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Studies in Steroid Total Synthesis. III. Preparation of Cortisone and Compound F[1]

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dl-3-Keto-16β,17β-dihydroxy-$\Delta^{4,9(11)}$-D-homoandrostadiene acetonide (I) has been converted to *dl*-cortisone acetate by a direct approach. Optically active cortisone and Compound F acetates have also been prepared by a similar scheme starting with $\Delta^{9(11),16}$-bisdehydro-21-norprogesterone (VIa), which had previously been obtained by total synthesis.

In his paper[2] on the total synthesis of steroids Woodward outlined a path of known reactions for converting his tetracyclic nucleus to cortisone. This method was so long and devious that it could not be construed as a feasible approach. Using *dl*-3-keto-16β,17β-dihydroxy-$\Delta^{4,9(11)}$-D-homoandrostadiene acetonide (I)[1,3] we have found a route which is both direct and practical. A distinguishing feature of this synthesis is that the cortical side chain and the eleven oxygen function are introduced without protecting the α,β-unsaturated ketone in ring A.

Our first objective was to introduce the 11-keto group into *dl*-3-keto-16β,17β-dihydroxy-$\Delta^{4,9(11)}$-D-homoandrostadiene acetonide (I). Hicks and Wallis[4] showed that hypobromous acid added to the 9(11)-double bond of methyl 3α-acetoxy-$\Delta^{9(11)}$-cholenate to give a 9-bromo-11-hydroxy derivative but in very low yield. At that time only $\Delta^{9(11)}$-steroids derived from bile acids were available. These have a *cis* configuration for rings A and B, and it is now clear that where these rings are *trans* or as in our case where a double bond at the ring juncture forces the rings to be relatively flat, the 9(11)-double bond is no longer abnormally inert.[5] The results of Fried and Sabo,[6] published after completion of this phase of our work, confirms these observations and now it appears that $\Delta^{9(11)}$-steroids have become very desirable intermediates for putting oxygen at carbon-11.

In the case of our tetracyclic ketone (I) the use of N-bromosuccinimide and sulfuric acid in aqueous acetone[7] gave a 79% yield of a very insoluble bromohydrin II, which crystallized from the reaction mixture. This compound was not easily purified as such but for characterization was smoothly converted to the epoxide V. With 3,20-diketo-17α,21-dihydroxy-$\Delta^{4,9(11)}$-pregnadiene 21-acetate (XIIIa)[6,8] we used N-bromoacetamide and perchloric acid[6] to prepare the bromohydrin.

Our route to *dl*-cortisone acetate utilized II. Oxidation with pyridine and chromic acid complex[9] gave a crude bromoketone which without purification was debrominated to give *dl*-3,11-diketo-Δ^4-16β,17β-dihydroxy-D-homoandrostene acetonide (IV). Cleavage of ring D by means of periodic acid followed by cyclization with piperidine acetate gave *dl*-11-keto-Δ^{16}-dehydro-21-norprogesterone (VI). Alkaline hydrogen peroxide[10] converted VI to the corresponding 16α,17α-epoxy derivative VII, which was very smoothly oxidized with silver oxide to the epoxy acid VIII. It is interesting to note that the oxidation of the corresponding α,β-unsaturated aldehyde VIa gave inferior results by this method.[2]

We were able to convert the epoxy acid VIII to its acid chloride by the action of oxalyl chloride on the dry sodium salt.[11] Here we were very fortunate since earlier experiments on the corresponding 17α-hydroxy acid or its acetate failed. The acid chloride IX without purification was treated with diazomethane to give a crystalline diazoketone X showing strong infrared absorption at 4.75 μ. Brief treatment of X with hot acetic acid gave the non-crystalline 21-acetoxy compound XI. Infrared spectra showed that there was no attack on the epoxide by the acetic acid. The reaction of XI with hydrogen bromide produced the desired *dl*-16β-bromocortisone acetate (XII). At this point we had considerable difficulty finding a suitable nickel to remove the halogen without harming the rest of the molecule. We found that commercial Raney nickel, modified first by washing neutral with water, displacing water with isopropyl alcohol, and then refluxing with acetone gave an excellent yield of *dl*-cortisone acetate (XIII),[12] as long as a small amount of acetic acid was added prior to using. Previously published procedures[10,13] were unsuccessful in our case and we found it necessary to have this acid present in order to prevent extensive epoxide formation.

At the conclusion of this part of our work the appearance of Fried and Sabo's publication further

(1) A portion of this subject matter has been reported in a preliminary communication: L. B. Barkley, M. W. Farrar, W. S. Knowles and H. Raffelson, THIS JOURNAL, **75**, 4110 (1953).

(2) *Cf.* R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952).

(3) L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Thompson, *ibid.*, **76**, 5014 (1954).

(4) E. M. Hicks, Jr., and E. S. Wallis, *J. Biol. Chem.*, **162**, 641 (1946); *cf.* H. E. Stavely, *Federation Proc.*, **9** (Part 1), 233 (1950).

(5) This conclusion is further substantiated by the reaction of $\Delta^{9(11)}$-steroids with osmium tetroxide which occurs readily when rings A and B are *trans* and not at all when *cis* [R. Hirschmann, C. S. Snoddy, Jr., and N. L. Wendler, THIS JOURNAL, **75**, 3252 (1953)]. This difference in reactivity is quite reasonable since the easy formation of 3,9-oxides in *cis* A/B steroids shows that ring A can be in a position to block rear attack and thus lower the reactivity of the corresponding $\Delta^{9(11)}$-steroids.

(6) *Cf.* J. Fried and E. F. Sabo, *ibid.*, **75**, 2273 (1953).

(7) *Cf.* L. H. Sarett, *J. Biol. Chem.*, **162**, 601 (1946).

(8) N. L. Wendler, R. P. Graber and A. C. Haven, U. S. Patent 2,640,838 (June 2, 1953), and THIS JOURNAL, **75**, 4722 (1953); S. Bernstein, R. Littell and J. H. Williams, *ibid.*, **75**, 4830 (1953).

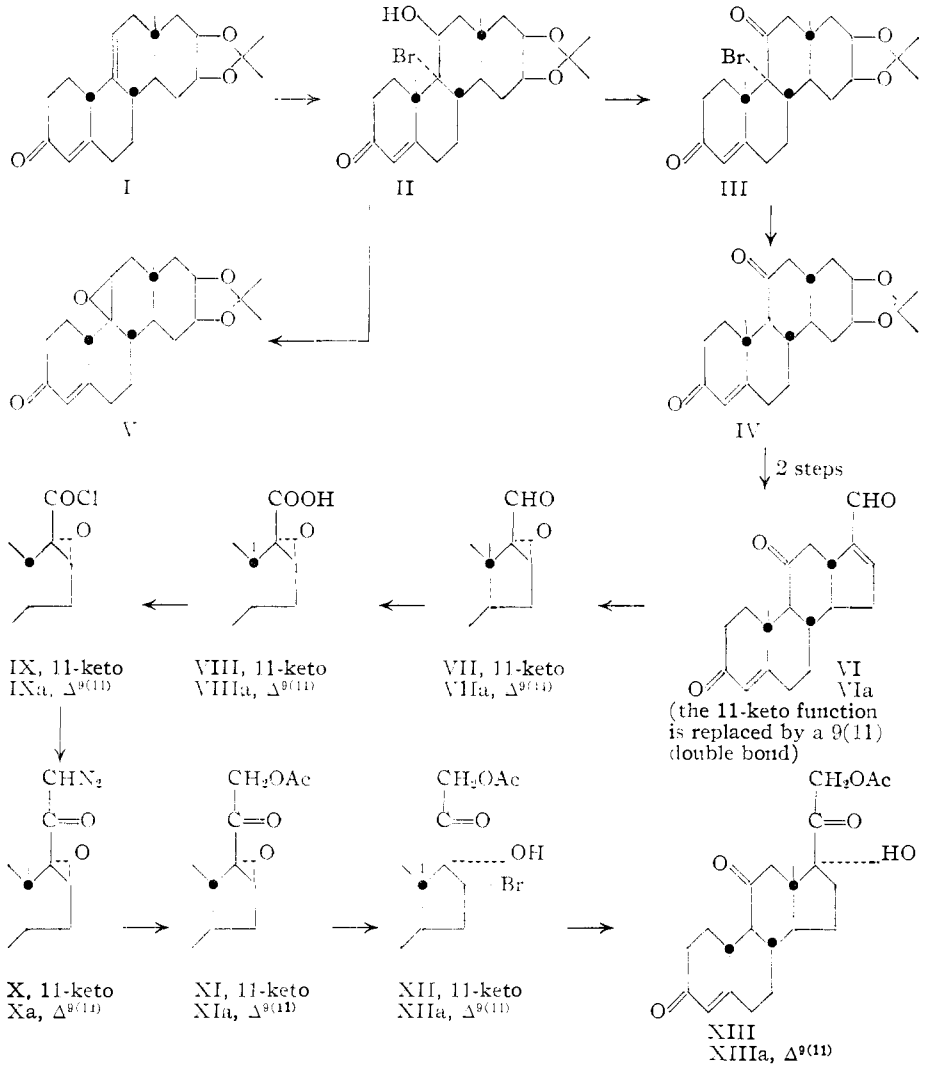
(9) A reagent first announced at the Gordon Research Conferences, A. A. A. S., New Hampton, N. H., August 4–8, 1952; *cf.* G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(10) *Cf.* P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, *ibid.*, **72**, 5145 (1950).

(11) *Cf.* A. L. Wilds and C. H. Shunk, *ibid.*, **70**, 2427 (1948).

(12) The first complete synthesis of *dl*-cortisone acetate was reported by L. H. Sarett, G. E. Arth, R. M. Lukes, R. E. Beyler, G. I. Poos, W. F. Johns and J. M. Constantin, *ibid.*, **74**, 4974 (1952).

(13) *Cf.* J. Pataki, G. Rosenkranz and K. Djerassi, *ibid.*, **74**, 5615 (1952).



confirmed the generality of our observation that 9(11)-double bonds are reactive as long as rings A and B are not *cis*. Subsequently for our synthesis of natural cortisone and Compound F we decided to attach the dihydroxyacetone side chain prior to introduction of oxygen at carbon-11. Thus using an exactly analogous series of reactions (VIa through XIIIa) optically active $\Delta^{9(11),16}$-bisdehydro-21-norprogesterone (VIa)[3] was converted to the known 3,20-diketo-17α,21-dihydroxy-$\Delta^{4,9(11)}$-pregnadiene 21-acetate (XIIIa)[6,8] whose melting point and rotation agreed with the literature. The conversion of XIIIa to cortisone acetate and the Kendall Compound F acetate paralleled Fried and Sabo's experience.[6]

The reactions described thus enable a direct approach to both cortisone and Compound F as well as other eleven oxygenated steroids by total synthesis.

Experimental

All rotations were measured in chloroform at 2% concentration unless otherwise stated. Analyses were done by Mr. A. Bybell of this Laboratory. Infrared spectra were run on a Perkin–Elmer recording spectrophotometer, model 21.

dl-9α-**Bromo-3-keto-11β,16β,17β-trihydroxy-Δ^4-D-homoandrostene Acetonide (II).**—A solution of 5.50 g. of I in 350 ml. of acetone and 60 ml. of water was cooled to 0–5° and 4.5 ml. of 1 *N* sulfuric acid was added. Subsequently a solution of 3.16 g. of N-bromosuccinimide in 45 ml. of acetone was added in two equal portions at a one-hour interval. After introducing the first portion an additional 55 ml. of water was added. After adding the second portion of the NBS acetone solution an additional 2 ml. of 1 *N* sulfuric acid solution was added to increase the acidity of the solution. The mixture was stirred for a total of five hours at 0–5°. After about 1.5 hours the crystalline bromohydrin began to separate. At the end of the five-hour period the excess N-bromosuccinimide was destroyed with 10% aqueous sodium sulfite and the solution was neutralized to *p*H 8 with 10% aqueous sodium carbonate. After filtration, the crystalline bromohydrin was dried at room temperature *in vacuo* to give 5.88 g. (84%), m.p. 192–194°.

dl-9β,11β-**Oxido-3-keto-16β,17β-dihydroxy-Δ^4-D-homoandrostene Acetonide (V).**—To a stirred slurry of 0.193 g. of II in 20 ml. of methanol at 25° was added 2 ml. of 0.5 *N* sodium hydroxide solution. After two hours the solution became clear and the methanol was evaporated *in vacuo*. The crystalline residue was washed with water and recrystallized twice from methanol, m.p. 191–193°.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.2; H, 8.7. Found: C, 74.2; H, 8.7.

dl-9α-**Bromo-3,11-diketo-16β,17β-dihydroxy-Δ^4-D-homoandrostene Acetonide (III).**—The chromium trioxide in pyridine reagent[9] was prepared as follows. To 32 ml. of dry pyridine at 5° was added 2.30 g. of chromium trioxide in small portions over a 0.5-hour period. To this stirred slurry was added a mixture of 4.50 g. of II in 80 ml. of dry pyridine maintaining the temperature at 5–10°. The bromohydrin was not very soluble in pyridine and had to be added as a thin slurry. This mixture was stirred for 16 hours at 25° after which the pyridine complex was filtered and washed with pyridine. Most of the pyridine was removed *in vacuo* below 25° and replaced with water whereupon the light brown crystalline product which separated was filtered. The yield of III was 3.98 g., m.p. 180–180.5° dec., and no attempt was made to purify it.

dl-**3,11-Diketo-16β,17β-dihydroxy-Δ^4-D-homoandrostene Acetonide (IV).**—To a solution of 4.76 g. of III in 320 ml. of glacial acetic acid and 109 ml. of water at 5° was added 7.7 g. of zinc dust. The mixture was stirred at 10–15° for 15 minutes then cooled to 5° and filtered. A large part of the acetic acid was evaporated at 10° *in vacuo*. The residue was extracted with ether and the ethereal extract washed with sodium carbonate solution and water. After drying and evaporating the solvent the crystalline residue was triturated with ether to give 2.8 g. of IV, m.p. 194–198°. Additional material was obtained from the mother liquors making the over-all yield of IV from II 54%. The analytical

sample was crystallized from benzene and ether, m.p. 199.5–202°.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.2; H, 8.7. Found: 73.8; H, 8.5.

dl-11-Keto-Δ^{16}-dehydro-21-norprogesterone (VI).—The ring contraction of IV, using first periodic acid to give a dialdehyde and second piperidine acetate, was carried out exactly as described previously.[2,3] The over-all yield was 65%. Crystallization from benzene–Skellysolve B gave the analytical sample, m.p. 205–207.5°.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.9; H, 7.7. Found: C, 76.5; H, 7.7.

dl-11-Keto-16α,17α-oxido-21-norprogesterone (VII).—To a solution of 0.200 g. of VI in 30 ml. of methanol at 0–5° was added 0.48 ml. of 2.65 *N* sodium hydroxide solution and 5.81 ml. of a solution of hydrogen peroxide in methanol containing 0.1157 mmole/ml. The mixture was held at 0–5° for 15 hours and then most of the methanol was removed *in vacuo* at 15–20°. The product was isolated by chloroform extraction, drying and evaporation of the solvent. Crystallization from ether–chloroform yielded 0.161 g. (76%) of VII, m.p. 243–245°.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.1; H, 7.4. Found: C, 72.8; H, 7.6.

$\Delta^{9(11)}$-Dehydro-16α,17α-oxido-21-norprogesterone (VIIa).—Following the procedure outlined above from VIa[3] an 82% yield of VIIa was obtained, m.p. 195–199°, $[\alpha]^{25}D$ +184°.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 77.0; H, 7.7. Found: C, 76.7; H, 8.0.

dl-3,11-Diketo-16α,17α-oxido-Δ^4-etiocholenic Acid (VIII).—To a silver oxide slurry prepared from 0.639 g. of silver nitrate and 5.7 ml. of 10% sodium hydroxide solution diluted with 5.7 ml. of dioxane was added 0.600 g. of VII over a 15-minute period at room temperature. The mixture was stirred for one hour longer at room temperature, filtered, the alkaline solution washed with ether and the ether discarded. The alkaline solution was carefully acidified with an equivalent amount of 0.5 *N* hydrochloric acid whereupon the crystalline acid separated. Crystallization from ether–ethyl acetate gave 0.551 g. (87%) VIII, m.p. 217–220° with decarboxylation. Carbon and hydrogen analysis indicated that this product was possibly a hemihydrate and it was converted with diazomethane to the methyl ester, m.p. 197–199°.

Anal. Calcd. for $C_{21}H_{26}O_5$: C, 70.4; H, 7.3. Found: C, 70.0; H, 7.5.

3-Keto-16α,17α-oxido-$\Delta^{4,9(11)}$-etiocholadienic Acid (VIIIa).—Following the procedure used for the preparation of VIII, VIIa was converted to VIIIa in 84% yield, m.p. 211–212° with decarboxylation, $[\alpha]^{25}D$ +166° (1% $CHCl_3$). This product also analyzed as if it were a hemihydrate and for characterization was converted with diazomethane to the methyl ester, m.p. 205–207°, $[\alpha]^{25}D$ +157°.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.8; H, 7.7. Found: C, 73.8; H, 7.7.

dl-11-Keto-16α,17α-oxido-21-diazoprogesterone (X).—The anhydrous sodium salt of VIII was prepared as follows: 0.630 g. of VIII was dissolved in methanol and was neutralized with one equivalent of sodium methoxide in methanol. The methanol was removed *in vacuo* and replaced with 20 ml. of anhydrous benzene which was also evaporated *in vacuo*. The dry sodium salt was suspended in 15 ml. of anhydrous benzene, cooled to 10° and treated with 4 drops of dry pyridine followed by 3.0 ml. of freshly distilled oxalyl chloride. The mixture was held at 10–15° for one-half hour then evaporated to dryness *in vacuo* at 15°. A fresh 10-ml. portion of anhydrous benzene was added, evaporated *in vacuo* below 15° and the crude acid chloride was then dissolved in dry benzene and added to an excess of ethereal diazomethane solution at 0°. After one hour at 0° the excess diazomethane and solvent were removed *in vacuo*, the residue was extracted with benzene and the benzene solution was evaporated to give 0.296 g. (45%) of X, m.p. 193–195°, which was used without further purification. From the residue remaining after the benzene extraction a substantial quantity of the sodium salt of VIII was recovered.

$\Delta^{9(11)}$-Dehydro-16α,17α-oxido-21-diazoprogesterone (Xa).—Following the above described procedure from VIIIa there was obtained a 65% yield of Xa, m.p. 169–170°, which was used without further purification.

dl-16α,17α-Oxido-3,11,20-triketo-21-hydroxy-Δ^4-pregnene Acetate (XI).—The diazoketone X was decomposed by heating in glacial acetic acid at 95° for 20 minutes. From 0.290 g. of X there was obtained 0.297 g. of non-crystalline XI whose infrared spectrum was in accord with the proposed structure.

16α,17α-Oxido-3,20-diketo-21-hydroxy-$\Delta^{4,9(11)}$-pregnadiene Acetate (XIa).—Non-crystalline XIa was obtained from Xa using the procedure as described for the preparation of XI. Since it resisted crystallization, it was used directly in the next step.

dl-16β-Bromocortisone Acetate (XII).—Non-crystalline XI (0.290 g.) was dissolved in 12 ml. of glacial acetic acid and 4 ml. of purified dioxane. The solution was cooled to 10°, 1.2 ml. of 10% hydrogen bromide in acetic acid was added and the mixture was held at 10° for 45 minutes. Evaporation of the solvent and crystallization of the residue from acetone–ether yielded 0.122 g. of XII, m.p. 238–240° dec.

3,20-Diketo-16β-bromo-17α,21-dihydroxy-$\Delta^{4,9(11)}$-pregnadiene 21-Acetate (XIIa).—Using the procedure as described above for the preparation of XII, the over-all yield of XIIa (m.p. 146–147° dec.) from the diazoketone was 44%.

dl-Cortisone Acetate (XIII).[12]—Active Raney nickel catalyst purchased from the Raney Catalyst Co., Chattanooga, Tenn., was thoroughly washed with water using a countercurrent washer until neutral and the water was then displaced with isopropyl alcohol. An isopropyl alcohol slurry containing 1.2 g. of nickel was refluxed in 12 ml. of acetone with stirring for one hour. Subsequently 0.24 ml. of glacial acetic acid, 1.2 ml. of water and 0.120 g. of XII in 12 ml. of acetone were added and the mixture was refluxed an additional four hours. The solution was filtered while hot and the nickel was washed with hot acetone. After evaporation of the acetone the residue was taken up in chloroform, washed with dilute sodium bicarbonate solution and water and dried over anhydrous magnesium sulfate. The residue remaining after removal of the solvent was recrystallized from acetone–ether to give 0.081 g. of XIII, m.p. 240–243°. Sarett reported 240–245°. The infrared spectrum of this material was identical with that of an authentic sample of cortisone acetate.

3,20-Diketo-17α,21-dihydroxy-$\Delta^{4,9(11)}$-pregnadiene 21-Acetate (XIIIa).[8]—Debromination of XIIa using the procedure described above was accomplished in 98% yield to give XIIIa, m.p. 233–236°, $[\alpha]^{25}D$ + 118° (1% $CHCl_3$).

9α-Bromo-17α-hydroxycorticosterone 21-Acetate (XIV).[6]—To a solution of 0.100 g. of XIIIa in 20 ml. of dioxane and 4 ml. of water at 20° was added 0.072 g. of N-bromoacetamide and 1.0 ml. of 10% perchloric acid. The solution was kept at 20° for 15 minutes then excess aqueous sodium sulfite was added. After chloroform extraction and evaporation of the solvent there remained 0.120 g. (95%) of crystalline residue which after washing with ether melted with decomposition at 127–129°.

17α-Hydroxycorticosterone 21-Acetate (XV).[6]—To a solution of 0.080 g. of XIV in 25 ml. of methanol and 25 ml. of water at room temperature was added 2.0 g. of zinc dust and 1.0 ml. of 5% copper sulfate solution. The mixture was stirred at room temperature for two hours and then extracted with chloroform. The chloroform extract was evaporated and the crystalline residue was washed with warm benzene. The benzene-insoluble material after recrystallization from acetone melted at 217–221° and its infrared spectrum was identical with that of an authentic sample of 17α-hydroxycorticosterone 21-acetate. A substantial quantity of XIIIa was recovered from the benzene soluble fraction.

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