[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORPORATION]

D-Homo Rearrangement of 11-Oxygenated 17α-Hydroxy-20-ketosteroids

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Reaction of 11-oxygenated 17α-hydroxy-20-ketopregnanes with refluxing acetic anhydride was found to produce D-homo rearrangement products rather than the expected 17α-acetoxy-20-ketosteroids.

Two methods are claimed to be satisfactory for the preparation of 17α-acetates from a 17α-hydroxy-20-ketone: reaction of the ketol with an acylating agent and an acid catalyst at room temperature,[1,2] or with refluxing acetic anhydride alone.[2]

By this last procedure 3α-acetoxy-17α-hydroxypregnane-11,20-dione (II) was reported to be converted into its diacetate XIV in good yield.[2] We attempted to prepare the same compound XIV from 3α,17α-dihydroxypregnan-11,20-dione (I). The use of acetic anhydride, either redistilled or not, gave no isolable XIV but a different compound. This was identified as a D-homo rearrangement product, since it was identical with the compound obtained from I upon reaction with boron trifluoride in acetic acid–acetic anhydride. With the 3-acetate II and refluxing acetic anhydride, however, we did obtain the expected 3,17-diacetate but in lower yield than the previous workers. The diacetate also was obtained from II if the acetic anhydride contained acetic acid.

Our studies were then extended to other 11-oxygenated 17α-hydroxy-20-ketosteroids. Both 3α,-11β,17α-trihydroxypregnan-20-one 11-acetate (III) and 3α,11α,17α-trihydroxypregnan-20-one 3,11-diacetate (IV) were converted to D-homo rearrangement products VI and X identical with those obtained by reaction with boron trifluoride. With all three starting materials, acetic anhydride gave at least as good yields as boron trifluoride.

The rearrangement products were all submitted to lithium aluminum hydride and sodium–alcohol reductions. Reaction of X with either reducing agent gave the same tetrol XIII. Reduction of IX and VI with lithium aluminum hydride gave two different tetrols (which we formulate as XI and XII) while reduction of IX with sodium gave the same tetrol XIII which had been obtained from X. These results suggest that the D-ring structures of IX and X are similar, while those of IX and VI are different. Unfortunately the yields in most of the reduction experiments were too low to permit positive conclusions to be drawn. However, further evidence was obtained from a study of the Zimmerman reaction on VI, IX and X, and by a comparison of molecular rotation differences.

The Zimmerman test for active methylene groups[3] was strongly positive with compound VI (derived from III) and essentially negative with IX (from I) and X (from IV),[4] indicating that IX and X have the 17a keto structures. In addition, the molecular rotation changes (ΔM_D) for the transformations II → IX and IV → X are in good agreement with the values reported by Fukushima[3] for the conversion of a 17α-hydroxy-20-ketosteroid to a 17α-hydroxy-17a-keto-D-homo-steroid, and the molecular rotation change for the transformations XV → VIII and III → VII are also in fair agreement with the expected value. However, the ΔM_D for the change XV → VI is far from the published figure (Table I).

TABLE I

MOLECULAR ROTATION DIFFERENCES

	$[\alpha]_D$	M_D	ΔM_D
3α,17α-Dihydroxypregnane-11,20-dione 3-acetate (II)	+50.3	+196	+276
3α,17α-Diacetoxy-17β-methyl-D-homoetiocholane-11,17a-dione (IX)	+109.4	+472	
ΔM_D (17α-OH,20-C=O → 17-OAc,17a-C=O) ~ + 290			
3α,11α,17α-Trihydroxypregnan-20-one 3,11-diacetate (IV)	− 7.7	− 33	+128
3α,11α,17α-Triacetoxy-17β-methyl-D-homoetiocholan-17a-one (X)	+19.9	+ 95	
ΔM_D (17α-OH, 20-C=O → 17-OH,17a-C=O) ~ + 135			
3α,11β,17α-Trihydroxypregnane-20-one 11-acetate (III)	+35.6	+140	− 15
11β-Acetoxy-3α,17aα-dihydroxy-17aβ-methyl-D-homoetiocholan-17-one (VII)	+32.5	+125	
3α,11β,17α-Trihydroxypregnane-20-one 3,11-diacetate (XV)	+62.6	+271	− 35
3α,11β-Diacetoxy-17aα-hydroxy-17aβ-methyl-D-homoetiocholan-17-one (VIII)	+54.2	+235	
ΔM_D (17α-OH,20-C=O → 17a-OH,17-C=O) ~ −70			
3α,11β-17α-Trihydroxypregnane-20-one 3,11-diacetate (XV)	+62.6	+271	−271
3α,11β,17aα-Triacetoxypregnane-17aβ-methyl-D-homoetiocholan-17-one (VI)	0.0	0	
ΔM_D (17α-OH,20-C=O → 17a-OAc,17-C=O) ~ + 40			

No simple explanation is immediately apparent to explain the fact that I, III and IV give D-homo products, and II the normal diacetate.[5] Pending

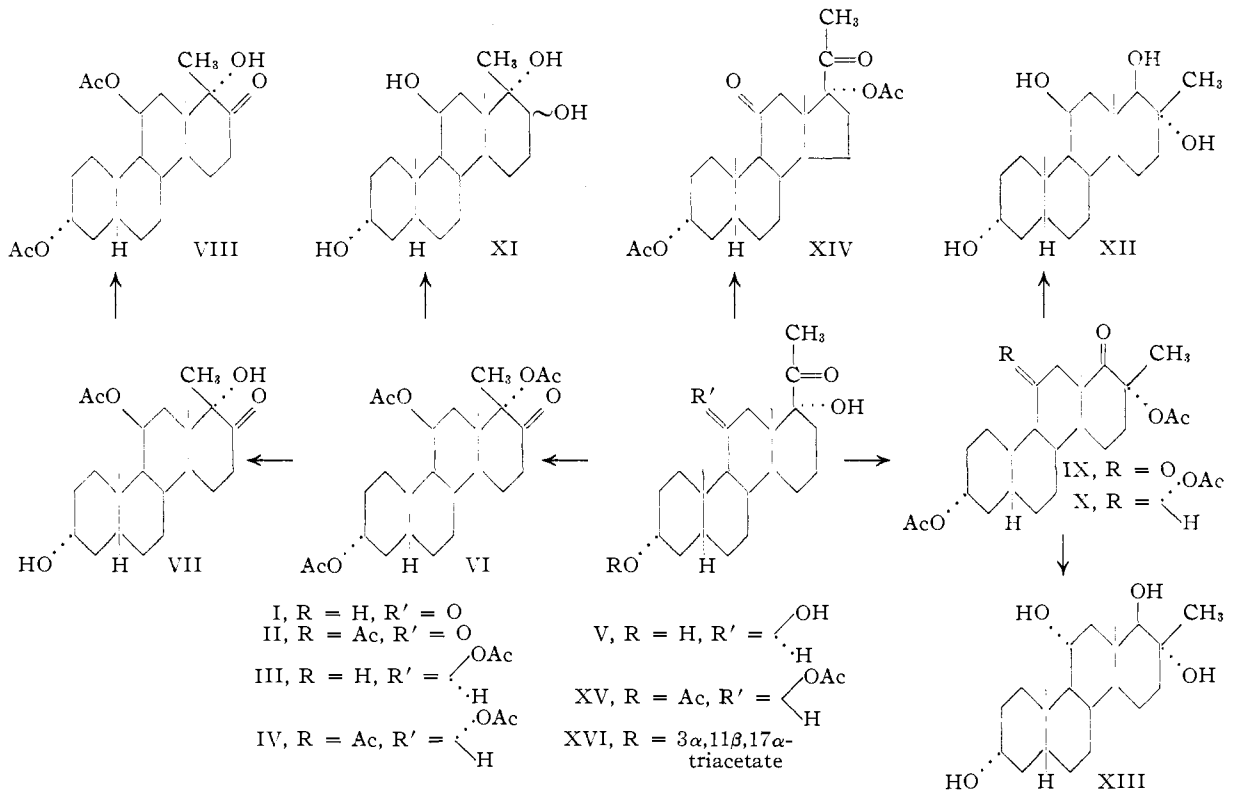
(1) R. Turner, THIS JOURNAL, **75**, 3489 (1953).

(2) Huang-Minlon, E. Wilson, N. Wendler and M. Tishler, *ibid.*, **74**, 5394 (1952).

(3) *Cf.* D. Fukushima, S. Dobriner, M. Heffler, T. Kritchevsky, F. Herling and G. Roberts, *ibid.*, **77**, 6585 (1955).

(4) The 12-methylene group of IX adjacent to the 11-ketone is apparently sufficiently hindered so that only a faint color is obtained in the Zimmerman reaction. The same faint color is obtained with I.

(5) It is, of course, quite possible that *mixtures* of D-homo and normal products are obtained which we have made no particular attempt to separate. However, one would presume that the fastest reaction of I with hot acetic anhydride would be formation of the 3-acetate II, and that therefore I and II should give the same isolable product.



further investigation, it would seem that the use of refluxing acetic anhydride to prepare 17α-acetates is not as satisfactory as room temperature acylations with an acid catalyst.

Experimental[6]

3α,11β,17aα-Triacetoxy-17aβ-methyl-D-homoetiocholan-17-one (VI). A.—A solution of 1.0 g. of 3α,11β,17α-trihydroxypregnan-20-one-11-acetate (III) in 35 ml. of acetic acid, 2 ml. of acetic anhydride and 2 ml. of boron trifluoride–ether complex was allowed to stand overnight at 25°. The mixture was poured into water, the solid removed by filtration and triturated with ether to give 0.08 g. of VI, m.p. 235–255°. One crystallization from methanol raised the m.p. to 258–262°.

B.—A solution of 10.0 g. of 3α,11β,17α-trihydroxypregnan-20-one in 100 ml. of C.P. acetic anhydride was refluxed for 12 hours. The solvent was removed under reduced pressure, and the crystalline residue sludged with 75 ml. of ether to yield 4.96 g. of VI, m.p. 260–263°. Two crystallizations from methanol raised the m.p. to 267–268°, $[\alpha]_D$ 0.0°.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.82; H, 8.62.

The use of acetic anhydride which had been freshly distilled through a glass-packed column gave the same compound, but in somewhat lower yield (0.2 g. from 1 g.). The infrared spectra of the two compounds prepared in (A) and (B) were identical, and did not match the spectrum of 3α,11β,17α-triacetoxypregnan-20-one. Both also gave strong Zimmerman tests.

11β-Acetoxy-3α,17aα-dihydroxy-17aβ-methyl-D-homoetiocholan-17-one (VII).—A mixture of 1.0 g. of VI, 0.5 g. of potassium carbonate, 40 ml. of C.P. methanol and 4 ml. of water was refluxed for 2.5 hours. The excess carbonate was then neutralized with acetic acid, the methanol removed under reduced pressure, and the residue diluted with water to precipitate 0.79 g. of crude material, m.p. 131–143°. The analytical sample, crystallized twice from ether–hexane, melted at 173–174°, $[\alpha]_D$ +32.5°.

(6) All m.p.'s are corrected. All rotations were taken in a one dm. tube in chloroform at a concentration of *ca.* 1% and at 25°. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.47; H, 9.31.

3α,11β-Diacetoxy-17aα-hydroxy-17aβ-methyl-D-homoetiocholan-17-one (VIII).—A solution of 130 mg. of VII in 4 ml. of pyridine and 1 ml. of acetic anhydride was allowed to stand 17 hours at 25°. The solution was then poured into ice and water containing excess hydrochloric acid to give 120 mg. of solid. Crystallization from ether–pentane gave 70 mg. of VIII, m.p. 197–201°, $[\alpha]_D$ +54.2°.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.85; H, 8.54.

3α,17α-Diacetoxy-17β-methyl-D-homoetiocholane-11,17a-dione (IX). A.—A solution of 1.0 g. of 3α,17α-dihydroxypregnane-11,20-dione (I) in 35 ml. of acetic acid, 2 ml. of acetic anhydride and 2 ml. of boron trifluoride–ether complex was allowed to stand overnight at 25°. Addition of water precipitated 1.15 g., m.p. 105–145°. Trituration with ether, followed by recrystallization from aqueous methanol, gave 0.38 g., m.p. 169–171°; lit.[7] m.p. 167–168.5°.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.62; H, 8.54.

B.—A solution of 1.0 g. of I in 25 ml. of C.P. acetic anhydride was refluxed for 12 hours. The solvent was removed under reduced pressure, the residue taken up in methylene chloride, the organic layer washed with dilute sodium carbonate solution, twice with water, dried and evaporated to yield 1.24 g. of a pale yellow resin which crystallized on the addition of methanol. Trituration with ether, followed by recrystallization from aqueous methanol, gave 0.51 g. of IX, m.p. 163–167°, $[\alpha]_D$ +109.4°. The use of acetic anhydride freshly distilled through a glass-packed column gave the same compound in slightly lower yield.

The infrared spectra of either sample was identical with that of the compound obtained by means of boron trifluoride, and was not identical with the spectrum of 3α,17α-diacetoxy pregnane-11,20-dione.

Treatment of 3α,11β,17α-triacetoxypregnan-20-one or 3α,17α-diacetoxypregnane-11,20-dione with refluxing acetic anhydride for 12 hours as described above resulted in almost quantitative recovery of starting material in both cases.

(7) N. Wendler, D. Taub, S. Dobriner and D. Fukushima, THIS JOURNAL, **78**, 5027 (1956).

3α,11α,17α-Triacetoxy-17β-methyl-D-homoetiocholan-17a-one (X). A.—A solution of 1.0 g. of 3α,11α,17α-trihydroxypregnan-20-one 3,11-diacetate (IV) in 35 ml. of glacial acetic acid was combined with 2 ml. of acetic anhydride and 2 ml. of boron trifluoride etherate. After standing for 16 hours at 30–35°, the reaction was poured into water, yielding 1.07 g. of a gel. Crystallization from hexane gave 0.94 g. of needles, m.p. 184–186°. The analytical sample, crystallized once more, melted at 186–189°, $[\alpha]_D$ +19.9°.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.23; H, 8.82.

B.—A solution of 1.0 g. of IV in 25 ml. of acetic anhydride was refluxed for 12 hours. The solvent was removed under reduced pressure, leaving a crystalline residue. Crystallization from aqueous methanol yielded 0.93 g. of X, m.p. 187–190°. A mixture melting point with the boron trifluoride product showed no depression, and the infrared spectra of the two were identical.

Lithium Aluminum Hydride Reductions. A.—A solution of 1.0 g. of IX in 45 ml. of tetrahydrofuran was added dropwise with stirring to a suspension of 2.0 g. of lithium aluminum hydride in 15 ml. of tetrahydrofuran. The suspension was stirred overnight at 25°, the excess hydride was decomposed by the addition of 10 ml. of ethyl acetate followed by 5 ml. of water, and the mixture poured into ice-water containing 25 ml. of concentrated hydrochloric acid. This was extracted with methylene chloride, the extracts washed with dilute sodium bicarbonate and water, dried and evaporated to give 0.65 g. of a crystalline residue. Two recrystallizations from ethyl acetate yielded 0.22 g. of XII, m.p. 260–275°. The infrared spectrum disclosed the absence of carbonyl or acetate groups.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.29; H, 10.65.

B.—The identical procedure was used for the reduction of 1.0 g. of VI; there was obtained 0.12 g. of XI, m.p. 260–270°. This material also did not possess any acetate or carbonyl groups, but its infrared spectrum was not identical with that of XII.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.52; H, 10.62.

C.—A solution of 1.0 g. of X in 30 ml. of tetrahydrofuran was added dropwise to a stirred suspension of 2.0 g. of lithium aluminum hydride in 50 ml. of anhydrous ether. The mixture was refluxed for 17 hours, then allowed to stand with stirring at room temperature for 48 hours. The reaction was cooled in an ice-bath, and the excess reagent destroyed by the addition of 2 ml. of water, 2 ml. of 15% sodium hydroxide and 6 more ml. of water. The resulting suspension was allowed to warm up to room temperature and stir for 20 minutes. The solids were removed by filtration and washed thoroughly with tetrahydrofuran and methylene chloride. The solids were stirred with 200 ml. of ice-water containing 20 ml. of concentrated sulfuric acid. Filtration gave 0.27 g. of crystals, m.p. 265–272°.

The original filtrate was evaporated to dryness to yield 0.50 g. of a gum; triturating with acetone gave 0.29 g. of crystals, m.p. 235–275°.

The two crystalline fractions were combined and recrystallized from ethanol–hexane to give 0.34 g. of XIII, m.p. 292–300°. The analytical sample, crystallized once more, melted at 300–307°.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.37; H, 10.13.

Sodium–Alcohol Reductions. A.—Ten portions of sodium totalling 2 g. were added to a refluxing solution of 0.50 g. of IX in 75 ml. of isopropyl alcohol; the total reaction time was 5 hours. The solution was then poured onto ice and 10 ml. of acetic acid was added to lower the *p*H to *ca.* 7. The solution was then extracted with methylene chloride, and the organic extracts were washed with water, dried and evaporated to yield 0.45 g. of a crystalline residue. Trituration with ethyl acetate left 0.17 g. Recrystallization from aqueous methanol gave 85 mg. of XIII, m.p. 230–237° with bubbling. Its infrared spectrum was identical with that of the $LiAlH_4$ reduction product of X.

B.—A similar sodium reduction of 0.50 g. of X gave 95 mg. of XIII, m.p. 265–278° with bubbling, identical in its infrared spectrum with the two other samples of XIII. The wide variation in m.p. between the three samples of compound XIII might possibly be due to varying degrees of solvation, but this could not be proven definitely.

3α,17α-Diacetoxypregnane-11,20-dione (XIV). A.—A solution of 2.0 g. of 3α,17α-dihydroxypregnane-11,20-dione-3-acetate (II) in 40 ml. of C.P. acetic anhydride was refluxed for 12 hours. The excess anhydride was decomposed at reflux by the slow addition of water, the solution poured into ice and water and the resulting precipitate filtered and dried: 1.67 g., m.p. 160–180°. Crystallization from methanol yielded 0.66 g., m.p. 195–199°, and 0.20 g. m.p. 192–197°.

B.—Repetition of the above experiment, with 1.2 g. of acetic acid added, gave 0.80 g. of XIV, m.p. 196–199°, $[\alpha]_D$ +50.4°; lit.[2] m.p. 203–204°, $[\alpha]_D$ +46.7° ($CHCl_3$).

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORPORATION]

Some Transformation Products of Cortisone Acetate

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Addition of HOBr to cortisone acetate, followed by treatment with potassium acetate, gave the 4,5α- and 4,5β-epoxides III and IV. Reaction of either of these with HBr, or warming the intermediate bromohydrins with acetic acid, gave 4-bromocortisone acetate (V). 4-Chlorocortisone acetate (VI) was prepared by the action of HCl on the β-epoxide. Compound VI was also the main product from the addition of HOCl to cortisone acetate. Opening the β-epoxide with acid gave the 4,5-glycol IX.

Relatively simple changes in the structure of cortisone have resulted in marked increase in corticoid activity. For example, introduction of a 9α-fluorine atom increases the glucocorticoid activity by a factor of about 9 with an even greater enhanced mineralocorticoid activity.[1] Even more startling, the introduction of an added double bond to produce 1-dehydrocortisone enhances the glucocorticoid activity three- to fourfold, without increasing the salt-retaining properties.[2] It seemed desirable, therefore, to prepare other simple derivatives of cortisone.

Addition of hypobromous acid (N-bromoacetamide and perchloric acid) to the 4,5-double bond of cortisone acetate, followed by treatment with potassium acetate, resulted in the formation of two epoxides: The major one had m.p. 224–227°, $[\alpha]_D$ +142°, and the minor product, m.p. 248–255°, $[\alpha]_D$ +34.9°. In order to help assign configurations, 4-cholesten-3-one was converted to its two epimeric epoxides; the β-epoxide[3] had $[\alpha]_D$

(1) J. Fried and E. Sabo, THIS JOURNAL, **76**, 1455 (1954).

(2) H. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. Perlman and M. Pechet, *Science*, **121**, 3136 (1955).

(3) P. Plattner, H. Heusser and A. Kulkarni, *Helv. Chim. Acta*, **31**, 1822 (1948).