The 3β-Acetoxy-(5,6)α,(16,17)α-dioxidopregnan-20-one (XVIII).—A 0.17-g. portion of diepoxide (XVII) (m.p. 193–196°) in 3 ml. of pyridine was acetylated with 6 ml. of acetic anhydride. After standing overnight the solution was poured into 30 ml. of water and the precipitate formed was collected by filtration, dried and crystallized from methanol, yielding the 3-acetate, m.p. 207–208°.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; CH_3CO, 11.08. Found: C, 70.71, 70.65; H, 7.67, 8.33; CH_3CO, 11.39.

3β-Acetoxy-(5,6)α,(16,17)α-dioxido-21-bromopregnan-20-one (XIX).—This was prepared as described for XII in the allo series above using 0.265 g. (0.000615 mole) of the dioxido compound XVI and 4.43 ml. (0.000615 mole) of a 0.278 *N* bromine solution. The crude product was crystallized from methanol giving 0.07 g. (24.3%) of the 21-bromo compound, m.p. 194–197°. Recrystallization from methanol–methylene chloride raised the melting point to 199–202°; $[\alpha]^{24}D$ −11° (0.61% in chloroform).

Anal. Calcd. for $C_{23}H_{31}BrO_5$: C, 59.10; H, 6.69; Br, 17.10. Found: C, 59.09; H, 6.93; Br, 16.89.

3β,21-Diacetoxy-(5,6)α,(16,17)α-dioxidopregnan-20-one (XX).—The 21-acetate was prepared from 0.07 g. of the above bromo compound by a procedure like that described for compound XIII in the allo series. The product crystallized from methanol, m.p. 192–194°.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.25; H, 7.68. Found: C, 67.46; H, 7.84.

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Selective Oxidation of Some Steroid Diols

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The selective oxidation at C-3 of steroid 3,21-diols by means of N-bromoacetamide has been utilized in an improved synthesis of both 11-dehydro-17α-hydroxycorticosterone and 17α-hydroxycorticosterone.

Both N-bromoacetamide (NBA) and N-bromosuccinimide (NBS) have become generally recognized as excellent oxidizing agents for the conversion of secondary alcohols to ketones. Oxidation by these reagents, first reported by Reich and Reichstein,[1] has been of great utility in the steroid field. Of special interest is the fact that, in many cases, these N-halogenated amides possess a selectivity of attack for secondary as compared with primary hydroxyl groups. Kritchevsky, Garmaise and Gallagher[2] have reported a case in which 3α,-17α,21-trihydroxypregnane,11,20-dione was oxidized selectively to the 3,11,20-trione in high yield.

During our early studies on the partial synthesis of cortisone, we observed the highly selective oxidation of 20-cyano-3α,21-dihydroxy-17-pregnen-11-one (I) to give almost exclusively 20-cyano-21-hydroxy-17-pregnene-3,11-dione (II). The diketone II was identical in all respects with that previously prepared by Sarett[3] *via* another route. This observation is surprising for two reasons. The 21-ol is an allylic alcohol (in contrast to the case reported by Gallagher,[2] *et al.*); as such, it might be expected to oxidize first.[4] Secondly, no addition of the reagent (or of the elements of HOBr) to the 17-unsaturation was experienced. Since this oxidation is completely selective and nearly quantitative, its use in the conversion of I to cortisone represented an improvement over the original procedure.[5] By this present method, the troublesome (21)-monoacetylation of I is obviated and oxidation of an osmate ester at a latter step[5] becomes unnecessary. In the revised sequence, a direct acidic cleavage of the osmate ester to 17α,21-dihydroxypregnane-3,11,20-trione 21-acetate was used.[6] The revised section of the partial synthesis of cortisone is shown in the reaction sequence I → V.

The trione V was converted to cortisone by the procedure described by Sarett[3] and by Mattox and Kendall, also by McGuckin and Kendall.[7,8] The cyanopregnene II was the starting point for a previously described[6] partial synthesis of 17α-hydroxycorticosterone (Kendall's compound F or hydrocortisone).

It is apparent that the cyanopregnene diol I is capable of existing as *cis* and *trans* isomers about the Δ^{17}-double bond. These two isomers have, in fact, been separated.[9] In addition to compound I, "iso" I has been oxidized successfully to "iso" II and acetylated to "iso" III. Since the seat of the isomerism is destroyed by osmium tetroxide hydroxylation of the Δ^{17}-bond, both III and "iso" III afforded V as expected. While the intermediate osmate esters (IV) in both the *normal* and the *iso* series should be expected to be different, characterization of these compounds was not carried out during the course of this work.

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Experimental

All melting points were taken in an open capillary, are uncorrected and were taken with uncalibrated Anschütz thermometers. Optical rotations are 1% in acetone.

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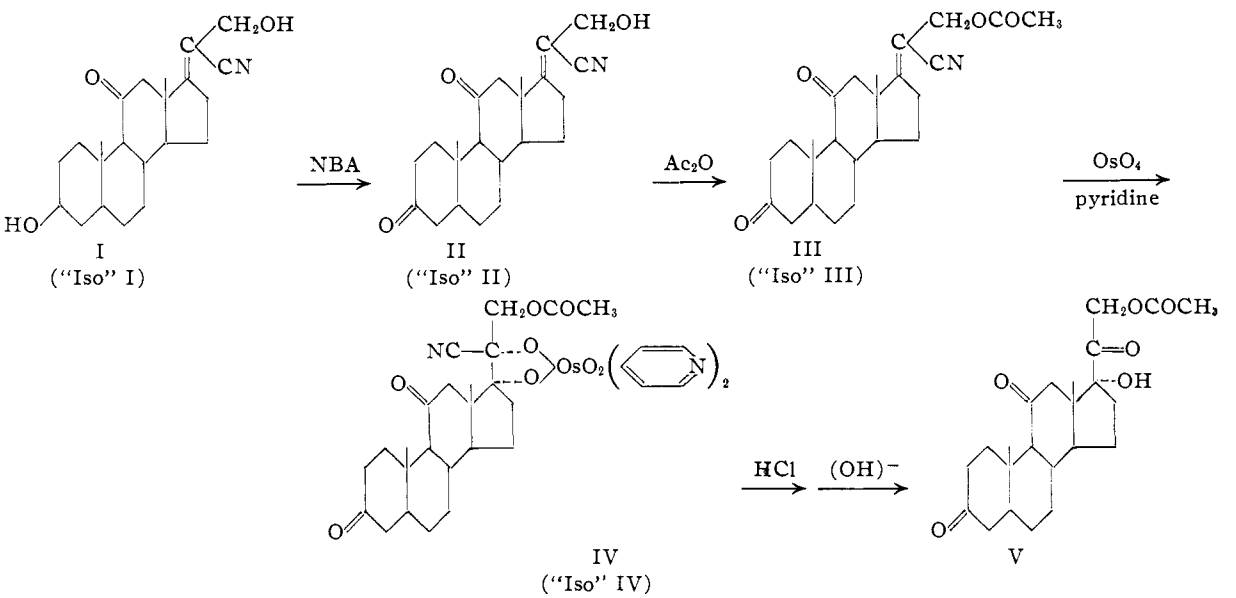

Selective Oxidation of 20-Cyano-3α,21-dihydroxy-17-pregnen-11-one (I) to the Dione II.—To a solution of 13.05 g. of crystalline NBA in 233 cc. of methanol, 3.6 cc. of pyridine and 12.7 cc. of water was added 15.00 g. (0.023 mole) of pure diol I. The mixture was stirred overnight at room temperature protected from light. At the end of this time (considerable crystallization had occurred) 4.2 cc. of allyl alcohol was added to discharge excess NBA followed by 4.4 cc. of 6 *N* hydrochloric acid for neutralization of the pyridine. Crystallization was forced to completion by slow (20 min.) addition of 900 cc. of water. After aging the mixture in an ice-bath for one-half hour, the crystalline product was removed by filtration, washed with water and dried, wt. 14.3 g. (96.5%), m.p. 254.1–255.1°.

Recrystallization from acetone afforded the analytical sample, m.p. 269.2–271.6°, $[\alpha]_D$ +28.6°; $\lambda_{max}^{methanol}$ 223 mμ, ε 13,680.

Anal. Calcd. for $C_{22}H_{29}O_3N$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.28; H, 7.93; N, 4.47.

Acetylation of Dione II to 20-Cyano-21-hydroxy-17-pregnene-3,11-dione 21-Acetate (III).—Ten grams of the dione II (0.028 mole) was mixed with 50.0 cc. of acetic anhydride and 2.3 cc. of pyridine was added as a catalyst. The mixture was stirred at 50° for three hours at which time the heating bath was replaced by a cooling bath. While carefully controlling the temperature at 45–50°, 9.0 cc. of water mixed with 19.0 cc. of glacial acetic acid was added slowly to decompose excess acetic anhydride. After stirring the mixture for one hour at 40–45° to ensure complete reaction, 500 mg. of zinc dust was added; vigorous stirring was continued for one hour at 40–45° to effect complete reduction of small amounts of unwanted bromoketones. The excess zinc was removed by filtration (after cooling to room temperature) and the product was crystallized by careful addition of 300 cc. of water. The acetate III was removed by filtration, washed with water and dried, wt. 10.78 g. (96.4%), m.p. 194.7–196.1°. The product melted at 197.6–198.4° after recrystallization from hot isopropyl alcohol, $[\alpha]_D$ +36.0°; $\lambda_{max}^{methanol}$ 222 mμ, ε 14,650.

Anal. Calcd. for $C_{24}H_{31}O_4N$: C, 72.51; H, 7.86; N, 3.52. Found: C, 72.70; H, 7.88.

17α,21-Dihydroxypregnane-3,11,20-trione 21-Acetate (V) from III.—The osmylation reaction was set up in a fashion very similar to that reported by Sarett[3]; 85.2 g. (0.214 mole) of the diketone III was mixed with 450 cc. of thiophene-free benzene, 63 cc. of pyridine and 58.5 g. (0.230 mole) of osmium tetroxide. These materials dissolved rapidly on swirling with only slight warming. The mixture darkened rapidly on standing; it was allowed to stand (tightly stoppered) for 72 hours.

At the end of the above time, the hydroxylated steroid was freed from its reduced osmium residue by the revised process first described in the partial synthesis of compound F.[5] The yield of V, crystallized from chloroform–petroleum ether, was 76.4 g. (88%), m.p. 229.0–231.0° and $[\alpha]_D$ +80.3°. A mixed melting point of this material with an authentic sample of V showed no depression.

"Iso" II from "Iso" I by Selective Oxidation with NBA.—Using an oxidation technique identical with that described in preparation of II from I, 100 g. (0.28 mole) of "iso" I was converted (over a 16-hour reaction period) to the 3-ketone, "iso" II. The crude ketone was obtained in 90% yield, m.p. 211.6–215.2°.

Recrystallization from aqueous methanol yielded the pure compound of melting point 228.9–230.7°, $[\alpha]_D$ +55.6°; $\lambda_{max}^{methanol}$ 222 mμ, ε 11,050.

Anal. Calcd. for $C_{22}H_{29}O_3N$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.62; H, 8.20; N, 3.86.

"Iso" III by Acetylation of "Iso" II.—Ten grams of the diketone ("iso" II) was mixed with 50 cc. of acetic anhydride and 2.3 cc. of pyridine; the mixture was held at 35° for three hours and worked up by quenching carefully with 220 cc. of water, cooling, aging and filtering; wt. 8.89 (79.5%), m.p. 128.0–129.5°.

Recrystallization from aqueous acetic acid gave the analytical sample, m.p. 132.7–133.8°; $\lambda_{max}^{methanol}$ 222 mμ, ε 13,300.

Anal. Calcd. for $C_{24}H_{31}O_4N$: C, 72.51; H, 7.86; N, 3.52. Found: C, 72.16; H, 7.64; N, 3.77.

17α,21-Dihydroxypregnane-3,11,20-trione 21-Acetate (V) from "Iso" III.—Fifty-five cubic centimeters of benzene and 3.1 cc. of pyridine were mixed with 4.26 g. (0.011 mole) of the "iso" dione III and 2.89 g. (0.0114 mole) of osmium tetroxide. The mixture was allowed to stand for 48 hours and was worked up in the fashion described[5] for hydroxylation of III to V.

The weight of crude product was 3.20 g. (74%), m.p. 225–228°. Recrystallization of this material from ethyl acetate gave a product melting at 228–230°; no depression in melting was observed when this sample was mixed with authentic V.

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