-12).

Anal. Calcd for $C_{22}H_{38}O_2$: C, 78.99; H, 11.45. Found: C, 78.79; H, 11.59.

23,24-Dinor-5β-cholan-12α-ol (12). This alcohol was prepared from diol **11** by Oppenauer oxidation followed by Wolff–Kishner reduction in the manner described above for the preparation of 24-nor-5β-cholan-12α-ol. From 0.925 g of diol there was obtained, after chromatography on Woelm activity II neutral alumina and elution with hexane–benzene (1:1), 0.471 g (53%) of alcohol **12** as a white solid. Recrystallization from aqueous methanol gave white crystals: mp 131–132 °C (Blickenstaff[3] reports mp 140–141 °C for this compound, prepared by a different route); NMR δ 0.64 (s, 3 H, H-19), 0.89 (s, 3 H, H-18), 3.95 (t, J = 4 Hz, 1 H, H-12).

Anal. Calcd for $C_{22}H_{38}O$: C, 82.95; H, 12.02. Found: C, 83.02; H, 11.92.

23,24-Dinor-5β-cholan-12-one (6). 23,24-Dinor-5β-cholan-12α-ol (**12**) was oxidized with Jones' reagent in the usual manner (vide supra). From 0.414 g of alcohol there was obtained, after recrystallization from aqueous acetone, 0.247 g (60%) of ketone: mp 184–185 °C; NMR δ 0.90 (d, J = 7 Hz, 6 H, H-20, H-21), 1.01 (s, 6 H, H-18, H-19).

Anal. Calcd for $C_{22}H_{36}O$: C, 83.48; H, 11.46. Found: C, 83.38; H, 11.53.

Reductions. Lithium–Ammonia. Method A. In a typical reaction, 0.122 g of 5β-pregnan-12-one in 14 mL of dry ether and 7 mL of methanol were added dropwise to a solution of 0.60 g of lithium in 30 mL of liquid ammonia. The reaction mixture was stirred at reflux for 0.25 h and quenched with methanol and the ammonia was evaporated. The residue was then taken up in water and extracted with three portions of ether. The ethereal extracts were washed with water and brine and dried and the solvent was removed to give 0.092 g of thick oil. Analysis by NMR indicated that this material was a mixture of 89% 12β-ol and 11% 12α-ol.

Method B. A solution of 0.272 g of 24-nor-5β-cholan-12-one in 20 mL of dry ether was added to 60 mL of liquid ammonia. Lithium was added in small pieces until a permanent blue color persisted and the reaction was stirred at reflux for 0.25 h. After quenching with methanol, the ammonia was evaporated and the product was isolated as described in part A to give 0.195 g of thick oil. TLC (silica gel G–benzene) showed one spot; however, analysis by NMR indicated that the product contained 81% 24-nor-5β-cholan-12β-ol and 19% of the 12-α-ol. This oil was dissolved in hexane–benzene (1:1) and chromatographed on Woelm activity II neutral alumina. Elution with the same solvent mixture gave first 0.104 g of a mixture of 12α- and β-ol while the later fractions afforded 0.071 g of 12β-ol as white crystals. Recrystallization from aqueous acetone gave the analytical sample: mp 103–104 °C; NMR δ 0.68 (s, 3 H, H-19), 0.92 (s, 3 H, H-18), 3.41 (m, 1 H, H-12).

Anal. Calcd for $C_{23}H_{40}O$: C, 83.07, H, 12.12. Found: C. 83.18; H, 12.29.

5β-Pregnan-12β-ol. The reduction of 0.211 g of 5β-pregnan-12-one by procedure A, using *tert*-butyl alcohol as a proton source, gave 0.158 g of a viscous oil which was homogeneous to TLC. Chromatography on activity II alumina and recrystallization from aqueous acetone gave white crystals: mp 94–95 °C; NMR δ 0.62 (s, 3 H, H-19), 0.91 (s, 3 H, H-18), 3.42 (m, 1 H, H-12).

Anal. Calcd for $C_{21}H_{36}O$: C, 82.83; H, 11.92. Found: C, 82.87; H, 12.01.

Sodium Borohydride. In a typical reaction, 0.043 g of 24-nor-5β-cholan-12-one was added to a solution of 0.20 g of sodium borohydride in 10 mL of methanol. The reaction mixture was heated at reflux for 1 h, concentrated to a small volume, poured into water, and extracted with two portions of ether. The ether extracts were washed with water and dried and the solvent was removed to give 0.035 g of a mixture of 12α- and 12β-ol. Analysis by NMR indicated that the mixture contained 72% 12α-ol and 28% of the 12β isomer.

Registry No.—8, 53574-08-6; **9,** 63714-54-5; **10,** 32652-58-7; **11,** 63714-55-6; **12,** 53574-01-9; 12α-acetoxy-5β-cholan-24-oic acid, 53609-15-7; 12α-acetoxy-24-nor-5β-cholane, 63714-56-7; 12α-hydroxy-24-nor-5β-cholan-3-one, 63714-57-8; 3α,12α-diacetoxy-23,24-dinor-5β-chol-20-ene, 63060-66-2; 3α,12α-diacetoxy-24-nor-5β-cholan-23-oic acid, 63714-58-9; 3α,12α-diacetoxy-23,24-dinor-5β-cholane, 63714-59-0; 12β-hydroxy-24-nor-5β-cholane, 63714-60-3; 5β-pregnan-12β-ol, 17996-85-9.

References and Notes

(1) (a) Part 1: J. W. Huffman, D. M. Alabran, T. W. Bethea, and A. C. Ruggles, *J. Org. Chem.*, **29,** 2963 (1964). (b) Presented in part at the 28th Southeast Regional Meeting of the American Chemical Society, October 27–29, 1976.

(2) (a) J. W. Huffman and J. T. Charles, *J. Am. Chem. Soc.*, **90,** 6486 (1968); (b) D. A. H. Taylor, *Chem. Commun.*, 476 (1969); (c) A. Coulombeau and A. Rassat, *ibid.*, 1587 (1968); (d) W. S. Murphy and D. F. Sullivan, *J. Chem. Soc.*, 999 (1972); (e) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 152–158 summarize much of this work.

(3) K. F. Atkinson and R. T. Blickenstaff, *Steroids,* **23,** 895 (1974), and several earlier papers in this series.

(4) S. Pataki, K. Meyer, and T. Reichstein, *Helv. Chim. Acta,* **36,** 1295 (1953).

(5) (a) J. W. Huffman and R. R. Sobti, *Steroids,* **16,** 755 (1970); (b) A. S. Vaidya, S. M. Dixit, and A. S. Rao, *Tetrahedron Lett.*, 5173 (1968).

(6) Subsequent to our preparation of this compound it was reported by Blickenstaff's group (ref 3).

(7) S. Ahmed, M. Alauddin, B. Caddy, M. Martin-Smith, W. T. L. Sidwell, and T. R. Watson, *Aust. J. Chem.,* **24,** 521 (1971).

(8) B. Riegel, R. B. Moffett, and A. V. McIntosh, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 234.

(9) A. Ruff and R. Reichstein, *Helv. Chim. Acta,* **34,** 70 (1951).

(10) We wish to thank Dr. W. E. Jefferson of the Department of Biochemistry, University of Tennessee Center for the Health Sciences for carrying these analyses.

(11) Hecogenin which has a tertiary center at C-20 behaves in a manner similar to the pregnanones. However, the fusion of the spiroketal ring system to the D ring of the steroid nucleus prevents the shielding of C-12 by the 21-methyl group (see ref 1a).

(12) J. W. Huffman and A. C. Ruggles, unpublished work. A. C. Ruggles, Ph.D. Dissertation, Clemson University, 1966.

(13) Reference 2e, pp 59–64.

(14) Using this torsional effect argument, the transition state leading to the 12α-ol has a very severe steric interaction between the attacking borohydride ion and C-21.

(15) (a) D. C. Wigfield and R. W. Gowland, *J. Org. Chem.,* **42,** 1108 (1977); (b) D. C. Wigfield and F. W. Gowland, *Tetrahedron Lett.*, 3373 (1976).

(16) Since the interaction of the solvent alcohol with the carbonyl oxygen is a necessary feature of any mechanism proposed for borohydride reductions (see ref 15), steric interactions involving this alcohol are of importance in governing the source of these reductions, just as are those interactions involving the borohydride ion.

(17) This observation is certainly correct using lithium as a reducing agent (ref 2). There are considerable differences in the reported relative amounts of borneol and isoborneol formed in the reduction of camphor by potassium in ammonia, however. We obtained a mixture containing approximately 20% isoborneol (ref 2a), while other workers have reported obtaining mixtures containing 60% of this isomer (ref 2c and 2d). Numerous attempts in our laboratory to duplicate the experiments reported in ref 2c and 2d have failed (J. W. Huffman and W. W. McWhorter, unpublished work).

(18) (a) F. Sondheimer, O. Mancera, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.,* **75,** 1282 (1953); (b) S. Bernstein, R. Littell, and J. H. Williams, *ibid.,* **75,** 1481 (1953).

(19) In most earlier proposals (ref 2a–d) a dianion has been proposed as an intermediate in these reductions. However, a valid objection to this postulate has been raised by House (ref 2e, p 157).

(20) All melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were taken as potassium bromide disks or liquid films on sodium chloride plates using a Perkin-Elmer Model 137 spectrophotometer and are reported in microns. Nuclear magnetic resonance spectra were obtained using a Perkin-Elmer Hitachi Model R-24 spectrometer and are reported in parts per million relative to tetramethylsilane (δ). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.