mixture of dibasic acids from the 15-min. run and 1.2 g. from the 90-min. run.

Chromatographic separation. A column was prepared similar to that of Marvel and Rands[4] with some modification. A 25-g. portion of dry silicic acid was thoroughly mixed in a mortar with 13 ml. of water and 1 ml. of 0.02% aqueous bromocresol green indicator. Two drops of concentrated ammonium hydroxide were added to impart a green color to the column. The mixture was slurried with 100 ml. of chloroform and packed into a chromatographic tube (23 mm. O.D. × 600 mm. long). Five pounds pressure of nitrogen was applied to the top throughout the packing and elution of the column. From each run, duplicate samples of the mixed dibasic acids (*ca.* 52 mg., weighed accurately) dissolved in 0.25 ml. of *t*-amyl alcohol and diluted to 2.5 ml. with chloroform, were added to separate columns and each washed down with 5 ml. of chloroform. The columns were eluted with 100-ml. portions of 1, 2, 3, 4, 5, 7½, 10, 20, 30, and 40% of *n*-butyl alcohol in chloroform. The percolate was collected in 10-ml. fractions, diluted with 20 ml. of absolute ethanol, and titrated with 0.0254*N* sodium hydroxide solution to the end point of *m*-cresol purple indicator. In all the runs four major peaks were encountered which were identified as suberic, pimelic, adipic, and glutaric acids by chromatographing a sample of the mixed dibasic acids to which known quantities of pure suberic, pimelic, adipic, and glutaric acids had been added. In addition there also appeared two small peaks at the beginning of the chromatograms from the 90-min. run, and the nature of the elution curves indicated these to be azelaic and sebacic acids. The mixture of the dibasic acids obtained from the 15-min. run consisted of 11.2 mole % glutaric, 35.6 mole % adipic, 34.0 mole % pimelic, and 19.2 mole % suberic acids, while the dibasic acids from the 90-min. run consisted of 19.2 mole % glutaric, 25.1 mole % adipic, 25.7 mole % pimelic, 18.9 mole % suberic, 6.8 mole % azelaic, and 4.3 mole % sebacic acids. The recovery of the dibasic acids during the elution process was nearly 100% of the amount introduced on the column.

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NEW ORLEANS, LA.

[CONTRIBUTION FROM THE NATURAL PRODUCTS RESEARCH DEPARTMENT OF SCHERING CORPORATION]

Halogenated Progesterones. II.[1] 17α-Oxygenated 9α,11β-Dihaloprogesterones

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The synthesis of some 9α,11β-dichloro-, 9α-chloro-11β-fluoro-, 9α-bromo-11β-fluoro- and 9α-bromo-11β-chloro-17α-acyloxyprogesterones is described. Some of these compounds show progestational activity when tested in rabbits.

Recent research on the synthesis of active progestational compounds has concentrated to a large extent on the preparation of various analogs of 17α-acetoxyprogesterone[2] in view of the enhanced and particularly the oral activity of the latter.[3]

Among derivatives of 17α-acetoxyprogesterone which have been reported are included 6α-methyl-17α-acetoxyprogesterone[4] and the corresponding 1-dehydro, 6-dehydro and 1,6-bisdehydro analogs,[4c] 6α - fluoro - 17α - acetoxyprogesterone[5] and the corresponding 1-dehydro, 6-dehydro and 1,6-bisdehydro analogs,[5b] 6α-chloro-17α-acetoxyprogesterone[6] and the corresponding 1-dehydro, 6-dehydro and 1,6-bisdehydro analogs,[6] 6α-bromo- and 1 - dehydro - 6α - bromo - 17α - acetoxyprogesterone,[6] 21 - fluoro - 17α - acetoxyprogesterone,[7] and the corresponding 6α - methyl[7] and 6 - dehydro-6-methyl[8] analogs, 21-chloro-,[7] 21-chloro-6α-methyl-[7], 21-bromo-,[7] 21-iodo-,[7] 6α-cyano-[9] 6α-nitro-[10], 1-dehydro-[6,11], 11β-acetoxy-[12], 9α-bromo-11β-hydroxy-[13] and 9α-fluoro-11-oxygenated-17α-acetoxyprogesterone[13].

In contrast to 17α-acetoxyprogesterone, 17α-hydroxyprogesterone caproate[3] is orally inactive

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but has found use as a long-acting injectable progestin,[14] and some analogs, such as the 1-dehydro[11] and 6α-chloro[6] derivatives have been prepared.

A new class of progestins, 9α,11β-dihaloprogesterones, has recently been reported from these laboratories.[1] In view of the biological activity of these compounds it was of interest to prepare the corresponding 17α-oxygenated analogs.

The requisite intermediate 17α-hydroxy-9(11)-dehydroprogesterone (III)[15] was prepared starting with 4-pregnene-11α,17α,21-triol-3,20-dione (I).[16] Compound I was converted to the 11α,21-ditoluenesulfonate Ia which was not purified but converted directly to 4-pregnene-11α,17α-diol-3,20-dione 11α-*p*-toluenesulfonate (II) by heating with excess sodium iodide in acetone and reducing the resulting 21-iodide *in situ* by the addition of acetic acid.[17] Solvolysis of II in acetic acid in the presence of sodium acetate[18] gave III.

Compound III was readily esterified with acetic acid in the presence of trifluoroacetic anhydride[19] to give 17α-acetoxy-9(11)-dehydroprogesterone (IV).[20]

Addition of chlorine, chlorine fluoride, bromine fluoride and bromine chloride, the latter three generated *in situ*, to IV resulted in the formation, respectively, of 9α,11β-dichloro-17α-acetoxyprogesterone (VII), 9α-chloro-11β-fluoro-17α-acetoxyprogesterone (VI), 9α-bromo-11β-fluoro-17α-acetoxyprogesterone (VIII), and 9α-bromo-11β-chloro-17α-acetoxyprogesterone (IX).[21] While most of the addition reactions proceeded quite rapidly the addition of chlorine fluoride, using *N*-chlorosuccinimide and hydrogen fluoride in the presence of pyridine, proved to be very sluggish and required about seven days reaction time to reach completion.[22] Compounds VII and IX were readily reconverted to IV with chromous chloride solution.[23]

Saponification of VII with methanolic potassium hydroxide furnished 9α,11β-dichloro-17α-hydroxyprogesterone (XI), which could be esterified with caproic acid in the presence of trifluoroacetic anhydride[19] to give 9α,11β-dichloro-17α-hydroxyprogesterone caproate (X). That no rearrangement had taken place during saponification was shown by conversion of XI to III by treatment with chromous chloride. The dichloro caproate X could also be prepared by esterification of III with caproic acid to give 9(11)-dehydro-17α-hydroxyprogesterone caproate (V) and chlorination of the latter with chlorine in the presence of pyridine.[1]

The 1-dehydro analog of compound VII, 1-dehydro - 9α,11β - dichloro - 17α - acetoxyprogesterone (XVII) was prepared by a reaction sequence starting with 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (XIIa).[24]

Thus the 21-hydroxy compound XIIb, obtained by hydrolysis of XIIa with perchloric acid in methanol,[25] was treated with methanesulfonyl chloride in pyridine to furnish 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-methanesulfonate (XIIe) which was converted to the 21-iodide and the latter reduced *in situ* to give 1,4,9(11)-pregnatrien-17α-ol-3,20-dione (XIII).

Attempts to esterify XIII to the 17-acetate led to an unexpected transformation involving aromatization of the A-ring[26]; therefore XIII was chlorinated directly to furnish 9α,11β-dichloro-1,4-pregnadiene-17α-ol-3,20-dione (XIV). This compound was also prepared from 9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione (XV)[27] *via* the 21-methansulfonate (XVI)[28] and reduction of the latter as described above. The dichloro alcohol XIV could be readily converted to 1-dehydro-9α,-11β-dichloro-17α-acetoxyprogesterone (XVII) by esterification in the usual manner.

The molecular rotations and ultraviolet maxima of the 9α,11β-dihalo-17α-acyloxyprogesterones described in this paper are listed in Table I. As observed previously[1] the presence of an 11β-fluoro substituent results in a markedly lowered molecular rotation in comparison with analogous compounds bearing other 11β-substituents.

As expected, most of the dihaloprogesterones reported here show enhanced progestational activity in rabbits in comparison with the nonhalogenated compounds.[29]

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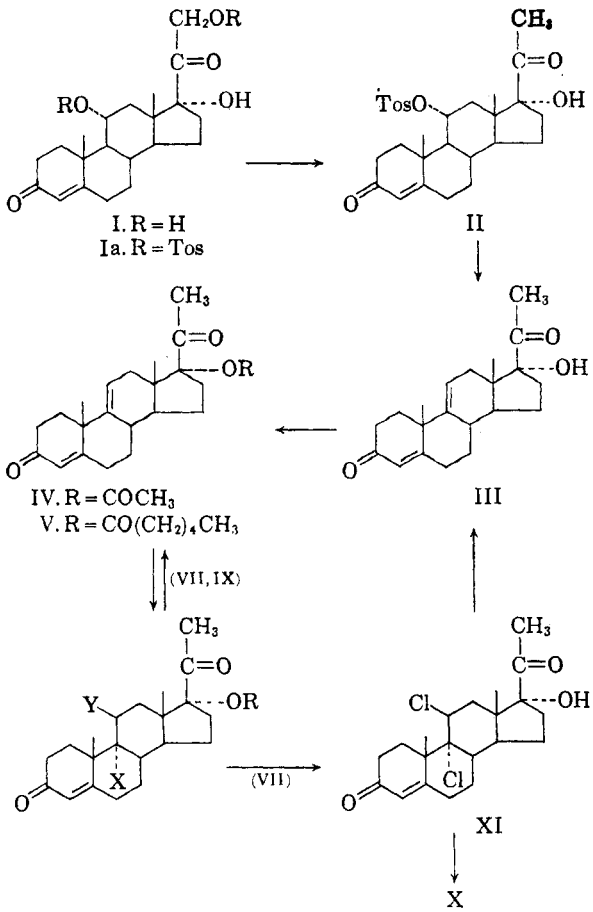
(28) This compound was first prepared by Dr. C. H. Robinson of these laboratories.

(29) We wish to thank Dr. M. Eisler and Mr. R. Neri of the Biochemistry Department of Schering Corp. for the biological testing. A full description of their findings will be published elsewhere.

Recently, it has been reported that in the case of 6α-substituted progesterones 1,2-dehydrogenation enhances the activity considerably.[4c,5b,6] It is therefore of interest that among progesterones unsubstituted at C-6 the 1-dehydro analogs show a lower activity than the parent steroid. This has been observed with 1-dehydro-17α-hydroxyprogesterone acetate and caproate,[11] and is also the case for 1-dehydroprogesterone.[30] In our series 1-dehydro-9α,11β-dichloroprogesterone shows one half the activity of 9α,11β-dichloroprogesterone[1] and similarly XVII has about one half the activity of VII, measured parenterally in rabbits.[30a]



	R	X	Y
VI.	$COCH_3$	Cl	F
VII.	$COCH_3$	Cl	Cl
VIII.	$COCH_3$	Br	F
IX.	$COCH_3$	Br	Cl
X.	$CO(CH_2)_4CH_3$	Cl	Cl

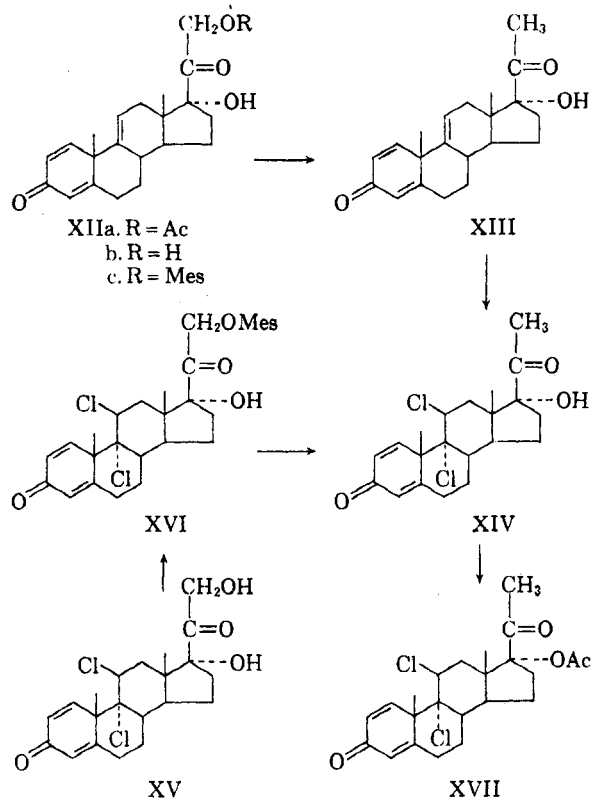


TABLE I

MOLECULAR ROTATIONS AND ULTRAVIOLET ABSORPTION MAXIMA OF 9α,11β-DIHALO-17α-HYDROXYPROGESTERONE ESTERS

Compound	Substituent 9α	Substituent 11β	MD(CHCl₃)	$\lambda_{max}^{CH_3OH}$ mμ
VI[a]	Cl	F	362	238
VII[a]	Cl	Cl	609	239
VIII[a]	Br	F	380	240
IX[a]	Br	Cl	690	242
X[b]	Cl	Cl	533	238
XVII[c]	Cl	Cl	496	238

[a] 17-Acetate. [b] 17-Caproate. [c] 1-Dehydro 17-acetate.

(30) Unpublished work of these laboratories.

EXPERIMENTAL[31]

4-Pregnene-11α,17α-diol-3,20-dione 11α-p-toluenesulfonate (II). To a solution of 20 g. of 4-pregnene-11α,17α,21-triol-3,20-dione in 200 ml. of dry pyridine at −70° was added with stirring a solution of 24 g. of *p*-toluenesulfonyl chloride in 120 ml. of methylene chloride. The mixture was stirred at −70° for 2 hr., then at about −20° for 70 hr. It was then diluted with methylene chloride and washed with water, 10% aqueous sulfuric acid, 10% sodium bicarbonate solution and water, and concentrated to an oil under reduced pressure.

The crude oily ditosylate was dissolved in 200 ml. of acetone, a solution of 24 g. of sodium iodide in hot acetone was added and the mixture heated on the steam bath for about 5 min. To the resulting suspension, 10 ml. of acetic

(30a) NOTE ADDED IN PROOF: After this paper was submitted for publication the synthesis of compound VIII was reported by C. G. Bergstrom and R. T. Nicholson, *J. Org. Chem.*, 25, 1263 (1960).

(31) Melting points were determined on the Kofler block. Rotations were measured at 25° in chloroform at about 1% concentration unless otherwise noted. Rotational and spectral data were obtained by the Physical Chemistry Department, Schering Corp.; we are indebted to Mr. R. Wayne for interpretation of infrared spectra. Microanalyses were performed by Mr. E. Conner and staff (Microanalytical Laboratory, Schering Corp.), Galbraith Laboratories, Knoxville, Tenn., and the Schwarzkopf Microanalytical Laboratory, Woodside, L. I.

acid was added and the mixture was heated for an additional 5 min. Sufficient aqueous sodium bisulfite solution was added with stirring to discharge the iodine color. The pale yellow suspension was poured into ice water and the resulting precipitate was filtered, washed, and dried to give 15.5 g. of crude II. Crystallization from acetone-hexane, after treatment with decolorizing carbon, afforded 10.0 g. of II, m.p. 132–139° dec. The analytical sample was recrystallized twice from acetone-hexane, m.p. 140–144° dec. $[\alpha]_D$ +52°, $\lambda_{max}^{CH_3OH}$ 229 mμ (ε 23,000), λ_{max}^{nujol} 2.94, 5.86, 5.98, 6.04, 6.18, 6.26, 8.50 μ.

Anal. Calcd. for $C_{28}H_{36}O_6S$: C, 67.18; H, 7.25; S, 6.39. Found: C, 66.58; H, 7.14; S, 6.84.

4,9(11)-Pregnadiene-17α-ol-3,20-dione (III). To a solution of 3.4 g. of anhydrous sodium acetate in 30 ml. of glacial acetic acid, heated to about 110°, was added 2.30 g. of II and the mixture heated under reflux for 35 min. It was then cooled, diluted with acetic acid and water, and the resulting crystalline precipitate was filtered, washed, and dried to give 1.27 g. of crude III, m.p. 205–210°. The analytical sample was crystallized from acetone-ether and acetone, m.p. 212–217°, $[\alpha]_D$ +69°, $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 16,800), λ_{max}^{nujol} 2.92, 5.86, 6.02, 6.18 μ. (Reported[15]: m.p. 214–216°, $[\alpha]_D$ +67°.)

4,9(11)-Pregnadiene-17α-ol-3,20-dione acetate (IV). A solution of 990 mg. of III in 10 ml. of glacial acetic acid and 2 ml. of trifluoroacetic anhydride was heated on the steam bath for 50 min., then cooled, and poured into ice water. The resulting precipitate was filtered, washed, and dried to give 1.067 g. of crude IV. Crystallization from acetone-ether afforded 636 mg., m.p. 231–239°. The analytical sample was recrystallized from acetone-ether, m.p. 238–241°, $[\alpha]_D$ +51°, $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 17,000), $\lambda\lambda_{max}^{nujol}$ 5.78, 6.00, 6.18, 8.08 μ. (Reported[13]: m.p. 243–246°, $[\alpha]_D$ +53°.)

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.56; H, 8.02.

4,9(11)-Pregnadiene-17α-ol-3,20-dione caproate (V). A solution of 1.000 g. of III in 10 ml. of caproic acid and 2 ml. of trifluoroacetic acid was flushed with argon and heated on the steam bath for 50 min. The mixture was then cooled, poured into water, and the acid was neutralized with sodium bicarbonate. The product was extracted with methylene chloride and the extracts were washed with 5% sodium hydroxide solution and water, dried, and concentrated to an oil which was chromatographed on Florisil. The fractions eluted with 10 to 25% ether in hexane were crystallized from pentane to give 697 mg. of V, plates, m.p. 110–115°, changing to needles, m.p. 124–126°. One recrystallization afforded analytically pure material, m.p. 126–128°, $[\alpha]_D$ +42°, $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 16,800), $\lambda\lambda_{max}^{nujol}$ 5.78, 5.82 (shoulder), 6.00, 6.20, 8.50 mμ.

Anal. Calcd. for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98. Found: C, 76.11; H, 8.94.

9α,11β-Dichloro-4-pregnene-17α-ol-3,20-dione acetate (VII). A solution of 500 mg. of 4,9(11)-pregnadiene-17α-ol-3,20-dione acetate (IV) in 20 ml. of carbon tetrachloride and 5 ml. of methylene chloride, containing 0.33 ml. of dry pyridine, was chilled to −20° and 0.89 ml. of a solution of chlorine in carbon tetrachloride (110 mg. of chlorine/ml.) added with stirring. After 15 min. at −20° the potassium iodide–starch test was negative[32] and the mixture was allowed to come to room temperature, diluted with methylene chloride, and washed with 5% hydrochloric acid, sodium bicarbonate, and water. The dried solution was concentrated to a glass under reduced pressure and the residue triturated with ether. The resulting solid was filtered and crystallized from acetone-hexane to give 371 mg. of VII, m.p. 214–219° dec. The analytical sample was recrystallized from acetone-hexane, washed with ether, and crystallized once more from acetone-hexane, m.p. 224–233° dec., $[\alpha]_D$ +138°, $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 17,150), $\lambda\lambda_{max}^{nujol}$ 5.80, 6.00, 6.14, 8.10 mμ.

Anal. Calcd. for $C_{23}H_{30}O_4Cl_2$: C, 62.58; H, 6.85; Cl, 16.06. Found: C, 62.63; H, 7.03; Cl, 15.90.

9α,11β-Dichloro-4-pregnene-17α-ol-3,20-dione (XI). A solution of 2.000 g. of 9α,11β-dichloro-4-pregnene-17α-ol-3,20-dione acetate (VII) in 50 ml. of 90% methanol containing 2 g. of potassium hydroxide was heated on the steam bath for 15 min. The resulting suspension was chilled and filtered and the crude product was washed with dilute methanol, dried, and crystallized from chloroform-hexane to give a total of 1.306 g. of XI. One recrystallization from acetone-ether gave analytically pure material, m.p. 220–227° dec., $[\alpha]_D$ +175°, $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 17,100), $\lambda\lambda_{max}^{nujol}$ 2.88, 5.88, 6.02, 6.16 μ.

Anal. Calcd. for $C_{21}H_{28}O_2Cl_2$: C, 63.16; H, 7.07; Cl, 17.76. Found: C, 63.09; H, 6.96; Cl, 17.92.

4,9(11)-Pregnadiene-17α-ol-3,20-dione (III) *from 9α,11β-dichloro-4-pregnene-17α-ol-3,20-dione* (XI). To a solution of 50 mg. of XI in 15 ml. of acetone, under carbon dioxide, was added 5 ml. of chromous chloride solution,[23] followed after a few minutes by an additional 3 ml. of chromous chloride solution. The mixture was shaken and allowed to stand for 10 min., then poured into water. The crude product (37 mg.) was filtered and crystallized from acetone-hexane to give pure III, Beilstein test negative, m.p. 212–217°, infrared spectrum identical with that of an authentic sample of III.

9α,11β-Dichloro-4-pregnene-17α-ol-3,20-dione caproate (X). (a) *From 4,9(11)-pregnadiene-17α-ol-3,20-dione caproate* (V). To a solution of 1.000 g. of V in 45 ml. of carbon tetrachloride containing 0.56 ml. of pyridine, chilled to −20°, was added 1.25 ml. of a solution of chlorine in carbon tetrachloride (140 mg. of chlorine/ml.). The mixture was stirred in the cold for 40 min., then allowed to stir overnight at room temperature. Methylene chloride was added and the solution was washed with 5% hydrochloric acid, bicarbonate, and water. Concentration of the solution under reduced pressure gave an oil which solidified on trituration with ether. The filtered product (466 mg.) was crystallized twice from acetone-ether, m.p. 149–155° dec., $[\alpha]_D$ +106°, $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 16,100), $\lambda\lambda_{max}^{nujol}$ 5.80, 5.86, 6.00, 6.14, 8.0 μ.

Anal. Calcd. for $C_{27}H_{38}O_4Cl_2$: C, 65.18; H, 7.70; Cl, 14.26. Found: C, 64.60; H, 7.72; Cl, 13.86.

(b) *From 9α,11β-dichloro-4-pregnene-17α-ol-3,20-dione* (XI). A mixture of 500 mg. of XI, 5 ml. of caproic acid and 1 ml. of trifluoroacetic anhydride was flushed with argon and heated on the steam bath. After 15 min. 1 ml. of trifluoroacetic anhydride was added, and the solution was heated an additional 45 min. It was then poured into aqueous sodium bicarbonate, stirred, and the product extracted with methylene chloride. The extracts were washed with 5% sodium hydroxide solution and water, dried, and concentrated to an oil which was filtered through Florisil with ether and methylene chloride. The crystalline fractions were combined and crystallized from acetone-hexane to give X, 146 mg., m.p. 139–144° dec. Recrystallization from acetone-ether raised the melting point to 143–153° dec. $[\alpha]_D$ +107°, $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 15,900), infrared spectrum identical with that of X obtained in (a).

Anal. Found: C, 64.67; H, 7.89; Cl, 14.21.

9α-Bromo-11β-chloro-4-pregnene-17α-ol-3,20-dione acetate (IX). To a solution of 450 mg. of IV and 2.0 g. of lithium chloride in 25 ml. of acetic acid was added 190 mg. of recrystallized (methylene chloride) *N*-bromoacetamide. A slow stream of hydrogen chloride was passed over the stirred solution for a few seconds until the solution became orange. Stirring was continued for 10 min., then the mixture was poured into ice water, and the solid precipitate filtered and triturated with ether. Crystallization from acetone-hexane furnished IX, 300 mg., m.p. 116–120° dec. The analytical sample was recrystallized from methylene chloride-pentane,

(32) The addition reactions were in general allowed to proceed until a negative test with potassium iodide–starch paper indicated complete consumption of reagent.

m.p. 124–129° dec. $[\alpha]_D$ +142°, $\lambda_{max}^{CH_3OH}$ 242 mμ (ε 15,600), $\lambda\lambda_{max}^{nujol}$ 5.76, 5.82, 5.98, 6.15, 7.94, 8.03 μ.

Anal. Calcd. for $C_{23}H_{30}O_4BrCl$: C, 56.85; H, 6.22; Br, 16.45; Cl, 7.30. Found: C, 57.23; H, 6.65; Br, 16.07; Cl, 7.35

4,9(11)-Pregnadiene-17α-ol-3,20-dione acetate (IV) *from 9α,11β-dichloro-4-pregnene-17α-ol-3,20-dione acetate* (VII) *and 9α-bromo-11β-chloro-4-pregnene-17α-ol-3,20-dione acetate* (IX). To a solution of 50 mg. of VII in 10 ml. of acetone, under carbon dioxide, was added 5 ml. of chromous chloride solution. The mixture was shaken and allowed to stand for 15 min., then poured into ice water. The product crystallized slowly to give 39 mg. of IV, m.p. 241–243°, Beilstein test negative, infrared spectrum identical with that of an authentic sample of IV.

Similarly, treatment of 45 mg. of IX with 7 ml. of chromous chloride solution gave 29 mg. of IV, m.p. 237–240°, infrared spectrum identical with that of authentic IV.

9α-Bromo-11β-fluoro-4-pregnene-17α-ol-3,20-dione acetate (VIII). To a stirred solution of 500 mg. of IV in 25 ml. of diethylacetic acid contained in a polyethylene bottle was added 3 ml. of a solution of hydrogen fluoride in chloroform-tetrahydrofuran (about 200 mg. of hydrogen fluoride/ml.) followed by 200 mg. of 95% *N*-bromoacetamide. The mixture was stirred at room temperature for 100 min., then poured into cold aqueous potassium carbonate solution. The mixture was stirred for 30 min., then extracted with methylene chloride, and the organic extracts were washed with 5% sodium hydroxide solution and water. The dried solution was concentrated and the product crystallized by addition of pentane to give 368 mg. of crude VIII. Recrystallization from methylene chloride-pentane afforded pure VIII, m.p. 176–180° dec. $[\alpha]_D$ +81°, $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 16,100), $\lambda\lambda_{max}^{nujol}$ 5.76, 5.82, 5.96, 6.15, 7.92, 8.02 μ.

Anal. Calcd. for $C_{23}H_{30}O_4BrF$: C, 58.85; H, 6.44; Br, 17.03; F, 4.05. Found: C, 58.54; H, 6.08; Br, 17.56; F, 3.85.

9α-Chloro-11β-fluoro-4-pregnene-17α-ol-3,20-dione acetate (VI). To a solution of 504 mg. of IV in 10 ml. of carbon tetrachloride, 10 ml. of methylene chloride, and 3 ml. of dry pyridine contained in a polyethylene bottle was added 195 mg. of 96% *N*-chlorosuccinimide followed by about 1.5 ml. of a solution of hydrogen fluoride in tetrahydrofuran-chloroform (about 120 mg. of hydrogen fluoride/ml.). After stirring at room temperature for 48 hr. the mixture was diluted with 15 ml. of methylene chloride and stirring continued. After an additional 24 hr., 1.5 ml. of hydrogen fluoride solution was added and the mixture allowed to stir for 90 hr. It was then poured into sodium carbonate solution, stirred, and the product extracted with methylene chloride. The extracts were washed, dried, treated with decolorizing carbon and the solvent was evaporated under reduced pressure. The residual oil was triturated with ether to give 250 mg. of crude VI. Crystallization from acetone-hexane furnished the pure compound (194 mg.), m.p. 210–215° dec., $[\alpha]_D$ +85°, $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 17,000), $\lambda\lambda_{max}^{nujol}$ 5.76, 5.81, 5.97, 6.13, 7.91, 8.00 μ.

Anal. Calcd. for $C_{23}H_{30}O_4ClF$: C, 65.01; H, 7.12; Cl, 8.34; F, 4.47. Found: C, 64.94; H, 6.98; Cl, 8.03; F, 4.20.

1,4,9(11)-Pregnatriene-17α,21-diol-3,20-dione (XIIb). A suspension of 5.00 g. of 1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (XIIa) in a mixture of 200 ml. of methanol and 5 ml. of 70% perchloric acid[25] was stirred at room temperature for 7 hr. At the end of this period the clear solution was poured into ice water and the precipitate isolated and dried *in vacuo* at 60° for 5 hr. to give XIIb, 3.80 g., m.p. 207–213°. Crystallization from acetone furnished the analytical sample, m.p. 220–228°, $[\alpha]_D$ +9.5° (pyridine), $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 15,500), $\lambda\lambda_{max}^{nujol}$ 3.05, 5.82, 6.01, 6.16, 6.24 μ.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.42; H, 7.62.

1,4,9(11)-Pregnatriene-17α,21-diol-3,20-dione 21-methanesulfonate (XIIc). To a solution of 7.5 g. of XIIb in 160 ml. of pyridine, cooled to −20°, was added 4 ml. of methanesulfonyl chloride. The mixture was stirred at −20° to −15° for 1 hr., then ice was added to hydrolyze the excess of reagent and the mixture poured into ice water. The gummy precipitate solidified on standing and was filtered and washed with water to give 7.4 g. of crude XIIc, contaminated with some 21-chloride (Beilstein test positive). The analytical sample was crystallized from acetone-ether-hexane and recrystallized twice from acetone-ether, m.p. 175–178° dec. $[\alpha]_D$ +52°, $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 15,100), $\lambda\lambda_{max}^{nujol}$ 3.00, 5.76, 6.02, 6.18, 6.23, 8.52 μ.

Anal. Calcd. for $C_{22}H_{28}O_6S$: C, 62.83; H, 6.71; S, 7.62. Found: C, 62.68; H, 6.77; S, 7.74.

1,4,9(11)-Pregnatriene-17α-ol-3,20-dione (XIII). To a warmed solution of 7.0 g. of crude XIIc in 300 ml. of acetone was added a hot solution of 20 g. of sodium iodide in 150 ml. of acetone. The mixture was heated under reflux for 2.5 hr., then 20 ml. of acetic acid was added and heating continued for 30 min. The iodine color was discharged by the addition of sodium bisulfite solution, then the mixture was poured into ice water. The filtered precipitate, 4.1 g., was crystallized from acetone-ether to give a total of 2.75 g. of XIII, m.p. in the range 216–230°. Recrystallization from acetone-ether furnished pure XIII, m.p. 226–230°, $[\alpha]_D$ −17°, $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 16,400), $\lambda\lambda_{max}^{nujol}$ 2.95, 5.86, 6.01, 6.17, 6.24 μ.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 77.27; H, 8.03. Found: C, 77.58; H, 8.35.

9α,11β-Dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione 21-methanesulfonate (XVI). To a solution of 1.000 g. of 9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione (XV) in 25 ml. of dry pyridine, chilled to 0°, was added 0.5 ml. of methanesulfonyl chloride. The solution was stirred in the cold for 45 min., then poured into ice water. The precipitate was filtered, dried and crystallized from acetone to give 1.015 g. of crude XVI. Two recrystallizations from acetone-ether gave pure XVI, m.p. 198–201° dec., $[\alpha]_D$ +155° (dioxane), $\lambda_{max}^{CH_3OH}$ 237 mμ (ε 15,200), $\lambda\lambda_{max}^{nujol}$ 2.87, 5.74, 6.01, 6.15, 6.21, 8.55 μ.

Anal. Calcd. for $C_{22}H_{28}O_6Cl_2S$: C, 53.77; H, 5.74; Cl, 14.43; S, 6.53. Found: C, 53.56; H, 5.79; Cl, 14.42; S, 6.38.

9α,11β-Dichloro-1,4-pregnadiene-17α-ol-3,20-dione (XIV). (a) *From 9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione 21-methanesulfonate* (XVI). To a warmed solution of 200 mg. of XVI in 250 ml. of acetone was added a solution of 1.0 g. of sodium iodide in 50 ml. of warm acetone. The mixture was boiled for 5 min., then 2 ml. of acetic acid was added and the mixture boiled an additional 10 min. Sodium bisulfite solution was added to discharge the iodine color, then the mixture was poured into water. The precipitate was filtered and crystallized from acetone-ether to give 162 mg. of XIV. Recrystallization from acetone-ether furnished the analytical sample, m.p. 234–239° dec., $[\alpha]_D$ +145°, $\lambda_{max}^{CH_3OH}$ 237 mμ (ε 14,900), $\lambda\lambda_{max}^{nujol}$ 2.96, 5.86, 6.02, 6.18, 6.24 μ.

Anal. Calcd. for $C_{21}H_{26}O_2Cl_2$: C, 63.48; H, 6.60; Cl, 17.85. Found: C, 63.13; H, 6.57; Cl, 17.86.

(b) *From 1,4,9(11)-pregnatriene-17α-ol-3,20-dione* (XIII). A mixture of 1.200 g. of XIII, 0.9 ml. of dry pyridine, 55 ml. of carbon tetrachloride, and 15 ml. of methylene chloride was chilled to −20°, and 1.5 ml. of a solution of chlorine in carbon tetrachloride (177 mg. chlorine/ml.) added. After stirring at −20° for 20 min. the mixture was allowed to warm to room temperature and stirred for 19 hr. It was then diluted with methylene chloride and acetone and the solution washed with 5% hydrochloric acid and 5% potassium bicarbonate. Concentration of the solution gave crystalline XIV, 1.099 g., m.p. 230–237° dec., $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 15,000), infrared spectrum identical with that of XIV prepared as in (a).

9α,11β-Dichloro-1,4-pregnadiene-17α-ol-3,20-dione acetate (XVII). A solution of 380 mg. of XIV in a mixture of 5 ml. of acetic acid and 1.25 ml. of trifluoroacetic anhydride was heated on the steam bath under argon for 2.25 hr. It was then poured into ice water and the mixture was stirred for a short time and filtered. The crude product was crystallized from acetone-hexane, giving 321 mg. of XVII, m.p.

235–245° dec. The analytical sample was recrystallized from acetone-ether, m.p. 242–247° dec., $[\alpha]_D$ +113°, $\lambda_{max}^{CH_3OH}$ 238 mμ (ε 15,300), $\lambda\lambda_{max}^{nujol}$ 5.77, 5.82, 6.00, 6.12, 6.19, 7.02, 7.96, 8.04 μ.

Anal. Calcd. for $C_{23}H_{28}O_4Cl_2$: C, 62.87; H, 6.42; Cl, 16.14. Found: C, 63.03; H, 6.50; Cl, 16.23.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. CLVI.[1] Ring D Unsaturated 16-Methylated Corticosteroids

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Two routes to 16α-methyl "S" (V) are described. While one route was straight-forward the second involved the novel hydrobromic acid–acetone cleavage of a 16β-methyl-16α,17α-oxido-20-keto steroid (IX) which led to a mixture of 16-methylene- and Δ[15]-16-methyl-17α-hydroxy-20-keto compounds (X). Catalytic reduction of X gave exclusively the 16α-methyl-17α-hydroxy-20-ketone (VI) readily convertible to V. Application of the hydrobromic acid opening to 16β-methyl-16α,17α-oxido-allopregnane-3β-ol-11,20-dione (XVI) gave predominantly the Δ[15]-16-methyl steroid (XVII) which was converted to Δ[15]-16-methylprednisone acetate (XXI).

Recently it has been demonstrated that introduction of a 16α-methyl substituent into the hydrocortisone or prednisolone molecule[3] as well as into 9-fluoro,[4] 6-fluoro[5a,e] and 6,9-difluorocorticoids[5b–d] increases anti-inflammatory activity while sodium retention is decreased. An ideal substrate for many of these cortical hormones would appear to be 16α-methyl-Δ[4]-pregnene-17α,21-diol-3,20-dione (Vb) (16α-methyl "S"), as fermentation with 11-hydroxylating organisms would lead to 16α-methylhydrocortisone or to 16α-methyl-11-epihydrocortisone. In this paper we describe the preparation of 16α-methyl "S" by two different routes as well as the preparation of the novel Δ[15]-16-methylprednisone acetate (XXI).

Our first route to 16α-methyl "S"[6] was straightforward[7] and unexceptional. 16α-Methyl-Δ[5]-pregnen-3β-ol-20-one acetate (I)[8] was chlorinated at low temperature in carbon tetrachloride yielding the 5α,6β-dichloride (II). Application of Gallagher's[9] 17-hydroxyl introduction followed. Prolonged treatment of II with boiling acetic anhydride in the presence of *p*-toluenesulfonic acid gave the Δ[17(20)]-enol acetate which was epoxidized with monoperphthalic acid. Alkaline hydrolysis then gave 5α,6β-dichloro-16α-methyl-allopregnane-3β,17α-diol-20-one (III), the over-all yield for this three-step sequence being somewhat low apparently due to the resistance of 16α-methyl-20-ketones to C_{-20} enol acetate formation. Bromination of III at C_{-21} in dioxane solution followed by successive displacement with sodium iodide and potassium acetate yielded the 21-acetate (IV), completing the build-up of the cortical side-chain. Oxidation of IV with 8*N* chromic acid in sulfuric acid–acetone[10] gave the 3-ketone-5,6-dichloride which, without isolation, was dechlorinated with zinc dust in hot acetic acid yielding 16α-methyl "S" 21-acetate (Va). The free 16α-methyl "S" (Vb) was readily obtained by low temperature saponification of Va with methanolic potassium hydroxide.

A second route to V proceeded from 16-methyl-Δ[5,16]-pregnadiene-3β-ol-20-one acetate[11] (VIII) which was converted to the 16α,17α-epoxide (IXa) by treatment with alkaline hydrogen peroxide. When the epoxide 3-acetate (IXb) in acetone solution was treated with concentrated aqueous hydrobromic acid for about twenty minutes at 5°, ep-

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