Anal. Calcd. for $C_{29}H_{46}O_9S_2$: C, 57.81; H, 7.64; S, 10.63. Found: C, 57.72; H, 7.83; S, 10.69.

Treatment of the dimesylate with sodium iodide in acetone at 100° for 18 hours resulted in recovery of the starting material.

2β,3β-Oxido-22a,5α-spirostane-12-one (XI).—To a solution of 450 mg. of the bromohydrin VII in 18 ml. of benzene and 36 ml. of petroleum ether (30–60°) was added 18 g. of basic alumina (Merck) and the reaction mixture was allowed to stand at room temperature for 30 minutes. After dilution with 250 ml. of acetone the alumina was filtered off and the filtrate was concentrated *in vacuo*. Crystallization of the residue from ether afforded 220 mg. of XI as fine needles, m.p. 233–236°, $[\alpha]^{chf}D$ +53°.

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.67; H, 9.41. Found: C, 75.51; H, 9.33.

2β,3α-Dihydroxy-22a,5α-spirostane-12-one (IX). A.—A solution of 200 mg. of the β-oxide XI in 50 ml. of acetone and 5 ml. of water was treated with 0.4 ml. of 2 *N* sulfuric acid and allowed to stand at room temperature for 48 hours. The reaction mixture was concentrated *in vacuo*, diluted with water and the product extracted with chloroform. The chloroform extracts were washed with water, saturated sodium chloride solution and dried over magnesium sulfate. The residue, after removal of the solvent *in vacuo*, was chromatographed on 2.5 g. of acid-washed alumina. The column was eluted with benzene–chloroform and chloroform–ethyl acetate mixtures. From the fractions corresponding to chloroform through 50% chloroform–ethyl acetate there was obtained 65 mg. of fine needles, m.p. 249–253°. Recrystallization from acetone afforded an analytical sample with m.p. 253–256°, $[\alpha]^{chf}D$ +19.7°.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.88; H, 9.26.

B.—Similar treatment of the α-oxide III[2] afforded the 2β,3α-diol IX, identified by mixed m.p. and infrared spectra.

C.—A suspension of 160 mg. of silver acetate in 25 ml. of acetic acid and 2.5 ml. of acetic anhydride was stirred under reflux with exclusion of moisture for 2 hours. After cooling to room temperature, 500 mg. of the bromohydrin acetate VIIa was added and the mixture was stirred at 100–110° for 8 hours. The reaction mixture was filtered and concentrated *in vacuo*. The residue was diluted with water and the crude product isolated by filtration. The product was dissolved in chloroform and the chloroform solution was washed with water, saturated sodium chloride solution, and dried over magnesium sulfate. The solvent was removed *in vacuo* and to the residue dissolved in 150 ml. of dry acetone, 2.0 g. of anhydrous copper sulfate was added, and the mixture was stirred at room temperature with exclusion of moisture for 3 days. The reaction mixture was filtered and the filtrate was shaken with 2.0 g. of anhydrous potassium carbonate. The residue, after filtration and concentration *in vacuo*, was chromatographed on 15 g. of basic alumina (Merck) and eluted with chloroform–ethyl acetate and ethyl acetate–methanol mixtures. Fractions corresponding to ethyl acetate through 5% methanol–ethyl acetate afforded 210 mg. of the 2β,3α-diol IX, identified by mixed m.p. and infrared spectra.

The dimesylate (IXa) was crystallized from chloroform–acetone, m.p. 232–233° dec.

Anal. Calcd. for $C_{29}H_{46}O_9S_2$: C, 57.81; H, 7.64; S, 10.63. Found: C, 57.96; H, 7.53; S, 11.07.

The dimesylate IXa was recovered unchanged on treatment with sodium iodide in acetone at 100° for 18 hours.

22a,5α-Spirostane-2,12-dione (X). A.—A solution of 509 mg. of the bromohydrin VII in 30 ml. of acetic acid was oxidized overnight at room temperature with 73.2 mg. of chromic anhydride. The reaction mixture was concentrated *in vacuo*, diluted with water and the crystalline product isolated by filtration. Crystallization from acetone gave 350 mg. of 3-bromo-22a,5α-spirostane-2,12-dione, m.p. 234–236° dec. The bromoketone was dissolved in 25 ml. of refluxing acetic acid and treated under reflux and stirring with 2.5 g. of zinc dust over a period of 1 hour. The reaction mixture was filtered, concentrated *in vacuo*, and diluted with water. The product was extracted with chloroform and the chloroform extract was washed with 5% sodium bicarbonate solution, water and dried over magnesium sulfate. Removal of the solvent followed by crystallization from ether gave 220 mg. of mica-like plates, m.p. 232–235°. Recrystallization from ether provided an analytical specimen, m.p. 234–237°, $[\alpha]^{chf}D$ +27.3°.

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.67; H, 9.41. Found: C, 75.83; H, 9.28.

B.—Reduction of 1.0 g. of the β-oxide XI in 10 ml. of tetrahydrofuran with 400 mg. of lithium aluminum hydride in 50 ml. of dry ether, followed by room temperature oxidation of the crude reduction product with 356 mg. of chromic anhydride in acetic acid afforded, after crystallization from ether, 700 mg. of X, m.p. 234–238°, mixed m.p. with material obtained from VII was not depressed.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA]

The Stereochemistry of the Hydride Reduction of Some Steroidal Ketones

BY WILLIAM G. DAUBEN, ERWIN J. BLANZ, JR., JAMES JIU AND ROBERT A. MICHELI

RECEIVED DECEMBER 19, 1955

The reduction of cholestan-2-one and cholestan-3β-ol-7-one by metal hydrides has been studied. With the 2-keto isomer, it has been found that the isomer composition of the epimeric cholestan-2-ols is 52% β and 37% α with $LiAlH_4$ and is 71% β and 16% α with $NaBH_4$. With the 7-keto isomer, the values are 45% β and 55% α with $LiAlH_4$ and 27% β and 73% α with $NaBH_4$. These results have been discussed in terms of the steric approach control and the product development control for hydride reduction presented in a previous study.

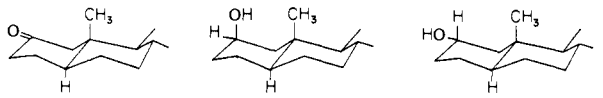
The stereochemical controlling factors which are involved in a hydride reduction of a carbonyl group were investigated recently in this Laboratory[1] and it appeared that two of the more important features were, first, the ease of formation of the organometallic complex between the carbonyl group and the hydride and, second, the relative energetics of the formation of the products once this initial complex was formed. These two effects were termed steric approach control and product development control, respectively. Based upon these concepts, generalizations with regard to the stereochemical outcome of a hydride reduction can be made. For example, when an unhindered ketone is reduced with $LiAlH_4$, the product composition will closely resemble that of the equilibrium mixture of the two isomers. When the more bulky sodium borohydride in methanol is used, the product will be richer in the unstable isomer than when $LiAlH_4$ is employed.

These concepts fitted well with the data obtained with simple alkylcyclohexanones but it is

(1) W. G. Dauben, G. J. Fonken and D. S. Noyce, THIS JOURNAL, 78, 2579 (1956).

desirable to extend them to compounds which possess a rigid structure and which have more clearly defined steric interferences. Compounds ideally suited for such a study are the steroidal ketones, for here not only has the series been extensively investigated but also the stereochemistry of the products is well established.

From the results obtained by various workers,[2-11] it would appear that there are three classes of steroidal ketones, the highly hindered type such as C_{11}, the unhindered type such as C_3 and the intermediate class such as C_7. With regard to the first two types, Barton[12] has pointed out that $LiAlH_4$ reduction of highly hindered ketones always yields the thermodynamically unstable, axial isomer while unhindered ketones yield the thermodynamically stable, equatorial isomer. The formation of the axial isomer from a hindered ketone would be predicted from a purely steric approach control consideration while the formation of the equatorial isomer from an unhindered ketone, such as a 3-keto-steroid, would be predicted on the basis of product development control. In order to better evaluate these two concepts, a ketone in which both effects could operate would be a better model. Cholestan-2-one (I) is such a compound, for here, in distinc-



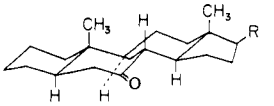
I II III

tion to the 3-keto isomer, steric approach control would predict a 2β-axial isomer (II) since the presence of the C_{10}-β-axial methyl group would give rise to a 1,3-diaxial type of non-bonded atom interaction and would greatly hinder, but not block, attack from the β-side. Product development control would predict a 2α-equatorial isomer (III).

Cholestan-2-one was prepared by the method of Ruzicka, Plattner and Furrer[13] and was reduced with $LiAlH_4$ in ether. The product composition was determined by isolation of the pure 2α and 2β epimers. It was found that although digitonin would precipitate the β-isomer, such a separation was not quantitative. Chromatography over silica gel did give a separation of isomers and by rechromatography of the middle fraction a total of 52% β and 37% α was obtained. Thus, in this case where the carbonyl group has been moved one carbon atom nearer the C_{10}-axial methyl group, the amount of top-side β-attack (in this case to give an equatorial isomer) is greater than in the 3-keto series where only 4% of β-attack occurs. Such a result clearly rules out a *pure* steric factor of the C_{10}-methyl, as was suggested by Shoppee and Summers,[3] as being the sole controlling force in the reduction of a 3-keto steroid. These data for the 2-keto compound show that the C_{10}-axial methyl group, although giving rise to a 1,3-diaxial type of non-bonded atom interaction and steric approach control, still is not the sole factor affecting the stereochemical course of the reaction when a small reagent such as $LiAlH_4$ is used and a product development control is still partially in effect.

In order to further evaluate both the steric aspects of the C_{10}-methyl group as well as the relative size of the reducing agents, $LiAlH_4$ and $NaBH_4$, cholestan-2-one was reduced by the latter reagent using methanol as the solvent. The isomer composition was found to be 71% β and 16% α. This increase in the amount of the axial isomer is in line with the concept that the reducing species present in $NaBH_4$ is of greater steric bulk and desires an equatorial attack and accentuates the steric approach control of the reaction.[1]

Cholestan-3β-ol-7-one is a similar case to the 3-keto isomer except there are more substituents surrounding the C_7-carbonyl group. If one extends the principle developed above for the 3-keto steroids that an axial methyl group on a γ-carbon plays a very minor role in steric approach control, then only the axial substituents on a β-carbon must be considered. A bottom-side attack on the carbon at C_7 would be hindered by the axial hydrogen atoms on C_5, C_9 and C_{14}. A top-side attack at this center would be hindered only slightly by the two γ-methyl groups at C_{10} and C_{13}. Thus, from



IV

a pure steric approach viewpoint, a top-side attack should be preferred and the 7α-axial isomer should predominate. The equilibrium composition of the two 7-hydroxy compounds has been shown by Barton and Rosenfelder[14] to be 80% β (equatorial) and 20% α (axial). Accordingly, the composition of the product obtained by $LiAlH_4$ reduction of a 7-ketocholestane derivative should be more rich in the α-isomer than the 20% present at equilibrium, the latter being the value expected from a pure product development controlled reaction. Two groups of workers have reduced such a 7 keto steroid with $LiAlH_4$ but the experiments were performed in a manner such that an accurate value for the isomer composition was not obtained. For example, Cremlyn and Shoppee[9] reduced cholestan-7-one with $LiAlH_4$ but they were only able to isolate a total of 66% of pure isomers, the remainder being an undefined intermediate fraction. The value for the pure compounds obtained, however, was 2 parts of β to one part of α. Fieser, Fieser and

(2) L. F. Fieser, M. Fieser and R. N. Chakravarti, THIS JOURNAL, **71**, 2229 (1949).

(3) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 687 (1950).

(4) L. H. Sarett, M. Feurer and K. Folkers, THIS JOURNAL, **73**, 1777 (1951).

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(6) W. G. Dauben, R. A. Micheli and J. F. Eastham, *ibid.*, **74**, 3852 (1952).

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(9) R. J. W. Cremlyn and C. W. Shoppee, *J. Chem. Soc.*, 3515 (1954).

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(11) D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955).

(12) D. H. R. Barton, *ibid.*, 1027 (1953).

(13) L. Ruzicka, Pl. A. Plattner and M. Furrer, *Helv. Chim. Acta*, **27**, 524 (1944).

(14) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

Chakravarti[2] have reduced 7-ketocholestanyl acetate with $LiAlH_4$ and have reported that their crude product possessed a rotation which indicated about equal amounts of the two isomers. When this crude reaction product was chromatographed, however, there was eluted 16% of a material which was not a dihydroxycholestane. Since the rotation of this material was not given, the product composition could not be given with certainty.

As the 7-ketocholestanyl acetate was more readily available than the simple 7-keto compound, the reduction of the former with $LiAlH_4$ was reinvestigated. The infrared spectrum of all crude reaction products was examined in order to establish the absence of any starting material but a separation into pure isomers was not undertaken since such a separation is not quantitative. The reduction product, however, was chromatographed over alumina to show that only dihydroxycholestanes were present and the optical rotation of the original material and the total dihydroxycholestanes after chromatography was taken. The rotation was the same for each material and indicated a composition of 55% α and 45% β. When the reduction was conducted with $NaBH_4$ in methanol, the composition was 73% α and 27% β. Such results are in line with the expectation that there is a higher degree of hindrance on the bottom side of the molecule to hydride reduction and that the reduction of a carbonyl group at C_7 is controlled both by steric approach and product development factors.

To date, no study has been reported which has investigated the possible steric effect of the solvent employed in a hydride reduction. In the case of the Meerwein–Pondorff reduction, however, Nace and O'Conner[5] have shown that the solvent does play an important role and that as the steric demands of the solvent increase the greater is the steric control of the reduction. Since the hydride would also be solvated, an attempt was made to see if the solvent would affect the isomer ratio. When tetrahydrofuran was used, there was an increase in the amount of the 7α-isomer (steric approach favored) formed, but the change was only 10%.

On the basis of the above results with the 2- and 7-ketocholestanes, it can be generalized that as the hindrance to approach of the $LiAlH_4$ reagent from one side or the other of the molecule increases, the effect will be reflected in the isomer ratio obtained. In the case of the cholestanones, this steric approach control will always act in the opposite direction to the product development control. For example, with 4-, 6- or 11-ketocholestanes, approach from the top-side of the molecule to give the equatorial alcohol is hindered by the axial methyl groups and as a result steric approach control favoring a bottom-side attack to yield the axial epimer is expected. The results of the $LiAlH_4$ reduction of compounds in these series are given in Table I and it is seen that the results predicted by the above concepts are obtained. The reduction of a 12-keto compound has not been examined in a quantitative manner but from the fact that at least 51% of the 12α-axial isomer was isolated, it would appear that the composition is in agreement with that expected by evaluating the steric factors present, *i.e.*, on the bottom-side, the axial hydrogens on C_9, C_{14} and C_{17} must be considered and on the top-side, only the axial methyl group on the adjacent C_{13}. To date, the reduction with $LiAlH_4$ of a 1-ketocholestane has not been reported but it would be predicted that the amount of the 1α-axial alcohol formed would be greater than that found in the equilibrium mixture. This same type of evaluation also can be employed for $NaBH_4$ reductions, but since this reagent is a more specially demanding reagent[1] the steric approach control will be expected to be of greater importance.

It is of interest to compare the results obtained in a $LiAlH_4$ reduction with those obtained by catalytic hydrogenation of a ketone in acid solution. The results obtained in this latter reaction by other workers are given in Table I. These data show that when the carbonyl group is at C_4, C_6, C_7 or C_{11} both reduction methods yield the same isomer ratio. When the carbonyl is at C_2, C_3 or C_{12} quite different isomer compositions are obtained and with these ketones the preparation of a specific isomer can be facilitated by the proper choice of the reducing agent. Barton[12] has given the generalization that "catalytic hydrogenation of both hindered and unhindered ketones in strongly acid media (rapid hydrogenation) affords the axial alcohol." The results in Table I show that this is an oversimplification, for the C_1- and C_{12}-ketones give exclusively the equatorial alcohol and the C_7 ketones yield mainly the equatorial alcohol.

TABLE I

REDUCTION OF CHOLESTANONES[22]

Position of carbonyl	Product composition, % — $LiAlH_4$ α	$LiAlH_4$ β	Catalytic hydrogenation α	Catalytic hydrogenation β
1	..	....	0	100[15]
2	37	52	0	100[13]
3	10	90[3,5,6]	75	25[16,17]
4	7	90[11]	0	100[18]
6	6	94[7]	0	100[7]
7	55	45	40	60[9,13,20]
11	0	100[4,8]	0	100[8]
12	50	...[19]	0	100[21]

(15) P. Striebel and Ch. Tamm, *Helv. Chim. Acta*, **37**, 1094 (1954).
(16) G. Vavon and B. Jakubowicz, *Bull. soc. chim. France*, **53**, 581 (1933).
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(19) W. Buser, *Helv. Chim. Acta*, **30**, 1378 (1947).
(20) W. G. Dauben, D. F. Dickel, O. Jeger and V. Prelog, *ibid.*, **36**, 325 (1953).
(21) A. Lardon and T. Reichstein, *ibid.*, **26**, 586 (1943).
(22) R. B. Wagner, R. F. Forker and P. F. Spitzer, Jr., THIS JOURNAL, **73**, 2494 (1951).

Experimental

Cholestan-2-one.—The ketone was prepared from cholestan-3β-ol following the procedure of Ruzicka, Plattner and Furrer,[18] m.p. 129–130° (lit.[18] 130–131°).

Reduction of Cholestan-2-one.—(a) $LiAlH_4$: A solution of 0.500 g. (1.29 mmoles) of the ketone in 40 ml. of dry ether was added to a solution of 0.260 g. of $LiAlH_4$ (6.85 mmoles) in 40 ml. of dry ether. The solution was stirred for 1 hour at room temperatures, cooled in ice and decomposed with 30 ml. of 20% H_2SO_4. The ether phase was separated, washed with water, $NaHCO_3$ solution and dried. The solvent was evaporated under reduced pressure at 70°, yield 0.495 g. (99%).

The residue was dissolved in 50 ml. of hexane and chromatographed on 20 g. of silica gel. Elution with 5% ether–95% hexane yielded 226 mg. of β-ol (m.p. 153–155°), 10% ether–90% hexane yielded 140 mg. of a mixture of epimers and 20% ether–80% hexane yielded 120 mg. of α-ol (m.p. 177–179°). Rechromatography of the center fraction yielded 33 mg. of β-ol (m.p. 153–155°), 39 mg. of α + β-ols and 58 mg. of α-ol (m.p. 177–179°). The total recovery was 259 mg. (52%) of β-ol and 178 mg. (37%) of α-ol. Recrystallization of the β-ol from methanol gave material melting 153.3–155.1° (lit.[13] 154–155°) and recrystallization of the α-ol from ether gave material melting 177.1–178.9° (lit.[13] 178–180°).

(b) $NaBH_4$: A solution of 0.2 g. (5.3 mmoles) of $NaBH_4$, prepared by first dissolving the hydride in 5 ml. of H_2O and then diluting with 20 ml. of MeOH, was added over a period of 20 minutes to a refluxing solution of 500 mg. of the ketone in 20 ml. of MeOH and 5 ml. of H_2O. After heating for 3 hours, the reaction mixture was decomposed with 3 ml. of concd. HCl and then heated for an additional hour. The mixture was cooled, diluted with H_2O and processed as above; yield 488 mg. The crude product was chromatographed as before. The original hexane eluate gave 22 mg. of unreacted ketone and the yield of pure β-ol was 342 mg. (71%), m.p. 153–155°, and of pure α-ol was 76 mg. (16%), m.p. 177–179°.

Cholestan-3β-ol-7-one.—In our hands, the preparation of this compound by direct hydrogenation of 7-ketocholesteryl acetate followed by alkaline hydrolysis, as described by Buser,[19] was found to yield material containing some unsaturated ketone (ϵ^{235} 3000). The following indirect method was employed in the present work.

7-Ketocholesteryl acetate (15.0 g., 0.034 mole), prepared in 65% yield from cholesteryl acetate by the procedure of Oppenauer and Oberrauch[23] using *t*-butyl chromate, was dissolved in 200 ml. of ethyl acetate and hydrogenated using 1.0 g. of PtO_2. After the uptake of hydrogen had ceased (1.2 moles), the catalyst was filtered and the solvent evaporated. The crude product had a m.p. of 134–140°.

The crude material was then dissolved in 200 ml. of acetic acid and hydrogenated using 1.0 g. of PtO_2 until no further uptake of hydrogen occurred. The catalyst was filtered, the solvent evaporated and the residue recrystallized from MeOH to yield 7-hydroxycholestanyl acetate, m.p. 95–105°, yield 9.20 g. (61%). The molar extinction at 235 mμ was 30.

The above solid (9.20 g., 0.021 mole) was dissolved in 125 ml. of acetic acid and oxidized with a solution of CrO_3 (2.28 g., 0.029 mole) in 4.0 ml. of H_2O and 150 ml. of acetic acid. The reaction was allowed to proceed for 16 hours at 20°. The solvents were removed under reduced pressure at 20–30°. The residue was diluted with H_2O, extracted 3 times with ether and the ethereal extracts washed with dilute H_2SO_4, $NaHCO_3$ solution and H_2O and then dried. After evaporation of the solvent, the material was recrystallized to yield 7-ketocholestanyl acetate, m.p. 146.3–147.4° (lit.[24] 148–149°), yield 8.08 g. The over-all yield based on 7-ketocholesteryl acetate was 54%.

The acetate (4.55 g., 0.01 mole) was saponified by refluxing for one hour with 125 ml. of EtOH containing 6.0 g. of KOH. The cooled reaction mixture was diluted with H_2O, filtered and recrystallized from aqueous EtOH to give 7-ketocholestanol, m.p. 156.3–158° (lit. 156–157°,[25] 164–165°,[24] yield 3.89 g. (94%).

Reduction of Cholestan-3β-ol-7-one Acetate with $LiAlH_4$.

(a) **Diethyl Ether as Solvent.**—A solution of 2.24 g. (5.03 mmoles) of the acetate in 50 ml. of dry ether was reduced in the usual manner with 100 ml. of an ethereal solution of $LiAlH_4$ containing 0.056 mmole per ml. The yield of epimeric 7-hydroxy compounds was 2.05 g. (100%), $[\alpha]^{25}D$ +28.1° (α + 0.285, *c* 1.012). The infrared spectrum of this material showed no band in the carbonyl region.

A sample (1.080 g.) of the crude mixture was absorbed on 30 g. of Woelm neutral alumina. Elution with benzene gave 3 mg. of non-crystalline material. Elution with redistilled ether gave 1.01 g. (93.5%) of the isomeric 7-hydroxy compounds, $[\alpha]^{26}D$ +26.9°, (α +0.286, *c* 1.062). This rotation corresponds to a mixture of 57% α and 43% β.[26]

(b) **Tetrahydrofuran as Solvent.**—A mixture of 0.500 g. (1.13 mmoles) of the acetate and 0.171 g. (4.55 mmoles) of $LiAlH_4$ in 60 ml. of tetrahydrofuran was heated under reflux for 1 hour and processed as above. A quantitative yield of crude product was obtained. Chromatography yielded 2 mg. of material with hexane. The mixture of epimeric 7-hydroxy compounds showed an $[\alpha]^{25}D$ +23.2° (α +0.252, *c* 1.086) which corresponds to 65% α and 35% β.

Reduction of Cholestan-3β-ol-7-one with $NaBH_4$.—To a solution of 0.822 g. (2.04 mmoles) of the compound in 40 ml. of MeOH and 10 ml. of ether was added a solution of 0.679 g. (18.4 mmoles) of $NaBH_4$ in 5 ml. of H_2O and 25 ml. of MeOH. The reaction mixture was stirred at room temperature for 22 hours and then heated under reflux for 2 hours. After cooling, ether was added and the solution acidified with 5% HCl until acid to congo red. The layers were separated and the aqueous layer extracted 3 times with ether. The combined etheral solution was washed with 5% HCl, H_2O and dried. Evaporation of the solvent gave 0.792 g. (96%) of crude product. Chromatography of 0.700 g. as described above yielded only 2 mg. of material with benzene. The mixture of isomeric 7-hydroxy compound had $[\alpha]^{22}D$ +19.8° (α +0.252, *c* 1.282) which corresponds to 73% α and 27% β.

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(25) A. Windaus and E. Kirchner, *Ber.*, **53**, 614 (120).

(26) The $[\alpha]D$ used for the pure epimers was +51.0° for 7β and +8.5° for 7α.

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[CONTRIBUTION FROM THE DEPARTMENT OF MEDICINE, WESTERN RESERVE UNIVERSITY, AND THE LAKESIDE HOSPITAL]

The Preparation of 16-Oxygenated Etianates and their Relation to Gitoxigenin[1]

BY H. HIRSCHMANN AND FRIEDA B. HIRSCHMANN

RECEIVED FEBRUARY 13, 1956

The preparation and reduction of both 17-epimers of methyl 3β-acetoxy-16-oxoetianate is described. The principal reduction product of the 17β-isomer is a *cis*-hydroxy ester which is shown to be methyl 3β-acetoxy-16β-hydroxyetianate. It gave a diacetate identical with a degradation product of gitoxigenin. The results strongly indicate that gitoxigenin is 16β-hydroxydigitoxigenin.

Gitoxigenin (I) has been obtained as the steroid moiety from several cardiac glucosides. It has been intensively studied in many laboratories, notably by Jacobs and his collaborators[2] and by Meyer,[3] who found it to differ from digitoxigenin by an additional hydroxyl group at C-16. The sole structural features not yet fully established concern configura-

(1) This investigation was supported by grant C-1679 of the National Institutes of Health, U. S. Public Health Service.

(2) (a) W. A. Jacobs and E. L. Gustus, *J. Biol. Chem.*, **79**, 553 (1928); (b) **82**, 403 (1929); (c) **86**, 199 (1930); (d) **88**, 531 (1930); (e) W. A. Jacobs and R. C. Elderfield, *ibid.*, **108**, 497 (1935).

(3) (a) K. Meyer, *Helv. Chim. Acta*, **29**, 718 (1946); (b) **29**, 1580 (1946); (c) **29**, 1908 (1946).