[CONTRIBUTION FROM RESEARCH LABORATORIES, CHEMICAL DIVISION, MERCK & CO., INC.]

The Configuration of Allosteroid 2,3-Diols. Stereochemical Restrictions to the Introduction of Unsaturation *via* Disulfonic Esters[1]

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The dependence on configuration of *allo*steroid, 2,3-diol disulfonic esters in the production of Δ^2-olefins with sodium iodide in acetone at 100° has been demonstrated and employed as an accurate diagnostic in the assignment of configuration. A new route to hecogenone from Δ^2-22a,5α-spirostene-12-one is described and a novel method for the reversible masking of ethenoid systems is proposed.

The conversion of a steroid glycol to its derived olefin through treatment of a disulfonic acid ester derivative with sodium iodide in acetone was first described in the case of the transformation of manogenin dimesylate (Ia) to Δ^2-22a,5α-spirostene-12-one (II).[1a,2] In this earlier work there was reported, among others, the conversion of manogenin to the α-oxide III and thence by successive reduction and oxidation to hecogenone (IV); the transformation of the latter to the Δ^2-olefin was similarly indicated. It has now been found possible to convert the olefin II to hecogenone by an alternate route involving the halohydrin formed by the reaction of chromyl chloride. In this connection Cristol and Eilar[3] in an original work demonstrated the utility of chromyl chloride in the formation from olefins of chlorohydrins which are positionally isomeric with those obtained by the action of hypochlorous acid. The results of the present work are in unique accord with these observations. Thus, Δ^2-22a,5α-spirostene-12-one (II) was converted by chromyl chloride to an intermediate chlorohydrin V and the latter on oxidation followed by reductive dechlorination provided hecogenone (IV) in good over-all yield. Treatment of the Δ^2-olefin II, on the other hand, with hypobromous acid produced a bromohydrin VII that was transformed by successive oxidation and debromination to 22a,5α-spirostane-2,12-dione (X). It is clear, therefore, that chromyl chloride produces the 2-halo-3-hydroxy isomer V in contrast to hypobromous acid, which gives the 2-hydroxy-3-halo derivative VII. These results, coupled with the known stereochemical outcome of the addition of halogens to Δ^2-allosteroid olefins[4] and the established direction of hydrolytic fission of 2α,3α-oxides,[5] are all in the best conformity with the transitory formation in the addition process of an α-onium ion with completing β-attack at C_2.

The configuration of the bromohydrin VII was confirmed by its smooth conversion to 2β,3β-oxido-22a,5α-spirostane-12-one (XI) by means of alkaline alumina according to the method of Ott and Reichstein.[6] The oxide XI on reduction with lithium aluminum hydride followed by oxidation with chromic acid produced the same 22a,5α-spirostane-2,12-dione (X) as that obtained by the alternate route from the bromohydrin VII (*cf.* above). Hydrolysis of the β-oxide XI with dilute acid yielded the 2β,3α-diol IX, identical with that afforded on similar treatment of the α-oxide III. In this connection Fürst and Plattner had originally effected similar directional transformations on the 2α,3α- and 2β,3β-oxidocholestanes.[5,7]

Hydroxylation of the Δ^2-olefin II with osmium tetroxide afforded the *cis*-α-diol (VI)[1] which readily gave an acetonide derivative VIb. On the other hand, treatment of the bromohydrin acetate VIIa with moist silver acetate[8] followed by hydrolysis afforded in excellent yield the *cis*-β-diol VIII. The latter, like the *cis*-α-diol VI, readily gave an acetonide derivative.

It was reported earlier[1b] that the ability to undergo acetonide formation distinguishes the *cis*-series (VI and VIII) from the *trans*-series (I and IX). In addition, differentiation within each series is made possible by the unique circumstance that the dimesylate derivatives Ia (2α,3β) and VIa (2α,3α) are smoothly converted to Δ^2-olefin II under conditions which leave VIII (2β,3β) and IX (2β,3α) essentially unchanged. These findings make possible, therefore, a simple and accurate configurational assignment to all four possible *allo*steroid 2,3-diols. By this analysis it becomes obvious that manogenin, the natural occurring diol, possesses the 2α,3β-configuration.[9]

The exceptional failure of the 2β,3β- and the 2β,3α-diol dimesylate derivatives VIIIa and IXa to undergo elimination with sodium iodide in acetone at 100° is of some interest in the light of experience with the dibromocholestanes. From a study of the rate of elimination of bromine from the dibromocholestanes, Barton and his associates[4] con-

(1) (a) Presented in part at the American Chemical Society Meeting-in-Miniature, Newark, N. J., January 28, 1952; (b) N. L. Wendler and H. L. Slates, *Chemistry & Industry*, 167 (1955).

(2) (a) N. L. Wendler, H. L. Slates and M. Tishler, THIS JOURNAL, **74**, 4894 (1952); (b) N. L. Wendler and H. L. Slates, U. S. Patents 2,695,287 and 2,695,288.

(3) S. J. Cristol and K. R. Eilar, THIS JOURNAL, **72**, 4353 (1950).

(4) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951); G. H. Alt and D. H. R. Barton, *ibid.*, 4284 (1954).

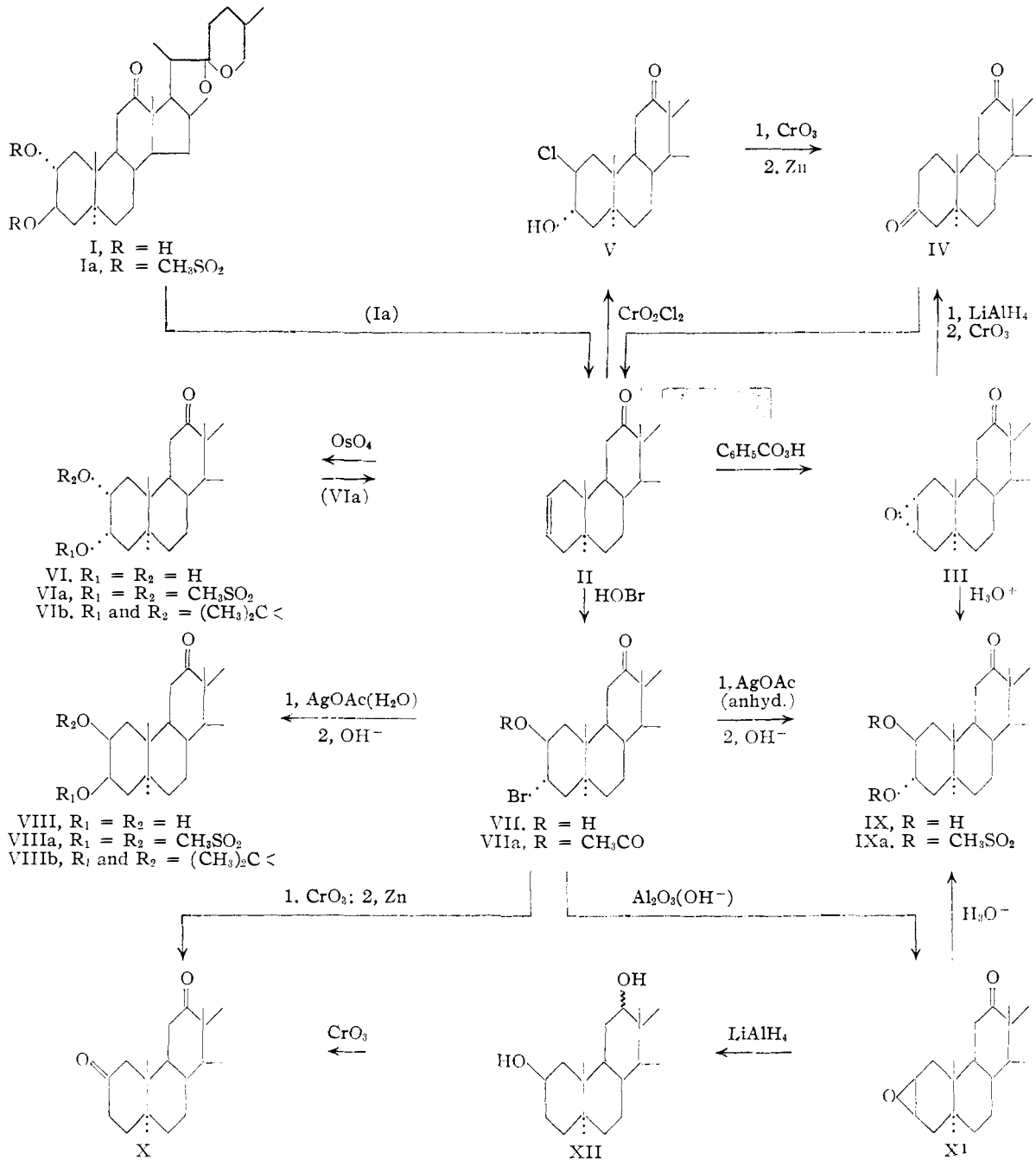
(5) A. Fürst and Pl. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949); Abs. Papers, 12th Internat. Cong. Pure Appl. Chem., New York, 1951, p. 409.

(6) G. H. Ott and T. Reichstein, *Helv. Chim. Acta*, **26**, 1799 (1943).

(7) J. Pataki, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 5375 (1951), have recently hydrolyzed the 2α,3α oxide in the gitogenin series to the corresponding 2β,3α-diol. These authors had prepared three of the four possible 2,3-diol isomers in the gitogenin series. Since the *cis*-β-diol had not been synthesized nor its ability to form an acetonide ascertained, configurational assignment to the natural genin was not completely unequivocal.

(8) (a) Method of S. Winstein, *et al.*, see for example, S. Winstein and R. E. Buckles, *ibid.*, **64**, 2787 (1942); (b) recently C. Djerassi, L. B. High, T. T. Grossnickle, R. Ehrlich, J. A. Moore and R. B. Scott, *Chemistry & Industry*, 474 (1955), have reported similar findings bearing on the structure of gitogenin; see also D. L. Kloss, L. F. Fieser and M. Fieser, THIS JOURNAL, **77**, 3829 (1955).

(9) J. Herran, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 5531 (1954), have recently deduced the same configuration for manogenin by another approach.



cluded, on the basis of the mechanism of Winstein, Pressman and Young,[10] that the 2β,3α-isomer should be most prone to elimination with iodide ion. Since the same arguments should apply equally to dehalogenation with zinc, wherein the metal instead of iodide ion exercises donor attack on halogen,[10] it was significant to observe that neither dimesylate Ia nor VIa suffered elimination with zinc in refluxing ethanol. It was thus suggested that the elimination reaction of the dimesylate derivatives with sodium iodide probably proceeds by way of initial displacement by iodide ion at one or both centers prior to the elimination process.[11] The reason for the failure of the 2β,3β- and 2β,3α-isomers to undergo this change is not clear.

In conclusion, it may be worth emphasizing the ease of reversibility, for example, of the *cis*-α-diol and the Δ²-olefin (VI ⇄ II); since *cis*-diols are convertible to base-stable acetonides or acid-resistant ester derivatives, there is potentially provided a method for masking double bonds during operations where such centers of unsaturation would otherwise be prone to attack.

(10) S. Winstein, D. Pressman and W. G. Young, THIS JOURNAL, **61**, 1645 (1939); see also J. Hine and W. H. Brader, Jr., *ibid.*, **77**, 361 (1955).

(11) This path has been shown to be the probable one in the sugar series; *cf.* N. K. Matheson and S. J. Angyal, *J. Chem. Soc.*, 1133 (1952).

Experimental[12]

Δ^2-22a,5α-spirostene-12-one (II).—Crude manogenin, containing Δ^9-dehydromanogenin and gitogenin,[13] 280 g., was dissolved in 2.5 l. of dry pyridine, cooled to 0°, treated with 300 g. of methanesulfonyl chloride at 0°, and allowed to stand at 0–5° for 24 hours. The reaction mixture was poured onto ice-water with vigorous stirring and the product isolated by filtration. Crystallization from acetone gave 305 g. of mixed dimesylate derivatives.

To a solution of 40 g. of the above mixture of mesylate derivatives in 2 l. of dry acetone was added 100 g. of sodium iodide and the reaction mixture was heated at 110° for 24 hours in a glass lined autoclave. The sodium methanesulfonate formed from the reaction was filtered off and washed with ether and chloroform. The combined organic filtrates were concentrated *in vacuo*, diluted with chloroform and ether and washed successively with 5% aqueous sodium thiosulfate, water and dried over magnesium sulfate. The residue, after removal of the solvents *in vacuo*, was crystallized from acetone to afford 19 g. of a mixture of Δ^2-olefins melting at *ca.* 180–190°.

The above olefin mixture, 19 g., was dissolved in 1 liter of refluxing *n*-butyl alcohol and treated with 48 g. of sodium over a period of 1.5 hours. After all the sodium had reacted, the butanol was removed *in vacuo* and the residue treated with water. The product was isolated by filtration, washed free of base with water, and dried *in vacuo*. The yield was 19 g.

The above product, 17 g., was dissolved in 800 ml. of acetic acid and oxidized overnight at room temperature with 2.7 g. of chromic anhydride. Methanol, *ca.* 200 ml., was added and the reaction mixture was concentrated *in vacuo* to about 200 ml. and diluted with 600 ml. of water. The crude product was filtered off, washed with cold dater and crystallized from acetone to yield 15 g. of a mixture of Δ^2-22a,5α-spirostene-12-one and Δ^2-22a,5α-spirostene.

The above mixture of Δ^2-olefins, 13.5 g., was separated chromatographically as already described[2] to afford 9.6 g. of Δ^2-22a,5α-spirostene-12-one, m.p. 197–199°.

Preparation of Hecogenone (IV) *via* the Chlorohydrin V.—In a reaction vessel protected from moisture, a solution of 2.0 g. of Δ^2-22a,5α-spirostene-12-one (II) in 30 ml. of chloroform at 0° was treated under vigorous stirring with a solution of 1.52 g. of chromyl chloride in 10 ml. of chloroform.[14] The reaction mixture was stirred at 0° for 2.5 hours and then decomposed with aqueous saturated sodium bisulfite solution. The organic layer was separated and the aqueous layer extracted three times with chloroform. The combined organic extracts were washed with water, saturated sodium chloride solution and dried over sodium sulfate. After removal of the solvent *in vacuo*, the crude product was dissolved in 90 ml. of acetic acid and oxidized overnight at room temperature with 300 mg. of chromic anhydride. The excess oxidizing agent was destroyed with methanol, the solution was concentrated to a small volume *in vacuo* and diluted with water. The product was extracted with chloroform and the chloroform solution was washed with water, saturated sodium chloride solution, and dried over sodium sulfate. After removal of the solvent *in vacuo*, the crude chloroketone was dissolved in 30 ml. of refluxing acetic acid and treated under reflux with 5.0 g. of zinc dust. The reaction mixture was filtered, concentrated *in vacuo* and diluted with water. The product was extracted with chloroform and the chloroform solution was washed with 5% sodium bicarbonate solution, water and dried over sodium sulfate. Removal of the solvent *in vacuo* and crystallization of the residue twice from ether afforded 450 mg. of hecogenone (IV), m.p. 236–239°, no depression on admixture with an authentic sample prepared by another route.[2]

2α,3α-Dihydroxy-22a,5α-spirostane-12-one (VI).—A solution of 2.0 g. of Δ^2-22a,5α-spirostene-12-one (II) in a mixture of 30 ml. of pyridine and 50 ml. of benzene was treated with 1.3 g. of osmium tetroxide and allowed to stand at room temperature for 5 days. The black reaction mixture was concentrated to dryness *in vacuo* and the residue was refluxed with a mixture of 90 ml. of water, 25 ml. of benzene, 50 ml. of methanol, 9.2 g. of sodium sulfate and 9.2 g. of sodium sulfite. The reaction mixture was extracted with chloroform and the chloroform extracts washed with water, dried over magnesium sulfate and concentrated *in vacuo*. The residue was crystallized from chloroform–hexane to afford VI as small needles, m.p. 242–245°. For analysis a 400-mg. sample was chromatographed on 20 g. of acid-washed alumina and eluted with benzene–chloroform and chloroform–ethyl acetate mixtures. Fractions corresponding to 2% ethyl acetate–chloroform through ethyl acetate afforded on crystallization from acetone 275 mg. of VI, m.p. 253–256°, $[\alpha]^{chf}D$ +16.3°. An additional 80 mg., m.p. 252–255°, was obtained as a second crop.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.52; H, 9.65.

The acetonide (VIb) was prepared from the diol by the method of Salamon and Reichstein[15] and crystallized from acetone, m.p. 270–273°; no –OH bands in the infrared spectra.

Anal. Calcd. for $C_{30}H_{46}O_5$: C, 74.04; H, 9.53. Found: C, 73.94; H, 9.07.

The dimesylate (VIa) was prepared as previously described[2] and crystallized from acetone, m.p. 240–241° dec.

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 VIa with sodium iodide in acetone at 100° for 18 hours afforded, in yield of 90%, Δ^2-22a,5α-spirostene-12-one, m.p. and mixed m.p. with an authentic specimen was 198–200°.

2β-Hydroxy-3α-bromo-22a,5α-spirostane-12-one (VII).—To a stirred solution of 3.0 g. of Δ^2-22a,5α-spirostene-12-one (II) in 50 ml. of dioxane was added a solution of 1.47 g. of N-bromosuccinimide in 14 ml. of water and 8.4 ml. of 1 *M* perchloric acid. The reaction mixture was stirred at room temperature for 2.5 hours, then concentrated *in vacuo* and diluted with water. The product was isolated by filtration, washed with cold water, and crystallized from acetone–hexane to give 2.4 g. of VII with m.p. 215–219° dec. Recrystallization from the above solvents afforded 2β-hydroxy-3α-bromo-22a,5α-spirostane-12-one, m.p. 219–221° dec., $[\alpha]^{chf}D$ +132°.

Anal. Calcd. for $C_{27}H_{41}O_4Br$: C, 63.65; H, 8.11; Br, 15.69. Found: C, 63.93; H, 8.10; Br, 15.59.

Acetylation of VII with acetic anhydride and pyridine at room temperature gave 2β-acetoxy-3α-bromo-22a,5α-spirostane-12-one (VIIa), crystallized from acetone, m.p. 229–231°, $[\alpha]^{chf}D$ +123°.

Anal. Calcd. for $C_{29}H_{43}O_5Br$: C, 63.16; H, 7.86; Br, 14.49. Found: C, 63.27; H, 7.87; Br, 14.52.

2β,3β-Dihydroxy-22a,5α-spirostane-12-one (VIII).—A mixture of 800 mg. of the bromohydrin acetate VIIa, 40 ml. of acetic acid, 16 microdrops of water and 256 mg. of silver acetate were heated at 100–110° with stirring for 6 hours. The reaction mixture was filtered and the filtrate concentrated to dryness *in vacuo*. The residue was saponified by refluxing for 1 hour with 110 ml. of 10% potassium hydroxide in methanol. The solution was filtered through Super-cel, concentrated *in vacuo* to a small volume and diluted with water. The product was filtered off, dissolved in chloroform, and the chloroform solution was washed with water, saturated sodium chloride solution and finally dried over magnesium sulfate. The residue, after removal of the solvent, crystallized readily from acetone to yield 350 mg. of VIII, m.p. 267–270°. An additional 110 mg. of somewhat lower melting point was obtained as a second crop. The analytical sample was recrystallized twice from acetone, m.p. 267–270°, $[\alpha]^{chf}D$ +23.6°.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.64; H, 9.21.

The acetonide (VIIIb) was prepared in the same manner as VIb and crystallized for analysis from acetone, m.p. 275–278°; no –OH in the infrared.

Anal. Calcd. for $C_{30}H_{46}O_5$: C, 74.04; H, 9.53. Found: C, 74.12; H, 9.07.

The dimesylate (VIIIa) was prepared as previously described[2] and crystallized from chloroform–hexane m.p. 250–252° dec.

(12) All melting points are corrected and were taken in open capillaries unless otherwise specified.

(13) The present procedure represents an improvement in the process for preparing pure II from the crude genin mixture. The original but more tedious process was described earlier, *cf.* reference 2.

(14) Method of Cristol and Eilar, see reference 3.

(15) I. Salamon and T. Reichstein, *Helv. Chim. Acta*, **30**, 1929 (1947).

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.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA]

The Stereochemistry of the Hydride Reduction of Some Steroidal Ketones

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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).