The Synthesis of C-18 Functionalized Hormone Analogs. III. Synthesis of Aldosterone[1a]

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The synthesis of aldosterone from 3β-acetoxy-11-oxo-5α-conanine (I) is described. Lithium aluminum hydride reduction of I gave the expected diol which was quaternized and subjected to a Hofmann reaction to afford 3β-hydroxy-20α-dimethylamino-11β,18-epoxy-5α-pregnane (IV). The hydroxyl group was oxidized and the amino group was eliminated to furnish a keto olefin VIII which was hydroxylated and acetylated to produce 20,21-dihydroxy-11β,18-epoxy-5α-pregnan-3-one 20,21-diacetate. This compound was oxidized to a 11,18-lactone and the 4,5-unsaturation was introduced by conventional methods. The resulting 3-oxo-11β,20,21-trihydroxy pregn-4-en-18-oic acid 11,18-lactone 20,21-diacetate (XIV) was deacetylated, converted to the 21-triphenylmethyl ether, and oxidized to the C-20 ketone. Removal of the trityl group afforded 11β,21-dihydroxy-3,20-dioxo-pregn-4-en-18-oic acid 11,18-lactone which has been converted to aldosterone.

The synthesis of aldosterone presents extraordinary difficulties which arise from the presence of the C-18 carbonyl function in the molecule. Early studies in this area were confined to total syntheses of the hormone[2-5] and afforded intermediates which were racemic. These syntheses must, therefore, include a resolution step at some point in order to furnish *d*-aldosterone. More recently, intramolecular free radical and ionic reactions, intended to introduce functionality at the unactivated C-18 angular methyl group of the intact steroid skeleton, have led to partial syntheses of the hormone.[1,6-8] A synthesis involving microbiological oxidation of intermediates derived from holarrhimine also has been described.[9]

This paper deals with the synthesis of aldosterone from 3β-acetoxy-11-oxo-5α-conanine (I), available by a convenient method developed in these laboratories.[10] In planning the synthetic route, attention was directed toward an early replacement of the C-18 nitrogen function in I by an oxygen moiety, in order to eliminate difficulties which might be caused by the basic group in subsequent steps. Among the operations which accomplish this conversion are methods leading to C-18 aldehydes[11,12] and 18,20-epoxides.[13] In the present case it appeared advantageous to establish directly a C-11,C-18 linkage to form the C-11,C-18 cycle found in aldosterone. Thus, in the initial steps, it was intended to open the pyrrolidine ring and ultimately to remove the resulting C-18 amine function. That quaternary ammonium salts and alkyl halides are similar in their behavior towards nucleophiles is well known[14] and advantage was taken of this fact to obtain an 11,18-epoxide.

In model experiments, 3β-hydroxy-5α-conanine was quaternized and then subjected to a Hofmann reaction to afford 3β-hydroxy-18-dimethylamino-5α-pregn-20-ene[15] which was resistant to quaternization. Prolonged treatment of the 18-dimethylamino compound with methyl iodide did, however, afford the quaternary salt. The fact that the nitrogen atom is poorly reactive in an SN2 reaction is not surprising, since substituents at C-18 are part of a neopentyl system. The C-18 nitrogen function in the conanines, on the other hand, displays more normal reactivity because of the reduction in hindrance due to the rigid cyclic system.

Using the methods established in the model reactions, I was first reduced to II and this diol was subjected to a modified Hofmann procedure,[16] but a mixture of compounds was obtained. The main product, isolated in 64% yield by direct recrystallization from methanol, had the correct analysis for the expected V, but analysis of the n.m.r. spectrum[17] showed that it was actually 11β,18-epoxy-20α-dimethylamino-5α-pregnan-3β-ol (IV). This compound arises from displacement of the quaternary nitrogen from C-18 by the 11β-hydroxyl group or the corresponding alkoxide ion.

The spectrum of IV showed a signal at 54 c.p.s. (0.91 p.p.m.) arising from the C-19 methyl group. The predicted[18] C-19 frequency for a 3β-hydroxy-5α-steroid is 52 c.p.s., and it is noteworthy that the C-11, C-18 ether introduced little change in this value, in contrast to the effect of the 11β-hydroxy group. A doublet at 52 c.p.s. and 58 c.p.s. is due to the C-21 protons which are spin-coupled to the C-20 proton,

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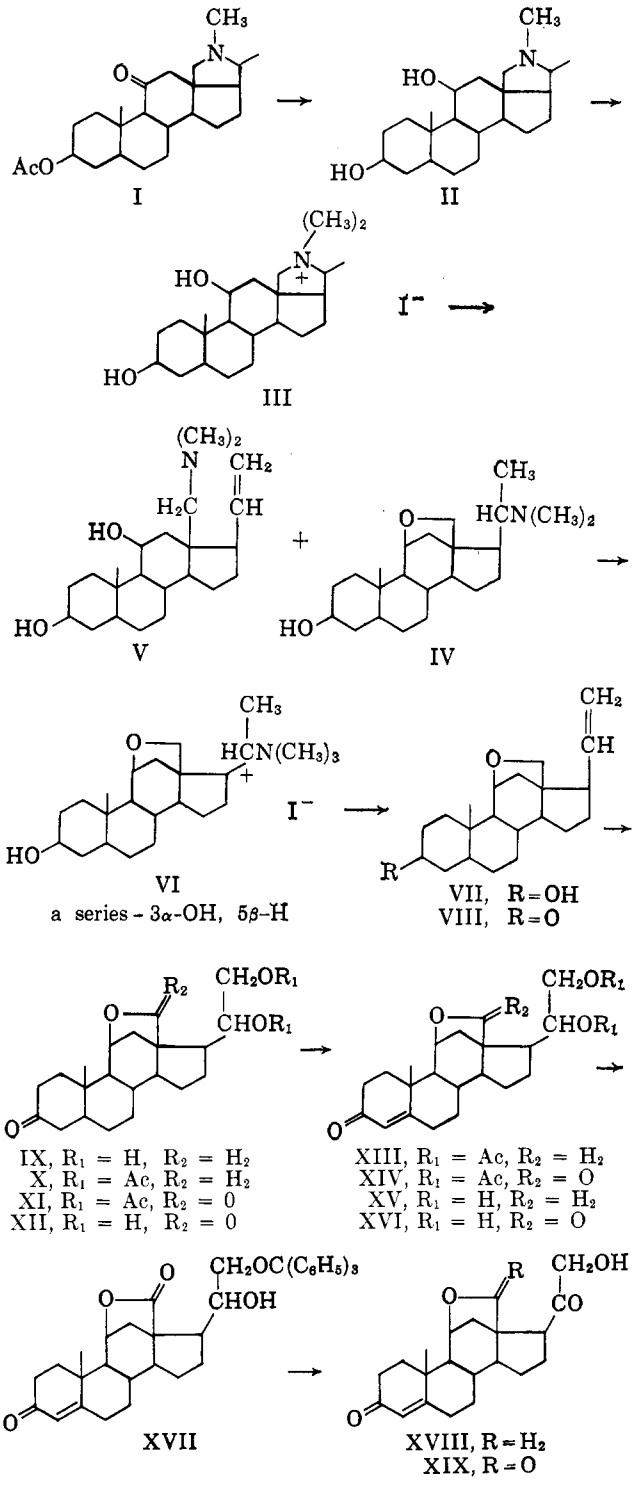

and the center of gravity of the C-21 proton signal is 55 c.p.s. (0.92 p.p.m.). An intense signal at 129 c.p.s. (2.15 p.p.m.) arises from the six protons in the dimethylamino group. The AB system of the two protons at C-18 produce a well resolved quartet centered on 210 c.p.s., the calculated values for the A and B frequencies being 206 c.p.s. (3.44 p.p.m.) and 214 c.p.s. (3.57 p.p.m.) and J = 8 c.p.s. An interesting feature of the spectrum is a doublet centered at 258 c.p.s. (4.66 p.p.m.). This stems from an AX-like system having a coupling constant of 6 c.p.s. and is assigned to the 11α hydrogen. Although this atom at first would appear to be part of an AXYZ system (11α-H, 9α-H, 12α-H, 12β-H), this, in fact, is not the case, as has been shown rigorously in an analagous 2,19-disubstituted steroid by Bhacca, Wolff, and Kwok[19] using triple resonance techniques at 100 Mc. An examination of a Courtauld model of IV shows clearly that the 9α-H and 12α-H bonds lie in a single plane and that this plane is at right angles with a plane passing through the 11α bond. Thus, the dihedral angle between the AY and AZ atoms is 90°, a condition which results in uncoupling, and the 11α-H is coupled only to the 12β-H. The 12β-H is coupled to both the 11α-H and 12α-H, and a pair of doublets should, therefore, be seen. The downfield doublet is centered on 145 c.p.s. (2.42 p.p.m.), but the upfield doublet is obscured by the dimethylamine signal at 2.15 p.p.m.

The structure of IV was confirmed by acetylation to afford a monoacetate which had no free hydroxyl group.

An amine fraction which was resistant to quaternization was then separated from the mother liquors obtained from the isolation of IV. This second compound had the same melting point and elemental analysis as IV, but mixture melting points were strongly depressed. The infrared spectrum had bands typical of a terminal double bond. That this compound has structure V was shown by the n.m.r. spectrum.

The n.m.r. spectrum of V showed a signal at 60 c.p.s. (1.08 p.p.m.) (expected[18] 67 c.p.s.) due to the C-19 methyl group and a peak at 134 c.p.s. (2.23 p.p.m.) resulting from the dimethylamino moiety. There also were observed a low broad hump centered on 208 c.p.s. (3α-H), a multiplet centered on 254 c.p.s. (11α-H), multiplets at 293 and 305 c.p.s. (terminal vinyl), and a very broad low signal centered on 343 c.p.s. (C-20 vinyl proton).

Compound V also was prepared by lithium aluminum hydride reduction of the corresponding 11-oxo compound, 3β-hydroxy-18-dimethylamino-5α-pregn-20-en-11-one.[10] An attempt to acetylate V with acetic anhydride–pyridine gave only water soluble material, which evidently arose fron cyclization to the pyrrolidinium cation of III or its C-20 epimer.

When the quaternary salt III was heated with potassium hydroxide in ethylene glycol, only the 11β,18-epoxide IV was obtained, and no 18-dimethylamino compound V could be detected in the reaction product.

Continuing with the main sequence, IV was quaternized to afford VI which was degraded to the 20,21-unsaturated compound VII. In this case, it was found that yields as high as 96% were obtained when the Hofmann elimination was carried out in dimethylformamide solution containing sodium methoxide. Since oxidative conversions at C-18 could not be carried out in the presence of the unsaturated side chain, attention was next directed towards protection of this portion of the molecule. Following methods used[20] to elaborate the side chain of corticosterone, 11β,18-epoxy-5α-pregn-20-en-3β-ol (VII) was oxidized to the 3-ketone VIII with chromic acid in acetone.[21] The n.m.r. spectrum of VIII displayed peaks at 67 c.p.s. (1.12 p.p.m.) due to the C-19 methyl. The expected value for a 3-oxo-5α-steroid is 63 c.p.s., again showing the small effect of the 11,18 cycle. An AB

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quartet centered on 210 c.p.s. is again due to resonance at 205 c.p.s. (3.41 p.p.m.) and 215 c.p.s. (3.59 p.p.m.) with J = 8 c.p.s., arising from the C-18 protons. A doublet centered on 268 c.p.s. (4.46 p.p.m.) (J = 7 p.p.s., 11α-H) once more is formed, but, again, the upfield pair is obscured. Finally, a series of complex multiplets extending from 294 c.p.s. to 310 c.p.s. are due to the vinyl protons.

Hydroxylation of the 20-ene VIII with osmium tetroxide gave the 20, 21-glycol IX. Whereas the melting point of IX indicated that a single C-20 epimer had formed, conversion to the diacetate X gave a substance of broader melting range which showed IX to be a mixture of C-20 epimers. Nevertheless, the purified products from subsequent operations did appear to be stereochemically homogeneous, and it is assumed that the osmium tetroxide reaction gave one epimer predominantly. Although a rigid proof of the configuration of the major hydroxylation product was not carried out, it is reasonable to consider IX to be mainly the 20α-epimer. Thus, reduction of C-20 ketones by lithium aluminum hydride affords the most hindered, or 20β-, alcohol,[22] owing to attack of the bulky hydride moiety on the least hindered side of the complexed carbonyl function.[23] The disposition in space of a C-20 ketone side chain and a 20,21-olefin are similar, and the steric requirements of the osmate ester and a 20-alcohol are qualitatively the same as well. Accordingly, formation of a bulky osmate ester in the hydroxylation of a 20,21-olefin should occur predominantly on the least hindered face of the double bond and give rise to the 20α,21-diol.

Because 3-oxo-5β-steroids more easily are converted into 3-oxo-Δ^4-steroids than are the corresponding 5α-steroids, the A/B *cis* derivatives, IIa, IIIa, IVa, VIa, VIIa, and VIIIa also were prepared. However, a single large scale osmylation of VIIIa gave almost none of the expected diol, apparently because the osmate ester failed to hydrolyze. Therefore, the subsequent steps were carried out on 5α-steroids. The methods of preparation of the A/B *cis* compounds were similar to those employed for the obtention of the corresponding A/B *trans* derivatives. However, IIa was prepared using sodium borohydride and subsequent alkaline hydrolysis rather than by the use of lithium aluminum hydride.

At this stage in the sequence, oxidation of the C-18 methylene group was required. Few methods are known for the oxidation of ethers to esters although chromic acid has been used occasionally for this purpose.[24,25] More recently, ruthenium tetroxide in carbon tetrachloride solution has been reported to be useful for this reaction.[26]

Under a variety of conditions, oxidation of 20,21-dihydroxy-11β,18-epoxy-5α-pregnan-3-one diacetate (X) with chromic acid, either in 95% acetic acid or acetone solution, gave only traces of lactone as shown by infrared examination of the crude reaction products. On the other hand, ruthenium tetroxide in carbon tetrachloride solution did oxidize X to afford the lactone XI in 30% yield (15% conversion). A portion of the lactone was strongly absorbed on the precipitated ruthenium dioxide, but was readily eluted with acetone. Unchanged X was easily separated from XI by virtue of the low solubility of the lactone in ethyl acetate.

Because of the relatively low yield of the lactone XI, it became desirable to test the subsequent steps of the reaction sequence using the 11β,18-epoxide X as a model compound. Accordingly, the improved methods of the Glaxo group[27] were utilized to introduce the 3-oxo-Δ^4 moiety into X. The resulting 20,21-dihydroxy 11β,18-epoxypregn-4-en-3-one diacetate XIII was hydrolyzed to afford the diol XV.

There remained now the problem of effecting a selective conversion of the C-20 hydroxyl function to a ketone. Acetylation has been used to block primary alcohol groups in the presence of secondary hydroxyl moieties for this purpose,[20] but the selectivity of the reaction is poor. Conversion of primary alcohols to triphenylmethyl ethers, a reaction well known in carbohydrate chemistry, has been used little in steroid transformations, although the trityl group has been employed to protect the cortisone side chain during epoxidation of the Δ^4 linkage.[28] Since chlorotriphenylmethane does not attack secondary alcohols under normal conditions, the use of this reagent to block the C-21 hydroxyl function was investigated.

Without isolation of intermediates, 20,21-dihydroxy-11β,18-epoxypregn-4-en-3-one (XV) was successively tritylated, oxidized, and cleaved to afford 21-hydroxy-11β,18-epoxypregn-4-ene-3,20-dione (XVIII). The *dl* form of this compound has been prepared by a different route.[29]

With the completion of the model experiments, the preparation of 3,20-dioxo-11β,21-dihydroxy pregn-4-en-18-oic acid 11,18 lactone (XIX) from the 20,21-diol diacetate XI was undertaken. Hydrolysis to the diol, tritylation, oxidation, and ether cleavage were carried out using the conditions already established to afford XIX which has been converted into aldosterone.[30] Compound XIX synthesized by this method was identical with a sample prepared by oxidation and hydrolysis[30] of aldosterone acetate.

Experimental

Melting points were taken in a Thomas-Hoover apparatus and are uncorrected. Rotations were determined in chloroform at 25° unless noted otherwise. We wish to thank the following members of the Analytical and Physical Chemistry Section of Smith Kline and French Laboratories: Mrs. Doris Rolston and staff for elemental analyses, Dr. Walter Thompson and staff for infrared and ultraviolet absorption spectra and X-ray diffraction patterns, and Dr. Walter Hamill and staff for rotations.

3β,11β-Dihydroxy-5α-conanine (II).—To a stirred, refluxing solution of 10 g. (0.263 mole) of lithium aluminum hydride in 400 ml. of tetrahydrofuran, a solution of 50 g. (0.129 mole) of 3β-acetoxy-11-oxo-5α-conanine (I)[10] in 500 ml. of tetrahydrofuran was added dropwise. After the addition had been completed, the mixture was stirred and refluxed for 1 hr., cooled in ice, and cautiously decomposed with 40 ml. of water. The resulting granular precipitate was removed by filtration and the filtrate

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was concentrated *in vacuo*. The residual oil was dissolved in methanol and precipitated with water to afford 38 g. (84%) of crystalline, solvated product, m.p. 100–103.5°. The analytical sample was obtained from aqueous acetone, m.p. 174–177°; $[\alpha]_D$ +70° (*c* 0.4).

Anal. Calcd. for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73. Found: C, 75.79; H, 10.75.

3α,11β-Dihydroxy-5β-conanine (IIa).—To a solution of 167 g. (0.43 mole) of 3α-acetoxy-11-oxo-5β-conanine[10] in 1500 ml. of methanol was added a solution of 70 g. of sodium borohydride in 350 ml. of water. The reaction mixture was cooled occasionally until it had moderated and was then refluxed for 16 hr. Potassium hydroxide (225 g.) was added to the cooled solution and refluxing was continued for 2 hr. The hot solution was filtered to remove a small amount of insoluble material, water was added until crystallization commenced, and the mixture was cooled. The product was collected and washed well with water yielding 115.9 g. (77%), m.p. 174–175°. The analytical sample was recrystallized from acetone–petroleum ether, m.p. 177.5–178.5°; $[\alpha]_D$ +81° (*c* 0.8).

Anal. Calcd. for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73. Found: C, 76.20; H, 10.79.

3β,11β-Dihydroxy-5α-conanine Methiodide (III).—A solution of 18.5 g. (0.0533 mole) of 3β,11β-dihydroxy-5α-conanine (II) and 25 ml. of methyl iodide in 100 ml. of benzene was heated under reflux for 2 hr., cooled, and diluted with ether. The crystalline precipitate was filtered and recrystallized from absolute ethanol to afford 21.6 g. (88%) of colorless needles, m.p. 269–271°. Recrystallization from absolute ethanol raised the melting point to 277–279°; $[\alpha]_D$ +47° (*c* 0.9 in methanol).

Anal. Calcd. for $C_{23}H_{40}INO_2$: C, 56.43; H, 8.24. Found: C, 56.14; H, 8.39.

3α,11β-Dihydroxy-5β-conanine Methiodide (IIIa).—3α,11β-Dihydroxy-5β-conanine (112 g.) was treated with methyl iodide as described for the 5α-isomer. The methiodide weighed 147 g. (93%) and decomposed at 265–266.5°. A sample for analysis was recrystallized from ethyl acetate–methanol, m.p. 269–270.5° dec.; $[\alpha]_D$ +29° (*c* 0.7 in methanol).

Anal. Calcd. for $C_{23}H_{40}INO_2$: C, 56.43; H, 8.24. Found: C, 56.55; H, 8.58.

3-Hydroxyconanine Methiodide.—A solution of 5 g. (0.015 mole) of 3-hydroxyconanine[1c] was quaternized in the same way as described for the preparation of III. After recrystallization from 2-propanol, there was obtained 6.3 g. (89%) of product, m.p. 256–262° dec. (lit.[15] m.p. 270° dec.); $[\alpha]^{25}_D$ +28° (*c* 0.5 in methanol).

Anal. Calcd. for $C_{23}H_{40}INO$: C, 58.34; H, 8.52. Found: C, 58.40; H, 9.04.

11β,18-Epoxy-20α-dimethylamino-5α-pregnan-3β-ol (IV). Method A.—Amberlite IRA-400 resin in the chloride form was washed with 10% sodium hydroxide solution until free of chloride ion (silver nitrate test). A solution of 17.7 g. (0.036 mole) of 3β,11β-dihydroxy-5α-conanine methiodide (III) in 300 ml. of methanol was passed through a column containing 100 g. of the hydroxide form of the resin. The column was washed with fresh methanol until the eluate became neutral. The total eluate was evaporated *in vacuo*, and the residue was heated at 170° under 20-mm. pressure for 10 min. until gas evolution ceased. The residue was recrystallized from methanol to afford 8.4 g. (64%) of colorless crystals, m.p. 180–183°. The analytical sample was obtained from methanol, m.p. 177–180°; $[\alpha]_D$ +74° (*c* 0.6).

Anal. Calcd. for $C_{23}H_{39}NO_2$: C, 76.40; H, 10.87; N, 3.87. Found: C, 76.44; H, 11.12; N, 4.03.

Method B.—A mixture of 2.0 g. of 3β,11β-dihydroxy-5α-conanine methiodide (III), 1.0 g. of potassium hydroxide, and 10 ml. of ethylene glycol was heated in an oil bath. As the temperature approached 100° a clear solution was obtained. The bath temperature was raised slowly to 150° and held there for 15 min. Water was added to the cooled mixture and the precipitated solid was extracted into methylene chloride. The organic layer was washed with water, dried, and evaporated to yield 1.23 g. (85%) of solid, m.p. 175–180°. Vapor phase chromatography of this material failed to show the presence of any isomeric 3β,11β-dihydroxy-18-dimethylamino-5α-pregn-20-ene (V) (see next paragraph). Only one peak, with the retention time of IV, prepared by method A, was observed whereas artificially prepared mixtures of IV and V were clearly separable on the same column. Recrystallization of the initially obtained solid gave 1.1 g. of IV, m.p. 176–180°, identical with material prepared under method A by mixture melting point and comparison of infrared spectra.

3β,11β-Dihydroxy-18-dimethylamino-5α-pregn-20-ene (V). Method A.—The methanol mother liquor from the recrystallization of IV (method A) was evaporated to dryness and the residue was dissolved in 75 ml. of benzene. The benzene solution was treated with 6 ml. of methyl iodide and heated under reflux for 2 hr. The resulting suspension was filtered to give 1.7 g. of salt which was not investigated further. Evaporation of the filtrate and recrystallization of the residue from acetone afforded 1.8 g. (14%) of product, m.p. 168–174°. Further recrystallization from acetone gave long colorless needles, m.p. 184–186°; $[\alpha]_D$ −3° (*c* 2).

Anal. Calcd. for $C_{23}H_{39}NO_2$: C, 76.40; H, 10.87. Found: C, 76.19; H, 10.97.

Method B.—A solution of 100 mg. of 3β-hydroxy-18-dimethylamino-5α-pregn-20-en-11-one[10] in 2 ml. of tetrahydrofuran was added to 50 mg. of lithium aluminum hydride in 2 ml. of tetrahydrofuran and refluxed for 1 hr. The reaction mixture was hydrolyzed with a few drops of water, filtered, and the solvent was evaporated. The residual solid was recrystallized from acetone to give 80 mg. of needles, m.p. 184–186°. Identity with material obtained from the Hofmann degradation (method A) was demonstrated by comparison of infrared spectra and X-ray diffraction patterns.

11β,18-Epoxy-20α-dimethylamino-5α-pregnan-3β-ol Acetate.—A solution of 8.4 g. (0.023 mole) of IV in 40 ml. of pyridine was allowed to react with 25 ml. of acetic anhydride during 18 hr. and then treated with several milliliters of water. The mixture was poured into 600 ml. of water, made alkaline with sodium hydroxide solution, and filtered. The resulting solid was recrystallized from absolute alcohol to afford 7.8 g. (86%) of colorless crystals, m.p. 229–235°. The analytical sample, obtained from another run, was recrystallized from acetone, m.p. 224–231°.

Anal. Calcd. for $C_{25}H_{41}NO_3$: C, 74.40; H, 10.24. Found: C, 74.62; H, 10.46.

11β,18-Epoxy-20α-dimethylamino-5β-pregnan-3α-ol (IVa).—A solution of 145 g. (0.30 mole) of 3α,11β-dihydroxy-5β-conanine methiodide (IIIa) in 1200 ml. of methanol was passed through a column of IRA 400 resin in the hydroxide form. The column was eluted with methanol until the eluate was neutral. The methanol solution was evaporated and the residue heated *in vacuo* to 180° (bath temperature) and held at that temperature for 20 min. until the solid had liquefied. The product solidified on cooling and after recrystallization from acetone weighed 72.2 g. (67%), m.p. 159–163.5°. Another recrystallization from acetone raised the m.p. to 163.5–167.5°; $[\alpha]_D$ +53 (*c* 1.0).

Anal. Calcd. for $C_{23}H_{39}NO_2$: C, 76.40; H, 10.87. Found: C, 76.29; H, 10.89.

11β,18-Epoxy-20α-dimethylamino-5β-pregnan-3α-ol Acetate.—The product was obtained from IVa by the same procedure as described for the corresponding 5α-compound and gave colorless needles from absolute alcohol, m.p. 186–190°; $[\alpha]_D$ +81° (*c* 3).

Anal. Calcd. for $C_{25}H_{41}NO_3$: C, 74.40; H, 10.24. Found: C, 74.23; H, 10.36.

3β-Hydroxy-18-dimethylamino-5α-pregn-20-ene.—This compound was obtained from 3β-hydroxyconanine methiodide by heating the hydroxide as described for the preparation of IV. The product formed colorless needles, m.p. 156–157° (lit.[15] m.p. 157°) upon recrystallization from methanol; $[\alpha]_D$ +29° (*c* 1.0).

Anal. Calcd. for $C_{23}H_{39}NO$: C, 79.94; H, 11.38. Found: C, 80.03; H, 11.69.

11β,18-Epoxy-20α-dimethylamino-5α-pregnan-3β-ol Methiodide (VI).—A solution of 7.9 g. (0.022 mole) of IV and 44 ml. of methyl iodide in 440 ml. of acetonitrile was heated under reflux for 18 hr. The solvents were removed *in vacuo* and the residue was recrystallized from methanol to furnish a total of 8.8 g. (80%) of colorless crystals, m.p. 264° dec.; $[\alpha]_D$ +25° (*c* 0.9 in methanol).

Anal. Calcd. for $C_{24}H_{42}INO_2$: C, 57.25; H, 8.41. Found: C, 57.04; H, 8.81.

11β,18-Epoxy-20α-dimethylamino-5β-pregnan-3α-ol Methiodide (VIa).—A solution of 70.2 g. (0.19 mole) of IVa and 435 ml. of methyl iodide in 1800 ml. of acetonitrile was heated under reflux for 18 hr. A portion of the solvent was evaporated until crystals began to form. On cooling, 53 g. of methiodide was obtained, m.p. 224° with decomposition when inserted at 215°. Further evaporation of the filtrate gave a second crop also decomposing at 224°, wt. 44 g., for a nearly quantitative yield. A sample was recrystallized from acetone–methanol, m.p. 228° dec.

Anal. Calcd. for $C_{24}H_{42}NO_2I \cdot 0.5\ CH_3OH$: C, 56.64; H, 8.53. Found: C, 56.59; H, 8.57.

11β,18-Epoxy-5α-pregn-20-en-3β-ol (VII).—A mixture of 10 g. (0.02 mole) of VI, 10 g. of sodium methoxide, and 100 ml. of dimethylformamide was heated with a free flame until gas evolution was substantially ended, and was then kept at 95° for 30 min. The mixture was poured into 100 ml. of water and the precipitated product was collected and dried to furnish 6.0 g. (96%) of colorless solid, m.p. 144–145°. The analytical sample was obtained from ligroin, m.p. 145–146°; $[\alpha]_D$ +45° (*c* 0.3).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.65; H, 10.13.

11β,18-Epoxy-5β-pregn-20-en-3α-ol (VIIa).—Fifty-one grams (0.10 mole) of VIa, 52 g. of sodium methoxide, and 500 ml. of dimethylformamide were treated as described for VII. The dried product was recrystallized from acetone–hexane to afford 27.8 g. (87%) of needles, m.p. 137–138°. The analytical sample was recrystallized again from acetone–hexane, m.p. 137–138.5°; $[\alpha]_D$ +58° (*c* 0.5).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.49; H, 10.25.

11β,18-Epoxy-5α-pregn-20-en-3-one (VIII).—A stirred solution of 28.5 g. (0.09 mole) of 11β,18-epoxy-5α-pregn-20-en-3β-ol (VII) in 1300 ml. of acetone was treated dropwise with 25 ml. of 8 *N* chromic acid solution. Following the addition of several milliliters of methanol, the reaction mixture was poured into water, and the product was collected and dried to furnish 26.7 g. (94%) of colorless crystals, m.p. 164–167°. A sample was recrystallized from acetone, m.p. 169–171°; $[\alpha]$ +77° (*c* 0.3).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.98; H, 9.61.

11β,18-Epoxy-5β-pregn-20-en-3-one (VIIIa).—A solution of 24.5 g. (0.077 mole) of 11β,18-epoxy-5β-pregn-20-en-3α-ol (VIIa) in 600 ml. of acetone was treated with 21.3 ml. of 8 *N* chromic acid solution at 27°, and the excess oxidizing agent was destroyed with methanol. The reaction mixture was poured into water and the precipitated solid was removed by filtration and dried to afford 22.6 g. (94%) of product, m.p. 103–105°. The analytical sample was obtained from hexane as colorless crystals, m.p. 103–105°; $[\alpha]_D$ +57° (*c* 3.0).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.34; H, 9.89.

20,21-Dihydroxy-11β,18-epoxy-5α-pregnan-3-one (IX).—A solution of 27 g. (0.086 mole) of VIII and 23 g. (0.09 mole) of osmium tetroxide in 1700 ml. of ether was kept at 27° for 72 hr. The clear supernatant liquid was decanted and to the black osmate ester was added a solution of 154 g. of sodium sulfite in a mixture of 980 ml. of ethanol and 670 ml. of water. The suspension was heated under reflux for 4 hr. and filtered while still hot. The filter cake was washed thoroughly with hot alcohol, and the combined filtrates were freed of alcohol by concentration *in vacuo*. The residual suspension was extracted with methylene chloride and the combined extracts were washed with water, dried over sodium sulfate, filtered, and evaporated. The residue was recrystallized from ethyl acetate to furnish 18.9 g. (63%) of colorless crystals, m.p. 205–216°. The analytical sample had m.p. 212–215°; $[\alpha]$ +89° (*c* 0.4).

Anal. Calcd. for $C_{21}H_{32}O_4 \cdot 0.5H_2O$: C, 70.55; H, 9.31. Found: C, 70.78; H, 9.46.

20,21-Dihydroxy-11β,18-epoxy-5α-pregnan-3-one Diacetate (X).—A solution of 10 g. (0.029 mole) of IX in a mixture of 20 ml. of acetic anhydride and 20 ml. of pyridine was heated under reflux for 30 min., cooled, and cautiously decomposed with 10 ml. of water. The mixture was poured into 400 ml. of water and the precipitated product was extracted into methylene chloride. The organic layer was washed successively with 5% hydrochloric acid, 5% sodium bicarbonate solution, and water, dried, filtered, and evaporated *in vacuo*. The residue was recrystallized from 80% methanol to afford 10.8 g. (87%) of colorless crystals, m.p. 140–155°. The melting point range indicates that this material is a mixture of C-20 epimers.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.22; H, 8.35.

From the mother liquors a higher melting substance was isolated and recrystallized from methanol, m.p. 171–173°. The spectrum and analysis of this material were the same as the m.p. 140–155° material, and it is evidently a single C-20 epimer; $[\alpha]_D$ +72° (*c* 0.4).

Anal. Found: C, 69.25; H, 8.66.

3-Oxo-11β,20,21-trihydroxy-5α-pregnan-18-oic Acid 11,18-Lactone 20,21-Diacetate (XI).—A solution of 13.1 g. (0.03 mole) of X in 500 ml. of carbon tetrachloride was allowed to react during 72 hr. with ruthenium tetroxide obtained from 40 g. of commercial ruthenium trichloride.[26] Ether was added to destroy excess oxidizing agent and the suspension was filtered. The filtrate was evaporated to afford 4.2 g. of a solid, m.p. *ca.* 140°, which was largely starting material. The ruthenium dioxide was extracted with 1 l. of boiling acetone and the filtered extract was evaporated. There was obtained 3.9 g. of crystals (42% based on unrecovered starting material), m.p. 200°. Recrystallization from ethyl acetate afforded colorless crystals, m.p. 242–246°; $[\alpha]_D$ +51° (*c* 2.0); λ_{max}^{Nujol} 5.65 (lactone), 5.75 (ester), 5.85 μ (ketone).

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.18; H, 7.88.

3-Oxo-11β,20,21-trihydroxy-5α-pregnan-18-oic Acid 11,18-Lactone (XII).—A mixture of 223 mg. (0.5 mmole) of XI, 45 ml. of methanol, and 6 ml. of 0.5 *N* potassium bicarbonate solution was heated under reflux in a nitrogen atmosphere for 1 hr. Most of the solvents were removed *in vacuo* and the product was extracted into methylene chloride. The washed, dried organic phase was evaporated, and the residue was recrystallized from ethyl acetate to afford colorless crystals of the diol, m.p. 195–197°; $[\alpha]^{25}_D$ +85° (*c* 1.4).

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.55; H, 8.47.

3-Oxo-11β,20,21-trihydroxy-pregn-4-en-18-oic Acid 11,18-Lactone 20,21-Diacetate (XIV).—A stirred solution of 10.15 g. (0.023 mole) of 3-oxo-11β,20,21-trihydroxy-5α-pregnan-18-oic acid 11,18 lactone 20,21-diacetate (XI) was acidified with 3.68 g. (0.046 mole) of hydrogen bromide in 13.8 ml. of acetic acid and then treated dropwise during 4 min. at 16° with 7.65 g. (0.048 mole) of bromine in 25 ml. of acetic acid. The solution was stirred for 16 min. at ambient temperature and poured into water. The precipitated solid was extracted into methylene chloride, and the extract was washed successively with water, 5% sodium bicarbonate solution, and water, dried, and evaporated *in vacuo*. The residual glassy 2,4-dibromo ketone showed λ_{max}^{Nujol} 5.65 (lactone), 5.75 μ (ester and 2,4-dibromo ketone).

To 100 ml. of stirred acetone there was added 10 g. of bromine, and when the solution became colorless 9.7 g. of sodium carbonate was added. After the solution became neutral it was filtered and diluted with acetone in a volumetric flask. An aliquot corresponding to 7.65 g. (0.056 mole) of bromoacetone was added to 250 ml. of hot acetone containing 68.5 g. (0.46 mole) of sodium iodide and the mixture was heated under reflux for 10 min. The crude 2,4-dibromo steroid dissolved in a small amount of acetone was then added, and the dark mixture was stirred and refluxed for 2.5 hr. when 12.6 g. (0.1 mole) of oxalic acid dihydrate was added and refluxing was continued for an additional hour.

The mixture was cooled, diluted with ethyl acetate, and filtered. The filtrate was washed with water, 5% sodium bicarbonate solution, and again with water. The washed extract was stirred with 32 g. of zinc dust and 18 ml. of glacial acetic acid until the iodine color was discharged and then filtered and washed again in the same way. The dried (sodium sulfate), filtered extract was evaporated *in vacuo* to afford 11.1 g. of crystalline solid, m.p. 175–180°; λ_{max}^{EtOH} 238 mμ (ε 12,400).

A solution of 10.4 g. of the crude compound was heated under reflux during 30 min. with 5.2 g. of Girard's reagent "T" in 150 ml. of absolute alcohol containing 5% glacial acetic acid. The cooled solution was treated with 20 ml. of formalin, kept at ambient temperature for 25 min. and poured into 1.5 l. of 1% sodium bicarbonate solution. The solution was extracted with three 150-ml. portions of ethyl acetate, and the aqueous layer was acidified to pH 1 with concentrated hydrochloric acid. It was set aside for 1 hr. and then extracted with ethyl acetate. The organic layer was washed with 5% sodium bicarbonate solution and then water, and finally dried (sodium sulfate) and evaporated *in vacuo*. There was obtained 6.2 g. (61%) of crystalline product, m.p. 175–185°; λ_{max}^{EtOH} 238 mμ (ε 17,000). A sample recrystallized from ethyl acetate had the same ultraviolet spectrum; m.p. 197–201°; λ_{max}^{Nujol} 5.65 (lactone), 5.75 (ester), 6.0 (C=O), 6.2 μ (C=C); $[\alpha]_D$ +123° (*c* 1.8).

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.47; H, 7.48.

20,21-Dihydroxy-11β,18-epoxy-pregn-4-en-3-one Diacetate (XIII).—This compound was prepared from X by the method described for the preparation of XIV. It formed colorless needles from methanol, m.p. 151–152°; $[\alpha]_D$ +139° (*c* 2.7).

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.71; H, 8.05.

20, 21-Dihydroxy-11β,18-pregn-4-en-3-one (XV).—A solution

of 680 mg. of 20,21-diacetate XIII in 25 ml. of methanol was treated with a solution of 680 mg. of potassium carbonate and 1.00 g. of potassium bicarbonate in 11 ml. of water at 50°, and enough water was added to make a clear solution. The hydrolysis was allowed to proceed at 27° for 18 hr., and the mixture was evaporated nearly to dryness *in vacuo*. The residue was partitioned between water and methylene chloride, and the washed, dried organic layer was evaporated. The residue was recrystallized from absolute alcohol to afford 451 mg. of colorless plates, m.p. 226–228°; $[\alpha]_D$ +178° (*c* 0.4).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.64; H, 9.12.

21-Hydroxy-11β,18-epoxy-pregn-4-ene-3,20-dione (XVIII).—A solution of 830 mg. (2.4 mmoles) of 20,21-dihydroxy-11β,18-epoxy-pregn-4-en-3-one (XV) in 15 ml. of pyridine was allowed to react with 700 mg. (2.5 mmoles) of chlorotriphenylmethane at 27° for 70 hr. and then at 95° for an additional 2 hr. After the addition of 2 ml. of water, the mixture was poured into water and the precipitated product was extracted into chloroform. The chloroform was washed successively with cold 20% sulfuric acid, 5% sodium bicarbonate solution, and water, and then dried, filtered, and evaporated.

The residue was dissolved in 2.5 ml. of acetone, treated with excess 8 *N* chromic acid solution, and kept at 27° for 10 min. The excess oxidant was destroyed by addition of 2-propanol and the mixture was poured into water. The product was extracted into chloroform, and the organic layer was washed with water, and then dried and evaporated.

The residue was dissolved in 50 ml. of 80% acetic acid and heated under reflux for 30 min. The mixture was poured into 500 ml. of water, and the precipitated triphenylcarbinol was removed by filtration. The filtrate was saturated with sodium chloride and extracted with chloroform until the extracts were transparent at 6.0 μ. The combined extracts were washed with a little water, dried, filtered, and evaporated. The residue formed colorless needles from ethyl acetate, m.p. 159–160°; λ_{max}^{EtOH} 240 mμ; λ_{max}^{Nujol} 2.9, 5.85, 6.0, 6.2 μ; $[\alpha]_D$ +135° (*c* 0.65).

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 73.13; H, 8.16.

3-Oxo-11β,20,21-trihydroxypregn-4-en-18-oic Acid 11,18-Lactone (XVI).—To a solution of 150 mg. of 20,21-diacetate XIV in 6 ml. of methanol there was added a solution of 150 mg. of potassium carbonate and 220 mg. of potassium bicarbonate in 2.2 ml. of water, and the resulting turbid mixture was treated with enough water to clarify it. The solution was kept at 27° for 18 hr. and evaporated *in vacuo* at 27°. The residue was taken up in water and chloroform, the layers were separated, and the chloroform layer was washed with water and dried. The filtered solution was evaporated and the residue was recrystallized twice from ethyl acetate to afford colorless crystals, m.p. 149–151°; $[\alpha]_D$ +170° (*c* 2.8).

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.71; H, 7.85.

3-Oxo-11β,20-dihydroxy-21-triphenylmethoxypregn-4-en-18-oic Acid 11,18-Lactone (XVII).—A solution of 6.1 g. (0.014 mole) of XIV in a mixture of 1200 ml. of methanol and 158 ml. (0.079 mole) of 0.5 *N* potassium bicarbonate solution was heated under reflux for 30 min. in a nitrogen atmosphere. There was added 500 ml. of water, and the solution was concentrated *in vacuo* to a slurry which was extracted with methylene chloride. The organic layer was washed with water, dried, and evaporated.

A solution of 4.2 g. (0.012 mole) of the crude diol in 200 ml. of pyridine was allowed to react with 3.62 g. (0.013 mole) of chlorotriphenylmethane during 72 hr. After the addition of 5 ml. of water, the pyridine was removed *in vacuo* and the residue was dissolved in methylene chloride. The solution was washed successively with 10% sulfuric acid, water, 5% sodium bicarbonate solution, and water, and then dried, filtered, and evaporated. The residue was recrystallized from methanol to afford 2.1 g. (30%) of product, m.p. 225–229°. The filtrate was evaporated to give a mixture of the diol and triphenylcarbinol which was used in another preparation. The analytical sample was obtained from methanol, m.p. 225–229°; $[\alpha]_D$ 104° (*c* 2.5); λ_{max}^{KBr} 5.65 (lactone), 6.0 (ketone), 6.2 μ (C=C), and phenyl bands.

Anal. Calcd. for $C_{40}H_{42}O_5 \cdot 0.5H_2O$: C, 78.53; H, 7.09. Found: C, 78.24; H, 7.09.

3,20-Dioxo-11β,21-dihydroxypregn-4-en-18-oic Acid 11,18-Lactone (XIX).—A solution of 1.47 g. of 3-oxo-11β,20-dihydroxy-21-triphenylmethoxypregn-4-en-18-oic acid 11,18-lactone (XVII) in 175 ml. of acetone was allowed to react with excess 8 *N* chromic acid solution during 15 min. The excess oxidant was destroyed with 2-propanol and the solution was poured into water. The product was isolated by extraction with methylene chloride and evaporation of the solvent.

Ninety milliliters of 80% acetic acid was added to the oxidized material. The solution was refluxed for 30 min., diluted with 600 ml. of water, and cooled. Precipitated triphenylcarbinol was removed by filtration and the filtrate was saturated with salt and thoroughly extracted with chloroform. The chloroform extracts were washed with 5% sodium bicarbonate, water, and then dried and evaporated. The crystalline residue was recrystallized from ethyl acetate to afford colorless needles, m.p. 211–220° (lit. m.p. 212–216°[2] and 216–223°[30]); λ_{max}^{KBr} 5.65, 5.85, 6.0, and 6.2 μ; $[\alpha]_D$ +183° (*c* 2.1) (lit.[2] +180°).

Anal. Calcd. for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 69.96; H, 7.25.

Aldosterone 21-acetate was oxidized to the 11,18-lactone, and the acetoxy group was hydrolyzed as described[30] to give compound XIX, m.p. 210–216°. Identity of this material with that prepared as previously described was shown by comparison of infrared spectra and X-ray diffraction patterns.