Contribution to the Stereochemistry and Mechanism of the Reduction of Enedione Systems by Zinc and by Lithium–Ammonia[1]

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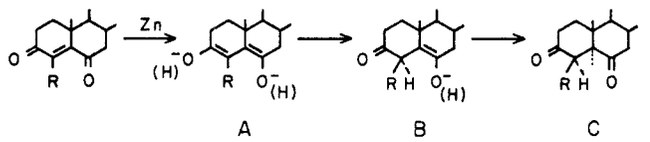
The intermediacy of a dienolic intermediate in the zinc reduction of several enediones has been established by trapping the dienol with acetic anhydride. The zinc reduction of 4-methylcholest-4-ene-3,6-dione has been reinvestigated and found to lead to the 4β-methyl-5α steroid as the product of kinetic control. An identical pattern was observed with lithium–ammonia reduction. The two-stage over-all *cis* addition of hydrogen has been rationalized on steric and mechanistic grounds.

The system zinc dust in alcoholic or acidic medium has found extensive application in the reduction of enedione systems.[3] Under kinetically controlled conditions, the stereochemical feature of this reduction appears to involve a *cis* addition[4] of hydrogen to the double bond which, in the case of two asymmetric centers, usually leads to the less stable product. However, under the relatively rigorous experimental conditions often employed, subsequent equilibration with formation of the thermodynamically stable epimer may occur. The most reasonable mechanism for this reaction involves the attack of zinc on one of the carbonyl functions to yield a dienediol intermediate (compound A of eq 1) which then undergoes kinetically controlled

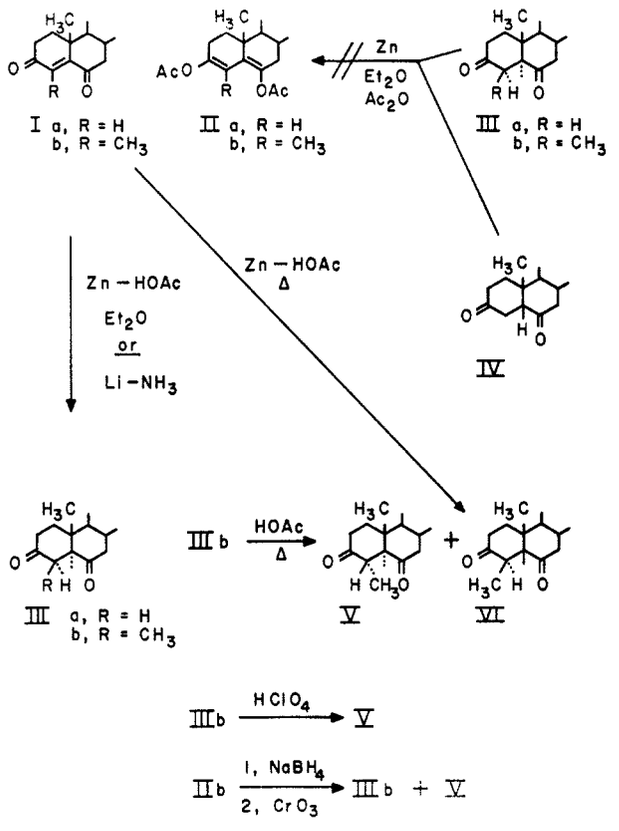


(1)

protonation in two steps. The appearance of the thermodynamically less favored product has been rationalized in terms of protonation from the least hindered side.[4d,e,5,6]

In order to study further the mechanism and stereochemistry of such reductions, we have investigated the reduction of several 3,6-diketo-Δ⁴-cholestene derivatives. Our first objective was to establish conclusively the intermediacy of an enolic derivative. It has been recently shown that enolate anions derived from saturated or unsaturated ketones may be readily trapped by reaction with acetic anhydride.[7] Therefore, the zinc reduction of cholest-4-ene-3,6-dione (Ia) was carried out at room temperature in dry ether containing acetic anhydride, but free of acetic acid. Chromatographic purification of the reaction mixture gave a 30% yield of dienol diacetate (IIa) which could only have arisen *via* an enolic intermediate since the other possible enol acetate precursors, 5α-cholestane-3,6-dione (IIIa) and 5β-cholestane-3,6-dione (IV), were recovered unchanged by identical treatment[8] (Scheme I); however, treatment of IIIa under forcing conditions (isopropenyl acetate–*p*-toluenesulfonic acid) led to authentic IIa.

SCHEME I



When the reduction of the enedione was carried out as described above, but with acetic acid added to the reaction mixture, no enol acetate could be detected and 5α-cholestane-3,6-dione was the sole reaction product. Under identical reaction conditions, 5β-cholestane-3,6-dione (IV) failed to isomerize; consequently

(1) Supported in part by Grant T-185 from the American Cancer Society.

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(3) For a brief summary of enedione reduction, see F. J. McQuillin, "Techniques of Organic Chemistry," Vol. XI, Part I, A. Weisberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 526.

(4) (a) J. F. McGhie, M. K. Pradhan, and J. F. Cavalla, *J. Chem. Soc.*, 3176 (1952); (b) D. H. R. Barton, N. J. Holness, K. H. Overton, and W. J. Rosenfelder, *ibid.*, 3751 (1952); (c) R. Budziarek and F. S. Spring, *ibid.*, 956 (1953); (d) C. S. Barnes and D. H. R. Barton, *ibid.*, 1419 (1953); (e) J. C. Banerjee, D. H. R. Barton, and R. C. Cookson, *ibid.*, 5041 (1957); (f) M. Yanagita and H. Ogura, *J. Org. Chem.*, **22**, 1092 (1957); (g) S. M. Kupchan and S. D. Levine, *J. Am. Chem. Soc.*, **86**, 701 (1964); (h) D. W. Theobald, *Tetrahedron*, **19**, 2261 (1963); **20**, 1455 (1964).

(5) (a) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955); H. E. Zimmerman, *J. Am. Chem. Soc.*, **78**, 1168 1956); (b) H. E. Zimmerman and W. Chang, *ibid.*, **81**, 3634 (1959); (c) H. E. Zimmerman and A. Mais, *ibid.*, **81**, 3644 (1959).

(6) For the related protonation of enolate anions in metal–ammonia reductions, see D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954); A. J. Birch, H. Smith, and R. E. Thornton, *ibid.* 1339 (1957); G. Stork, P. Rosen, and N. L. Goldman, *J. Am. Chem. Soc.*, **83**, 2965 (1961); G. Stork and T. Tsuji, *ibid.*, **83**, 2783 (1961); G. Stork and S. Darling, *ibid.*, **86**, 1761 (1964); M. J. T. Robinson, *Tetrahedron*, **21**, 2475 (1965).

(7) H. J. Ringold and S. K. Malhotra, *J. Am. Chem. Soc.*, **84**, 3402 (1962); H. O. House and V. Kramer, *J. Org. Chem.*, **28**, 3362 (1963); G. Subrahmanyam, S. K. Malhotra, and H. J. Ringold, *J. Am. Chem. Soc.*, **88**, 1332 (1966).

(8) Initially it was hoped that the stereochemistry of protonation at C-4 could be determined in the simple case of Ia by the zinc–acetic acid reduction of 4-deuteriocholest-4-ene-3,6-dione and establishment in the nmr of the coupling pattern of the C-4 and C-5 protons. However, we were unable to resolve the desired spectrum and this approach was abandoned.

the protonation at C-5 must occur exclusively from the α face with direct formation of the thermodynamically more stable product.

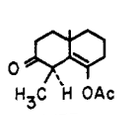
In order to investigate the stereochemistry of protonation at C-4,[8] the zinc reduction of the 4-methylenedione (Ib) was reinvestigated. Fieser[9] first reduced Ib with zinc in boiling acetic acid and isolated two saturated diones of mp 123–124° (V) and 189–190° (VI), with the former predominating. Subsequently, Julia and Lavaux[10] and Mori[11] established the stereochemistry of V as the 4α-methyl-5α compound and VI as the 4β-methyl-5β isomer, both substances having the methyl group in an equatorial position. In our hands, the zinc reduction of Ib at room temperature in ether–acetic anhydride gave a good yield of the anticipated enol acetate (IIb). When reduction was carried out at ambient temperature with zinc–acetic acid in ether, the principal product was a 4-methyl-3,6-dione (IIIb), mp 179–182°, different from Fieser's two substances. This compound was characterized on chemical grounds and subsequently by direct comparison[12] with the Julia and Mori samples as the unstable 4β-methyl-5α isomer with the methyl group in an axial position. It may be noted that the treatment of IIIb at room temperature with zinc–ether–acetic anhydride gave only unreacted starting material; therefore formation of the enol acetate IIb must be attributed to enolate trapping. When reduction was carried out in hot acetic acid under Fieser's conditions, the reaction product consisted of a 3:1 mixture of V and VI in accord with the reported[9] reduction pattern. (See Scheme I).

The treatment of IIIb for a brief period with perchloric acid in acetic acid led in high yield to the 4α-methyl-5α isomer (V) which establishes the latter as the most stable of the four possible isomers. When IIIb was simply heated in boiling acetic acid, isomerization also occurred to yield a 4:1 mixture of the 4α-methyl-5α compound (V) and the 4β-methyl-5β isomer (VI). Thus it is clear that the initial product of the zinc reduction stems from a kinetically controlled protonation of a dienol species at the 4α,5α positions while V and VI are secondary products due to acid and/or thermal isomerization. Thermal isomerization also occurred when IIIb was heated above its melting point since thin layer analysis of the melt showed the presence of a substantial percentage of V and VI. Also, attempts to analyze IIIb by glpc were unsuccessful since the substance isomerized on the column to a 65:35 mixture of V and VI.[13] The pure 4β-methyl-5β isomer (VI), as well as V, was found to be stable on glpc[13] and therefore thermal inversion at C-4 (*via* enolization) which leads to V must be faster than inversion at C-5. Although the point has not been rigorously established, it is also probable that the same order of enolization holds in the perchloric acid catalyzed isomerization.

Although the syntheses of Julia and Lavaux and of Mori and their structural assignments for IIIb, V, and VI appear to be unequivocal, further support may be offered by our nmr studies of IIIb and V. The stable 4α-methyl-5α-dione (V) exhibited the 19-methyl resonance at 58.8 cps,[14] a position which essentially coincides with that of 5α-cholestane-3,6-dione (IIIa) (59.0 cps) and is in accord with an α-oriented 4-methyl group. A proton doublet centered at 143.4 cps may be assigned to the 5α proton and the coupling constant of J = 11.5 cps is consistent only with a *trans* arrangement of the C-4 and C-5 protons. The unstable dione IIIb exhibited the 19-methyl protons at 67.2 cps, the deshielding being due to the axial 4β-methyl group. A complementary deshielding of the 4β methyl was also observed (doublet centered at 84.6 cps, J = 7.5 cps) while the 4α-methyl group of V appeared as a doublet at 61.0 cps, J = 6.0 cps.

It was also of interest to carry out the reduction of 4-methylcholest-4-ene-3,6-dione (Ib) by means of lithium–ammonia. In this case, product formation would occur by protonation of a dienolate anion, while in the zinc–acetic acid case the species undergoing protonation could be the dienolate anion, the enol–enolate, or the neutral dienol. The lithium–ammonia reduction of Ib (with ammonium chloride quenching) gave the 4β-methyl-5α compound IIIb, identical with the product from the room-temperature zinc reduction. This strongly supports the proposed mechanism and intermediacy of some type of dienolic intermediate in the zinc reduction.

Finally, the sodium borohydride reduction of 3,6-diacetoxy-4-methylcholest-3,5-diene (IIb) was investigated. In simple cases, such reduction involves the successive alkaline hydrolysis of the enol acetate, protonation of the intermediate anion, and finally hydride reduction of the ketone.[15] Reduction of IIb furnished a mixture of the epimeric diols of the 4α- and 4β-methyl series with the latter predominating. After separation by tlc, the major fraction was oxidized with Jones reagent to furnish 4β-methyl-5α-cholestane-3,6-dione (IIIb), while the minor fraction gave 4α-methyl-5α-cholestane-3,6-dione (V). It is likely that the 4α-methyl compound was formed by base-catalyzed inversion of a 3-keto-4β-methyl compound which could be the 4β-methyl-5α-dione or the 3-keto-6-enol acetate (VII). Since the latter is a β,γ-unsaturated ketone,



VII

enolization and equilibration of the 4β-methyl group could compete ratewise with subsequent hydride reduction of the ketone. At any rate, it is quite clear that the favored kinetic pathway involves 4α,5α protonation in the borohydride hydrolysis just as in the

(9) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4386 (1953).

(10) S. Julia and J. Lavaux, *Bull. Soc. Chim. France*, 1223 (1963).

(11) H. Mori, *Chem. Pharm. Bull. Japan*, **12**, 1224 (1964).

(12) We are grateful to Professor S. Julia and Dr. H. Mori for infrared spectra and for generous samples of the authentic diones IIIb, V, and VI. The melting points reported for IIIb are 163–165°[10] and 181–183°.[11] All three samples of IIIb exhibited identical infrared spectra and chromatographic behavior on thin layer chromatography. Our sample and that of Mori gave no melting point depression on admixture. The lower melting point of the Julia and Lavaux[10] sample appears to be due to polymorphism.

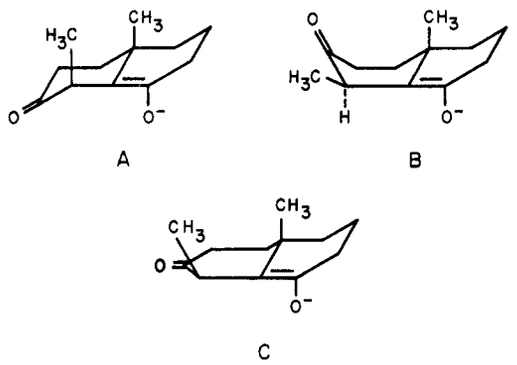
(13) On silica gel thin layer plates with the developing system ethyl acetate–cyclohexane (22:78), IIIb exhibited an R_f value of 0.55 while V and VI were inseparable with an R_f of 0.61. On glpc (3% SE-30 on Gas Chrom P, 240°, helium flow 30 cc/min), the 4α-methyl-5α-dione (V) and the 4β-methyl-5β-dione (VI) exhibited retention times of 24 and 21 min, respectively.

(14) The nmr spectra were obtained on a Varian Model A-60 spectrophotometer. All spectra were run in deuteriochloroform with tetramethylsilane as internal standard.

(15) W. G. Dauben and J. F. Eastham, *J. Am. Chem. Soc.*, **73**, 4463 (1951); W. G. Dauben, R. M. Micheli, and J. F. Eastham, *ibid.*, **74**, 3852 (1952).

zinc–acetic acid reduction and in the lithium–ammonia reduction.

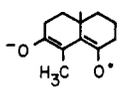
The 4α,5α protonation of a dienol intermediate in the zinc–acetic acid and lithium–ammonia reduction may be rationalized in the following manner. For purposes of discussion, it is unimportant whether the actual species that first undergoes C protonation is a dianion (most likely under the strongly basic lithium–ammonia conditions), an enol–enolate, or even neutral dienol species, which are additional possibilities in zinc–acetic acid.[16] The question of whether protonation occurs first at C-4 or C-5 appears answerable strictly on steric grounds. Since approach to 4α is completely unhindered while the C-5 position is shielded by axial protons at 1α, 7α and 9α, it is most likely that the initial protonation occurs at 4α to yield the 3-keto-4β-methyl-Δ⁵ derivative (compound B of eq 1). The preference for 4α over 4β protonation must also stem, at least in part, from steric hindrance on the β face owing to the 2β proton and the C-19 angular methyl substituent. Considering only chair forms, the formation of B (eq 1) involves preferential equatorial protonation despite the fact that axial (4β) protonation would be stereoelectronically favored by overlap both with the 3-ketone and the 5(6) double bond.[17] Further, the 4β-methyl group is in an axial configuration.



With ring A in a chair conformation, the proposed 4β-methyl-Δ⁵ intermediate would be destabilized by the 1,3 interaction of the 4β-methyl and the C-19 methyl substituents. However, a 4α-methyl group would be severely eclipsed by the oxygen substituent at C-6 and it is not clear whether the 4α-methyl-(equatorial) Δ⁵ derivative would be more stable than the 4β methyl compound, in particular if the 6-hydroxyl group is in the anionic form and heavily solvated. The nonbonded interactions of a 4β-methyl group can be relieved if, instead of the chair conformation, ring A adopts a boat (B) or "flattened"[18] (C) conformation. Either conformation B or C relieves the methyl–methyl interaction without eclipsing the 4-methyl and 6-oxygen function and it is quite probable that B or C are of lower energy than A and even than the 4α-methyl-Δ⁵ compound. Also, if the transition state for 4α protonation of the dienol intermediate resembles the boat or flattened conformer, then protonation can occur in an axial sense which permits continuous overlap with both the developing 3-ketone and the 5(6) double bond. In summary, we suggest that the 4β-methyl-Δ⁵ intermediate exists in the boat or flattened conformation and therefore 4α protonation is favored by approach from the least hindered side, by product stability, and by favorable overlap in the transition state.

The stereochemistry of the addition of the second proton, which involves attack at 5α rather than at 5β, requires little explanation. The steric hindrance to 5α protonation, owing to axial hydrogen interactions on the α side, would be at least offset by interaction with the angular methyl substituent on the β side and also by the π electrons of the carbonyl group when ring A is in a boat conformation. Therefore, it is probable that the dominant factor in the second step is stereoelectronic[17] in nature and that axial 5α protonation occurs because of favorable overlap with the developing C-6 ketone while a 5β proton would be equatorial to ring B.

(16) The possibility of a radical anion intermediate cannot be excluded.



(17) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956); S. K. Malhotra and H. J. Ringold, *ibid.*, **86**, 1997 (1964).

(18) N. L. Allinger and M. A. Da Rooge, *ibid.*, **84**, 4561 (1962).

Experimental Section[19]

3,6-Diacetoxycholest-3,5-diene (IIa).—Cholest-4-ene-3,6-dione (I)[20] (0.3 g) in absolute ether (25 ml) and acetic anhydride (0.4 ml) was treated with activated[21] zinc dust (3 g) and the suspension stirred for 24 hr at room temperature under nitrogen. The mixture was diluted with hexane and filtered; the zinc was repeatedly washed with the same solvent. The filtrate was washed with water, dried, and evaporated *in vacuo* to yield a gummy residue which was taken up in a small volume of acetone and applied to 1-mm plates of silica gel. Development with ethyl acetate–benzene (15:85) and elution of the fast-moving zone gave 3,6-diacetoxycholest-3,5-diene (II) (0.11 g) as a pale yellow gum. Rechromatography in the same system gave the analytical specimen as an oil: ultraviolet λ_{max} 244 mμ (ε 10,600); λ_{max}^{KBr} 5.75 μ; nmr 350 cps (C-4 H, doublet, J = 1.5 cps), 126 (acetate methyls), 62.4 (19-methyl), and 41.4 (18-methyl).

Anal. Calcd for $C_{31}H_{48}O_4$: C, 76.85; H, 9.92. Found: C, 76.57; H, 10.08.

5α-Cholestane-3,6-dione (IIIa).—Cholest-4-ene-3,6-dione (I) (12 mg) in ether (1 ml) and acetic acid in acetic anhydride (5%, 0.25 ml) was stirred for 16 hr with 0.12 g of zinc dust. Work-up as above and spotting on a thin layer silica gel plate demonstrated the absence of enol acetate (II) and the formation of IIIa as the sole reaction product. Crystallization from acetone–hexane gave a sample, mp 169–171°, which was identical (infrared and mixture melting point) with an authentic specimen.

Attempted Isomerization of 5β-Cholestane-3,6-dione (IV) by Zinc–Zinc Acetate in Acetic Acid.—A solution of 5β-cholestane-3,6-dione (8 mg) in absolute ether (1 ml) containing acetic acid (0.1 ml) was stirred for 22 hr at room temperature with zinc dust (60 mg) and zinc acetate (60 mg). Analysis of the isolated product revealed only unreacted IV.

Attempted Formation of II from 5α-Cholestane-3,6-dione (IIIa) and from 5β Cholestane-3,6-dione (IV) by the Action of Zinc–Acetic Anhydride.—When either IIIa or IV (24 mg) was treated for 18 hr in a boiling solution of ether (8 ml) containing acetic anhydride (0.2 ml) and zinc dust (0.24 g), only unreacted starting material was found. The addition of zinc acetate was also found to be without effect.

Formation of 3,6-Diacetoxycholest-3,5-diene (II) from 5α-Cholestane-3,6-dione (IIIa) under Forcing Conditions.—A solution of IIIa (0.15 g) in isopropenyl acetate (20 ml) containing

(19) All melting points were taken on a Fisher-John apparatus and are uncorrected. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol. Thin layer chromatography was carried out on silica gel G (E. Merck AG, Darmstadt), the spots being developed either by 2,4-dinitrophenylhydrazine reagent or phosphomolybdic acid. Microanalyses were carried out by Midwest Microlaboratories, Indianapolis, Ind.

(20) L. F. Fieser, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 189.

(21) Zinc was activated by a brief treatment with 2% dilute hydrochloric acid. The material was then successively washed with water, ethanol, and ether, and dried at 90° *in vacuo*.

p-toluenesulfonic acid (60 mg) was slowly distilled over a 16-hr period. The solution was then concentrated under reduced pressure and the residue taken up in ether and washed. Evaporation of the dried solvent left a gum which, after purification by silica gel thin layer chromatography (benzene–ethyl acetate 85:15), gave 90 mg of II identical with the product obtained above.

3,6-Diacetoxy-4 methylcholest-3,5-diene (IIb).—4-Methylcholest-4-ene-3,6-dione[9] (Ib) (0.32 g) dissolved in ether (25 ml) containing acetic anhydride (0.4 ml) was stirred with activated zinc dust (2.5 g) for 16 hr under nitrogen. After the usual work-up, the product was purified by chromatography on silica gel plates with benzene–ethyl acetate (85:15) as the developing solvent. The fastest moving zone was eluted with acetone and gave 0.25 g of the enol acetate (IIb) as a clear gum. Repeated chromatography furnished an analytically pure specimen although the material would not be crystallized: ultraviolet, λ_{max} 236 mμ (ε 13,300); λ_{max}^{KBr} 5.75 μ; nmr 127 cps, 124 (acetate methyls), 100 (4-methyl), 61.2 (19-methyl), and 40.8 (18-methyl).

Anal. Calcd for $C_{32}H_{50}O_4$: C, 77.06; H, 10.11. Found: C, 76.82; H, 10.19.

4β-Methyl-5α-cholestane-3,6-dione (IIIb) by Zinc–Acetic Acid Reduction of Ib at Room Temperature.—A solution of 4-methylcholest-4-ene-3,6-dione (Ib) (0.4 g) in ether (25 ml) was treated with glacial acetic acid (0.8 ml) and zinc dust (4 g). The mixture was stirred for 16 hr under nitrogen and then diluted with benzene (25 ml) and filtered. The residue was washed with benzene and the combined organic extracts were washed to neutrality, dried, and evaporated. Crystallization from hexane gave 0.2 g of IIIb: mp 179–182° with prior softening at 172°, $[\alpha]_D$ +5° (lit. mp 181–183°,[11] $[\alpha]_D$ −2°; mp 164–165°,[10] $[\alpha]_D$ +6°[12]); λ_{max}^{KBr} 5.85 μ; nmr 84.6 cps (4β-methyl doublet, J = 7.5 cps), 67.2 (19-methyl), and 41.4 (18-methyl).

Anal. Calcd for $C_{28}H_{46}O_2$: C, 81.1; H, 11.18. Found: C, 81.02; H, 11.28.

The solid remaining after crystallization of the main fraction melted at 170–175° and had an infrared spectrum almost identical with IIIb. Thin layer chromatography, however, indicated contamination by a small amount of the 4β-methyl-5β-dione (VI) or of the 4α-methyl-5α-dione (V).[13]

Attempted Formation of the Dienol Acetate (IIb) from IIIb by the Action of Zinc–Acetic Anhydride.—A solution of IIIb (50 mg) in ether (5 ml) and acetic anhydride (0.1 ml) was stirred with zinc dust (0.6 g) and zinc acetate (50 mg) for 20 hr. Starting material of mp 175–180° was recovered.

Isomerization of 4β-Methyl-5α-Cholestane-3,6-dione (IIIb) to 4α-Methyl-5α-Cholestane-3,6-dione (V).—Perchloric acid (70%, 1 drop) was added to a solution of IIIb (79 mg) in acetic acid (2.5 ml). After standing for 1 hr, the mixture was poured into water and the resulting precipitate (70 mg) crystallized from methanol to yield 60 mg of the 4α-methyl isomer V: mp 124–126°, $[\alpha]_D$ −31° (lit.[9] mp 123–124°, $[\alpha]_D$ −19°). This material was found to be identical with a sample kindly provided by Mori:[11] λ_{max}^{KBr} 5.85 μ; nmr 143 cps (5α H, doublet, J = 11.5 cps), 60.6 (4α-methyl, doublet, J = 6.0 cps), 58.8 (19-methyl), and 41.4 (18-methyl).

Anal. Calcd for $C_{28}H_{46}O_2$: C, 81.1; H, 11.18. Found: C, 81.3; H, 11.32.

Equilibration of 4β-Methyl-5α-cholestane-3,6-dione by Zinc–Hot Acetic Acid.—A solution of IIIb (100 mg) in acetic acid (8 ml) was treated with zinc dust (1 g) and the mixture boiled for 16 hr. The cooled mixture was filtered and poured into water. The resulting precipitate, after crystallization from hexane, yielded 8 mg of 4β-methyl-5β-cholestane-3,6-dione (VI), mp 187–191°. This material was identical with authentic samples kindly supplied by Julia and Mori and, as previously noted by Julia and Lavaux,[10] VI exhibited a doublet in the infrared spectrum, λ_{max}^{KBr} 5.85 and 5.91 μ. The mother liquors exhibited no recovered IIIb on thin layer chromatography and were analyzed by glpc[13] as an 85:15 mixture of V and VI.

Reduction of 4-Methylcholest-4-ene-3,6-dione (Ib) by Zinc–Acetic Acid at Elevated Temperature.—A mixture of Ib (125 mg) and zinc dust (1.25 g) in glacial acetic acid (15 ml) was boiled for 18 hr as described by Fieser.[9] The product was analyzed by thin layer chromatography and glpc and was found to consist of a 3:1 mixture of 4α-methyl-5α-cholestane-3,6-dione (V) and 4β-methyl-5β-cholestane-3,6-dione (VI). A sample of IIIb heated for 5 hr in acetic acid, but in the absence of zinc, gave a 4:1 ratio of V and VI.

4β-Methyl-5α-Cholestane-3,6-dione (IIIb) by Lithium–Ammonia Reduction of Ib.—Lithium (37 mg) was added to 40 ml of liquid ammonia and stirred for 10 min before the addition of 79 mg of dione IIIb in dry tetrahydrofuran (5 ml). Stirring was continued for 5 min and the reaction then quenched by the addition of solid ammonium chloride. The ammonia was allowed to evaporate in a stream of nitrogen, water was added, and the precipitate collected. The infrared spectrum of the crude product was identical with that of IIIb and thin layer chromatography showed only a single spot. Crystallization from hexane gave 40 mg of IIIb, mp 179–182°.

Sodium Borohydride Reduction of Enol Acetate IIb and Oxidation of Resulting Diols.—A solution of IIb (0.15 g) in tetrahydrofuran (5 ml) was cooled to 0° and treated, under nitrogen, with a solution of 0.8 g of sodium borohydride in methanol (9 ml) and water (1 ml). The reaction mixture became warm and the vigorous reaction soon subsided. After standing overnight, water was added and the solution acidified with dilute hydrochloric acid. The mixture was then extracted with chloroform, the organic layer washed with water, and the solvent removed. The oily residue (0.12 g), which consisted of a mixture of 4α- and 4β-methyldiols, was applied to a thick plate of silica and developed with 1:1 ethyl acetate–benzene. The fast-moving zone, which contained the alcohols of the 4β-methyl series, was eluted with acetone. Removal of the solvent gave a semisolid (42 mg, fraction A). The more polar zone (20 mg, fraction B) contained mostly the diols of the 4α-methyl series. Fractions A and B were separately oxidized as described below.

Oxidation of the Diols of 4β-Methyl Series (A).—Fraction A (24 mg) was dissolved in acetone (2 ml) and 8 *N* chromic acid in sulfuric acid was added to the ice-cooled solution until the brown color persisted. Methanol was added to destroy the excess of chromic acid and the ketone was then precipitated by the addition of water. The product (30 mg) exhibited an infrared spectrum identical with that of 4β-methylcholestane-3,6-dione (IIIb); crystallization from hexane furnished a sample with mp 179–182°. Mixture melting point determination and thin layer behavior also confirmed the identity.

Oxidation of the Diols of 4α-Methyl Series.—Fraction B (20 mg) was oxidized with chromic acid as described above. Thin layer chromatography of the product on silica gel (9:1 benzene–ethyl acetate) gave zones corresponding to 4β-methyl-5α cholestane 3,6-dione and 4α-methyl-5α-cholestane-3,6-dione (V), with the latter product predominating. Identity of the two substances was confirmed by infrared comparison, mixture melting point determination, and thin layer chromatographic behavior.

Registry No.—IIa, 13392-05-7; IIb, 13392-06-8; IIIa, 2243-06-3; IIIb, 1058-65-7; V, 1058-64-6; VI, 986-50-5.