shaken with a benzene solution of steroid in the *absence* of dioxane or *t*-butyl alcohol.

Oxidation of 12-methylene-tigogenin to hecogenin. 0.4 g. of 12-methylene tigogenin[7] in 100 ml. of *t*-butyl alcohol was oxidized with a solution of 1.7 g. of sodium metaperiodate, 0.42 g. of potassium carbonate, and 0.05 g. of potassium permanganate in 100 ml. of water, shaking the mixture in a 500-ml. bottle. Infrared analysis for carbonyl indicated maximum formation in 5 hr. The solution was extracted with benzene, yielding after the usual work-up 0.3 g. of hecogenin, m.p. 250–253°, infrared spectrum identical with that of an authentic specimen.

Oxidation of 3β-acetoxy-16-pregnen-20-one. A solution of 0.42 g. of 3β-acetoxy-16-pregnen-20-one in 100 ml. of *t*-butyl alcohol was shaken overnight with the aqueous oxidation solution used above. The aqueous mixture was further diluted with water and extracted with ether. The ether solution contained a negligible weight of steroid. The aqueous layer was acidified with hydrochloric acid and the resultant precipitate extracted with ether to yield 0.4 g. of amorphous glass. The infrared absorption spectrum showed, as might be expected, a strong carboxyl carbonyl band at 1700 cm.$^{-1}$.

Under the above reaction conditions stigmasterol and 3β,20-diacetoxy-17-pregnen-20-one were recovered unchanged.

(7) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **79**, 5029 (1957).

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[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH OF G. D. SEARLE AND CO.]

Steroidal Aldosterone Blockers. I

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Received January 5, 1959

The synthesis and specific biological activities of a variety of C-17 steroidal 5 and 6 membered spirolactones are presented. The 19-nor compound with a 5 membered lactone (Xa) is the most potent aldosterone blocker.

Since the first reports of the antialdosterone activity of several steroidal 17-spirolactones[1(a),(b)] we have prepared a number of new spirolactones in order to test the effect on blocking activity of changes in both the lactone and steroid portions of the molecule. It is our purpose in this article to record the experimental details of synthesizing the drugs reported in earlier communications[1(a),2] and to report on some of the new compounds in this series.

The first member of this series to show aldosterone blocking activity was 3-(3-keto-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (VIa). This was prepared by the sequence shown on Chart 1. The Grignard reagent of 17α-ethynyl-5-androstene-3β,17β-diol (Ia)[3] was carbonated in good yield to give an acetylenic acid (IIa). The acetylenic bond was selectively reduced to an olefin by catalytic hydrogenation over palladium on calcium carbonate using dioxane and pyridine as solvents. The resulting product on treatment with mineral acid yielded an unsaturated lactone (IIIa) which could be readily reduced to a saturated lactone (Va) by hydrogen over palladium on charcoal. Oxidation of IIIa and Va by the Oppenauer method produced the corresponding 3-oxo-4-ene compounds IV and VIa.

Because of the interesting antialdosterone activity of VIa we decided to make the correponding 19-nor compound. To this end the spirolactone side chain was built onto a steroid nucleus containing an aromatic A ring by the same series of reactions used in the androstane series (Chart I). 17α-Ethynyl-3-methoxy-1,3,5(10)-estratrien-17β-ol[4] (Ic) was carbonated to give an acetylenic acid (IIc) which could be hydrogenated partially or completely to give an unsaturated (IIIc) or saturated (Vc) lactone. As shown on Chart 2, the A ring of this could be most effectively reduced to the dihydroaromatic system (VIIIa) by preparing the sodium salt (VIIa) of the saturated lactone (Vc) and reducing this with lithium in ammonia and *t*-butyl alcohol.[5] Hydrolysis of the enol ether (VIIIa) with dilute acetic acid afforded a compound (IXa) in which simultaneous lactonization of the liberated hydroxy acid had occurred. On the other hand, hydrolysis with mineral acid gave the compound (Xa) containing not only a lactone, but also a conjugated ketone. Xa was also prepared by treating IXa with strong acid. Lactonization of the hydroxy acids was best accomplished by treating them with strong acid in solution; stirring the precipitated hydroxy acid with aqueous acid was usually ineffective.

In the hope of reducing the triple bond and aromatic A ring simultaneously the acetylenic acid (IIc) was subjected directly to reduction by lithium in ethanol and ammonia. After hydrolysis of the uncharacterized intermediate enol ether with strong acid, there was obtained not only the satu-

(1) (a) J. A. Cella and C. M. Kagawa, *J. Am. Chem. Soc.*, **79**, 4808 (1957). (b) C. M. Kagawa, J. A. Cella, and C. G. Van Arman, *Science*, **126**, 1015 (1957).

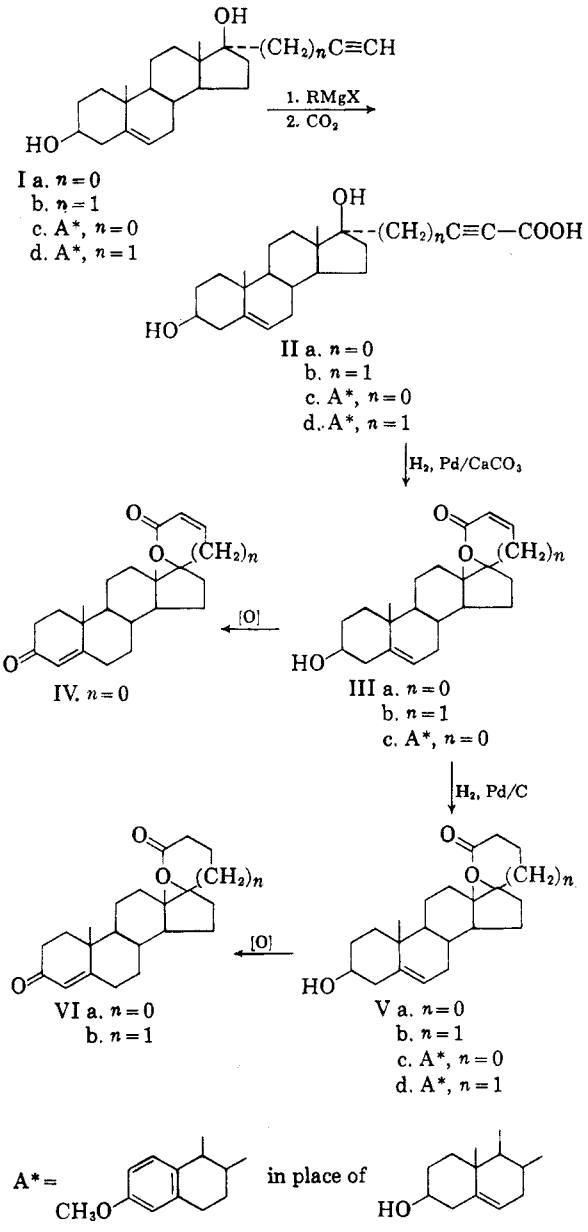
(2) J. A. Cella, U. S. Patent **2,705,712**, April 5, 1955.

(3) H. E. Stavely, *J. Am. Chem. Soc.*, **61**, 79 (1939).

(4) F. B. Colton, U. S. Patent **2,666,769**, June 19, 1954.

(5) This is a modification of the Birch reduction described by A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953) which was developed by Dr. H. Dryden of these laboratories.

Chart I

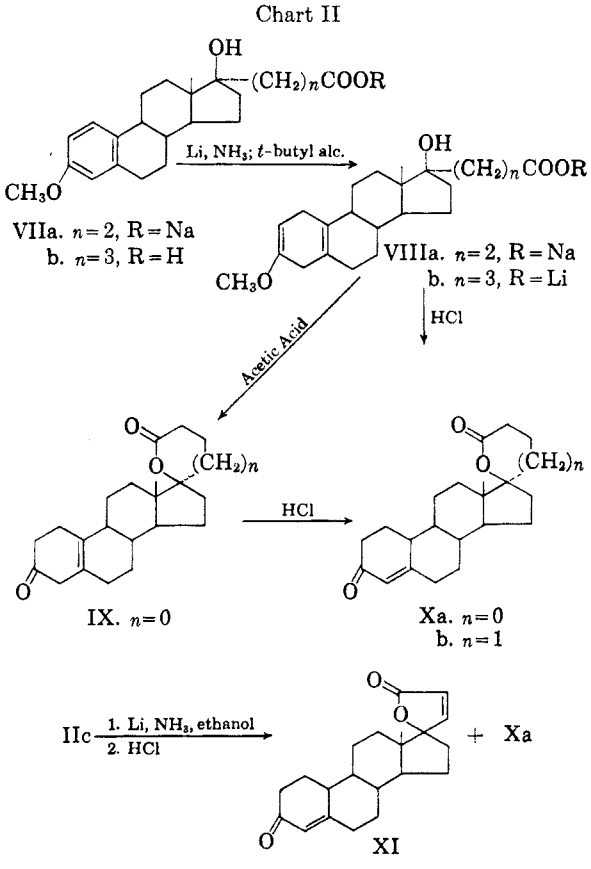


rated lactone (Xa) but also the unsaturated lactone (XI).

We now turned our synthetic efforts to making the six-membered lactones analogous to VIa and Xa. The same sequence of lactone building reactions was used on 17α-propargyl-5-androstene-3β,17β diol[6] (Ib), *e.g.*, carbonation of the Grignard reagent to give 4-(3β,17β-dihydroxy-5-androsten-17α-yl)-2-butynoic acid (IIb). This compound (IIb) was hydrogenated stepwise to the saturated lactone (Vb), which was oxidized by the Oppenauer method to the corresponding 3-oxo-4-ene derivative (VIb).

The 19-nor six-membered lactone was prepared by a similar route. Estrone methyl ether was reacted with propargyl bromide in the presence of zinc to yield Id. This was carbonated as described earlier to yield IId which was then hydrogenated to the corresponding 4-[17β-hydroxy-1,3,5(10)-estratrien-17α-yl]butanoic acid which was lactonized to Vd. The free acid (VIIb) was reduced to a dihydroaromatic intermediate (VIIIb) which was acidified without isolating, to give 4-(3-oxo-17β-hydroxy-19-nor-4-androsten-17α-yl)butanoic acid which yielded the lactone (Xb) by treatment with *p*-toluenesulfonic acid in benzene. Xb was also prepared by an alternate route. The Grignard reagent of Ic was treated with ethylene oxide to give 1-[3-methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]-1-butynol-4, which was reduced catalytically to the corresponding 1-[3-methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]butanol-4. Chromic acid oxidation of this diol yielded the lactone (Vd). This method was not so satisfactory as the other because of the poor yield in the Grignard step.

Chart II



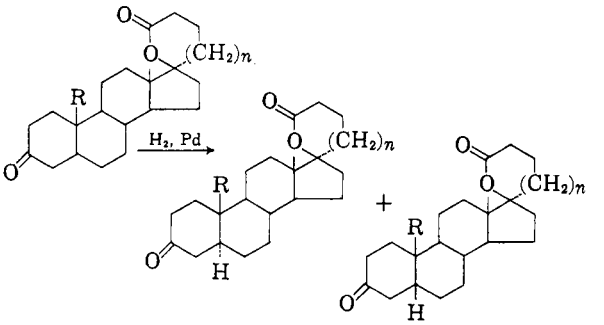
Some of the lactones containing a 3-oxo-4-ene system were hydrogenated in the presence of palladium (Chart III), to yield a mixture of epimers at C-5 which was separated by chromatography. The first of these was VIa, which gave about a 70–30 mixture of A/B *trans* (XIIa) to A/B *cis* (XIIIa). The stereochemistry of XIIa was established by hydrogenating Va in neutral alcohol to give a single compound (XIV),[7] which was oxidized in good

(6) C. W. Greenhalgh, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951).

(7) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., Reinhold, New York, p. 375.

yield to XIIa. The other isomer (XIIIa) was therefore assigned the A/B *cis* configuration.

Chart III



VI. a, R = CH_3, n = 0
VI. b, R = CH_3, n = 1
X. a, R = H, n = 0

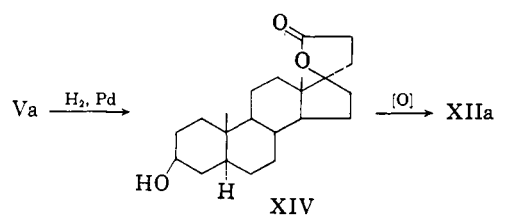
XII. a, R = CH_3, n = 0
b, R = CH_3, n = 1
c, R = H n = 0

XIII. a, R = CH_3, n = 0
b, R = CH_2, n = 1
c, R = H n = 0

Catalytic hydrogenation of Xa yielded two dihydro isomers (XIIc and XIIIc). The stereochemistry of XIIc was established as the A/B *trans* ring fusion by reducing Xa with lithium in ammonia and alcohol[8] and then oxidizing the uncharacterized product with chromic acid to give a single compound (XIIc). The configuration of XIIIc was therefore A/B *cis*.

Similar treatment of VIb with hydrogen over palladium gave two dihydro isomers (XIIb and XIIIb) in the six-membered series. The stereochemistry of these isomers was assigned by analogy to the two previous cases, *e.g.*, the *trans* isomer was eluted first from a chromatographic column and the *trans* isomer is lower melting.

Biology.[1(b),9] The anti-DCA blocking activities available are in Table I. Active compounds were screened further against aldosterone. Examination of the blocking activities listed in Table I will show that changing the 3-oxo-4-ene system to a 3-hydroxy-5-ene, 3-oxo-4,5-dihydro, or an aromatic A ring reduces blocking activity as does introducing a double bond at C-20 to C-21, or expansion of the lactone to a six-membered ring. On the other hand, going from the normal series to the 19-nor compound enhances activity. Hence the most active compound of this series is Xa.



XIV

(8) W. S. Johnson, E. R. Roger, J. Szmuszkovicz, H. I. Hadler, J. Ackerman, B. K. Bhattacharyya, B. M. Bloom, L. Stalmann, R. A. Clement, B. Bannister, and H. Wynberg, *J. Am. Chem. Soc.*, **78**, 6289 (1956).

TABLE I

Compound	Relative Blocking Potency[a]	Compound	Relative Blocking Potency[a]
IV	<0.01	XIIa	0.3
Va	0.1	XIIb	<0.1
Vc	<0.01	XIIc	0.6
VIa	1.0	XIIIa	<0.01
VIb	0.08	XIIIb	<0.1
IXa	0.8	XIIIc	<0.3
Xa	3.8	XIV	0.1
Xb	1.0		

[a] VIa was arbitrarily assigned the value of 1.0. A dose of 0.22 mg. of VIa produces a 50% block of the effect of 12 μg. of desoxycorticosterone acetate on the urinary Na/K ratio in adrenalectomized rats.

EXPERIMENTAL

General. The microanalyses and optical determinations recorded here were carried out by Dr. Robert T. Dillon and his associates of these laboratories.

A number of preparations were made by the same general procedures. These are listed and reference is made to them under specific preparations where they were used.

Temperatures are reported in degrees centigrade. Melting points were determined on a Fisher-Johns block and are reported uncorrected. Ultraviolet spectra were determined in methanol.

Procedure A. Carbonation of acetylenic Grignard reagents. One g. of the ethynylated steroid was dissolved in 5 ml. of tetrahydrofuran. This solution is added to a refluxing solution of 6 ml. of 3*M* methylmagnesium bromide in 15 ml. of tetrahydrofuran. The tetrahydrofuran was previously purified by distillation from excess Grignard reagent. The resulting gray suspension was stirred and refluxed for 24 hr. It gave a strong positive test for RMgX at this point. A slight positive pressure of carbon dioxide was then maintained over the rapidly stirred solution for 24 hr. The mixture was poured into excess ice-cold 0.2*M* sulfuric acid and most of the solvent removed by vacuum distillation. The crude granular product was filtered, washed free of mineral acid, and set to dry.

Procedure B. Preparation of unsaturated lactones from acetylenic acids. One g. of 17α-steroidylalkynoic acid (II) was dissolved in 10 ml. of dioxane containing 1 ml. of pyridine. This solution was stirred under hydrogen at atmospheric pressure in the presence of 0.3 g. of 5% palladium on calcium carbonate until one equivalent was absorbed. The stirring was then stopped, the catalyst filtered off, and the solvent removed by vacuum distillation. The viscous residue was dissolved in 10 ml. of cold ethanol and 1.4 ml. of concentrated hydrochloric acid added. After standing for 5 min. the solution was diluted with 175 ml. of cold water and the crude unsaturated lactone collected by filtration and set to dry.

Procedure C. Oppenauer oxidation of 3β-hydroxy lactones. One g. of the appropriate 3β-hydroxy-5-ene lactone (V) was dissolved in a boiling solution of 25 ml. of toluene and 8 ml. of cyclohexanone. Five ml. of toluene was removed by distillation to insure dryness. Then to this refluxing solution was added a solution of 0.5 g. of aluminum isopropylate in 5 ml. of toluene. The resulting solution was refluxed and stirred for an additional 20 min. whereupon it was cooled to 95° and 5 ml. of water added. The heterogeneous mixture was cooled to room temperature and made strongly acid with 6*N* sulfuric acid. The layers were separated, washed, and each back-extracted. The combined organic layers

(9) The biological testing was carried out by Dr. C. M. Kagawa and his associates of these laboratories. The experimental details of testing will be reported elsewhere.

were then steam distilled exhaustively. The cooled distillation residue was extracted with chloroform. This extract was dried and evaporated to dryness to give the crude 3-oxo-4-ene lactone (VI).

Procedure D.[5] *Reduction of aromatic compounds to dihydroaromatic compounds with lithium in ammonia and t-butyl alcohol.* A solution of 10 g. of the aromatic acid or salt (VII) in 150 ml. of *t*-butyl alcohol and 150 ml. of tetrahydrofuran was diluted to 650 ml. with anhydrous ammonia in a flask equipped with a sealed stirrer and a Dry Ice condenser. Then 5.5 g. of lithium wire was added during a 30-min. period, producing a heterogeneous mixture of a deep blue ammonia layer and an oily bronze colored lithium-ammonia alloy layer. Stirring was adjusted so as to produce thorough mixing of the two layers. After 3 hr., 25 ml. of ethanol was added to destroy any unreacted lithium. An additional 25 ml. of ethanol was added, the condenser removed, and the ammonia allowed to evaporate under a stream of nitrogen overnight. Then 200 ml. of water was added and the mixture vacuum distilled until about 250 ml. of reaction mixture remained. This mixture was then worked up in a suitable way which will be described for the individual compounds.

17α-Propargyl-5-androstene-3β,17β-diol (Ib). The following modification of the method of Jones *et al.*[6] was employed. Freshly distilled propargyl bromide (64.2 g.) was added during a 20-min. period to a stirred, refluxing suspension of 35.2 g. of 20-mesh zinc (acid washed and dried with solvents) and 36 g. of dehydroisoandrosterone acetate in 1 l. of tetrahydrofuran. When about half of the bromide had been added, a vigorous reaction set in which required ice bath cooling. After 5 min. the reaction subsided, whereupon the balance of the bromide was added at a rate to cause spontaneous refluxing. When the spontaneous effect ceased, the mixture was refluxed for 15 min. longer, then cooled and poured into 2 l. of water containing 100 ml. of 12*M* hydrochloric acid. Extraction with benzene and removal of solvent gave the crude acetate as a brown crystal paste which was then saponified by refluxing under nitrogen for 0.5 hr. with 25 g. of potassium hydroxide in 1 l. of methanol. After dilution with 8 l. of water, the precipitate was collected on a funnel, rinsed free of base and dried (40 g.). Since an infrared spectrum at this point showed the presence of unreacted ketone, the crude product was refluxed with 15 g. of Girard's T reagent and 15 ml. of acetic acid in 380 ml. of absolute alcohol for 0.5 hr. Work-up in the conventional manner yielded the crude propargyl derivative (Ib) which, after crystallization from methanol, weighed 20 g. and melted at 152–154°.

3-Methoxy-17α-propargyl-1,3,5(10)-estratrien-17β-ol (Id). The procedure for preparation of this compound from estrone-3-methyl ether was like that for 17α-propargyl-5-androstene-3β,17β-diol (Ib). The reaction was a little sluggish and, after the exothermic period, reflux was continued for 2 hr. The crude propargyl derivative was separated from unreacted starting material by means of Girard's T reagent and recrystallized from methanol. From 10 g. of estrone-3-methyl ether 2.9 g. of the starting material was recovered and 6.0 g. of the desired product, melting at 49–60°C., was obtained. Infrared spectrum (KBr), 2.82μ, 3.05μ, (O—H, ≡C—H).

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.18; H, 8.65.

3β,17β-Dihydroxy-5-androsten-17α-ylpropynoic acid (IIa). Procedure A was used on 25 g. of 17α-ethynyl-5-androstene-3β,17β-diol.[3] The crude product was dissolved in 250 ml. of tetrahydrofuran and 12.1 g. of triethylamine added. The triethylamine salt, 28.8 g., which precipitated was dissolved in 300 ml. of 50% aqueous dioxane and the boiling solution then acidified with concentrated hydrochloric acid. Upon chilling, 20 g. of IIa precipitated as a monohydrate, m.p. 234–235° dec. (loses H_2O at 120–140°), $[\alpha]_D$ −132.5° (dioxane).

Anal. Calcd. for $C_{22}H_{30}O_4.H_2O$: C, 70.18; H, 8.57. Found: C, 70.19; H, 8.46.

4-(3β,17β-Dihydroxy-5-androsten-17α-yl)-2-butynoic acid (IIb). Procedure A was used on 4.58 g. of 17α-propargyl-5-androstene-3β,17β-diol (Ib). The crude product (4.9 g.) was triturated with 30 ml. of boiling chloroform to give 3.5 g. of the desired acid (IIb), m.p. 201–205°. A sample, m.p. 203–206°, for analysis was obtained by recrystallization from acetonitrile.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.09; H, 8.83.

3-Methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-ylpropynoic acid (IIc). Procedure A was used on 132 g. of 17α-ethynyl-3-methoxy-1,3,5(10)-estratrien-17β-ol (Ic).[4] The 142 g. of dark yellow crude acid was suspended in 2 l. of boiling carbon tetrachloride for 5 min. The slurry was cooled to room temperature and filtered. The white solid was rinsed on the funnel with 100 ml. of carbon tetrachloride and dried to give 108 g. of anhydrous acid (IIc) melting at 198–200° with decomposition. About 15 g. of Ic can be recovered from the liquors. Crystallization of the acid IIc from 50% aqueous dioxane gave a monohydrate, m.p. 204–207° dec. (-H_2O, 120–140°), $[\alpha]_D$ −17.7° (diox.).

Anal. Calcd. for $C_{22}H_{26}O_4.H_2O$: C, 70.94; H, 7.58. Found: C, 70.74; H, 7.93.

4-[3-Methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]-2-butynoic acid (IId). Procedure A was used on 6.5 g. of 17α-propargyl-3-methoxy-1,3,5(10)-estratrien-17β-ol (Id). The crude dry product was suspended in 35 ml. of boiling carbon tetrachloride for 5 min. and the slurry then cooled to room temperature. Filtration yielded 7.0 g. of acceptable product IId. Crystallization from 50% aqueous ethanol gave an analytical sample, m.p. 187.5–191.5° dec.

Anal. Calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.25; H, 7.95.

3-(3β,17β-Dihydroxy-5-androsten-17α-yl)propenoic acid lactone (IIIa). Procedure B was used on 0.2 g. of acetylenic acid hydrate IIa. Two crystallizations of the crude product from aqueous methanol yielded 0.07 g. of the desired product IIIa, m.p. 201–203°, $[\alpha]_D$ +2° ($CHCl_3$), ϵ^{220} 9550.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.95; H, 8.81.

4-(3β,17β-Dihydroxy-5-androsten-17α-yl)-2-butenoic acid lactone (IIIb). Procedure B was used on 3.0 g. of acetylenic acid IIb. The crude product (IIIb) was not characterized but rather used directly in the preparation of Vb.

3-[3-Methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]propenoic acid lactone (IIIc). Procedure B was used on 5 g. of acetylenic acid hydrate IIc. The 4.0 g. of crude lactone was recrystallized from ethyl acetate to yield 2.55 g. of unsaturated lactone IIIC, m.p. 170–173°, $[\alpha]_D$+94° (diox.).

Anal. Calcd. for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.17; H, 7.45.

3-(3-Oxo-17β-hydroxy-4-androsten-17α-yl)propenoic acid lactone (IV). Procedure C was used on 0.81 g. of IIIa. The crude product was chromatographed over silica gel and the product eluted with 10% ethyl acetate–90% benzene. Upon crystallization from ethyl acetate–cyclohexane there was obtained 0.30 g. of unsaturated lactone IV, m.p. 153.5–154.5°, $[\alpha]_D$ +203.5° ($CHCl_3$), ϵ^{237} 20,200, IR (KBr) 5.78μ (unsaturated lactone).

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.41; H, 8.44.

3-(3β,17β-Dihydroxy-5-androsten-17α-yl)propanoic acid lactone (Va). The unsaturated lactone (IIIa) (20 g.) was dissolved in 225 ml. of absolute ethanol and treated with hydrogen at atmospheric pressure and at room temperature in the presence of 4 g. of 5% palladium on carbon. When one equivalent of hydrogen was absorbed the reaction was stopped, the catalyst filtered off, and the filtrate evaporated to dryness. The residue was recrystallized from ethyl acetate. There was obtained 14 g. of Va, m.p. 190–191°, $[\alpha]_D$ −91.5° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.40; H, 9.90.

4-(3β,17β-Dihydroxy-5-androsten-17α-yl)butanoic acid lac-

tone (Vb). The crude lactone IIIb derived from 3.0 g. of IIb was dissolved in 50 ml. of absolute ethanol containing 0.1 ml. of concentrated hydrochloric acid and hydrogenated at atmospheric pressure over 0.5 g. of 5% palladium on carbon. After one equivalent of hydrogen was absorbed the reaction was stopped. The catalyst was filtered off and the filtrate diluted with water. Extraction of the aqueous phase with chloroform yielded upon evaporation of the extracts, 3 g. of the saturated lactone Vb as a viscous oil which resisted crystallization. The infrared spectrum showed a peak at 5.80μ, characteristic of a six-membered saturated lactone. The crude product was used directly in the next step.

3-[3-Methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]-propanoic acid lactone (Vc). A solution of 2.55 g. of IIIc in 150 ml. of ethyl acetate was treated with hydrogen at atmospheric pressure in the presence of 0.5 g. of 5% palladium on charcoal at 21°. When hydrogen uptake had ceased the catalyst was filtered off and the solvent evaporated. The residue was recrystallized from ethyl acetate–isopropyl ether to yield 1.8 g. of Vc, m.p. 150–152°, $[\alpha]_D$ +12.5° (diox.).

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.49; H, 8.13.

4-[3-Methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]-butanoic acid lactone (Vd). To 6.5 g. of IId dissolved in 130 ml. of ethanol, 2.0 g. of triethylamine was added to form the salt. The solution was hydrogenated over 1.0 g. of 5% palladium on carbon at room temperature at about 24 p.s.i. of hydrogen pressure. Hydrogen uptake ceased in 40 min. The solution was filtered to remove the catalyst and evaporated to a small volume which was poured into an excess of dilute hydrochloric acid. The product was collected on a funnel and washed free of acid with water. After drying, the product was crystallized from ethyl acetate to yield 4.05 g. of 4-[3-methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]-butanoic acid (VIIb), m.p. 164–168.5° dec.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.15; H, 8.66. Found: C, 74.31; H, 8.77.

To obtain the lactone (Vd), 3.1 g. of hydroxy acid was dissolved with 100 mg. of *p*-toluenesulfonic acid in 500 ml. of benzene and the solution distilled slowly to a residual volume of 100 ml. The residual solution was washed twice with water and dried over sodium sulfate. Removal of solvent *in vacuo* and two crystallizations of the residue from ethyl acetate yielded 1.5 g. of Vd, m.p. 161–166°, after vacuum drying at 100° for 2 hr.

Anal. Calcd. for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.57; H, 8.46.

3-(3-Oxo-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (VIa). Procedure C was used on 10 g. of Va. The crude product was recrystallized from ethyl acetate to yield 4.8 g. of the 3-oxo-4-ene lactone (VIa), m.p. 148–150° (polymorph melts 163–165°), $[\alpha]_D$ +76.5° ($CHCl_3$), ϵ^{241} 17,000.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.31; H, 8.94.

4-(3-Oxo-17β-hydroxy-4-androsten-17α-yl)butanoic acid lactone (VIb). The crude product (Vb) was oxidized according to Procedure C. This crude product was chromatographed over silica and the product eluted with 15% ethyl acetate–85% benzene. The crude fractions weighing 1.2 g. were recrystallized twice from ethyl acetate–isopropyl ether to give 0.7 g. of VIb, m.p. 192–193°, ϵ^{240} 17,000. Infrared spectrum (KBr) 5.77μ (six-membered lactone).

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.43; H, 9.09.

3-(3-Oxo-17β-hydroxy-19-nor-4-androsten-17α-yl)propenoic acid lactone (XI) *and 3-(3-oxo-17β-hydroxy-19-nor-4-androsten-17α-yl)propanoic acid lactone* (Xa) *by direct reduction of IIc.* A suspension of 7.8 g. of the hydrate of IIc in 500 ml. of *t*-butyl alcohol and 1 l. of ammonia was treated with 8.0 g. of lithium added portionwise over a period of 30 min. After a total of about 2 hr. all the lithium had reacted and the ammonia was allowed to evaporate overnight in a stream of nitrogen. The solution was quenched with 250 ml. of water and the *t*-butyl alcohol removed by distillation. Then the solution was made acid with acetic acid and the product extracted with ether. The tacky product obtained from the ether was dissolved in 50 ml. of methanol and treated with 2 ml. of concentrated hydrochloric acid for 1 hr. to complete isomerization of the 5(10) double bond and to insure closure of the lactone ring. This was quenched in water and the product extracted with ether. Upon removal of the ether the gummy residue was chromatographed over silica using mixtures of benzene and ethyl acetate as developing solvents. In the 10% ethyl acetate eluate there was obtained by crystallization from ethyl acetate–isopropyl ether, 0.14 g. of the unsaturated lactone (XI) m.p. 117–118°, $[\alpha]_D$ +55.2° (diox.), $\epsilon^{239.5}$ 18,700, infrared (KBr), 5.78μ (unsatd. five-membered lactone carbonyl).

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.48; H, 8.84.

Elution with 15% ethyl acetate yielded after crystallization from ethyl acetate 1.0 g. of the saturated lactone (Xa), m.p. 135.5–137° (another form melted 126.5–127°), $[\alpha]_D$ +22.7° ($CHCl_3$), ϵ^{240} 17,500. The analytical sample melted at 137–138°.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.49; H, 8.34.

Sodium 3-[3-methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]propanoate (VIIa). A solution of 124 g. (0.35 mole) of acetylenic acid IIc and 40.4 g. of triethylamine in 1 l. of absolute ethanol was hydrogenated[10] over 12.4 g. of 5% palladium on carbon at about 500 p.s.i. at laboratory temperature. The reaction was complete in about 25 min.

To this solution of the triethylamine salt of 3-methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-ylpropanoic acid was added with good mixing a solution of 28 g. (0.7 mole) of sodium hydroxide in 200 ml. of methanol. A dense white precipitate of the sodium salt formed promptly. After 5 hr. the salt was collected on a funnel, rinsed with 100 ml. of alcohol and finally dried in a vacuum oven at 75° for 12 hr. to give 116 g. of the desired product (VIIa) which is completely soluble in warm water. The mother liquor was vacuum evaporated to a small volume and then poured into an excess of dilute hydrochloric acid. After several hours the granular precipitate was collected on a funnel, rinsed free of mineral acid and dried to furnish 20 g. of a mixture of the hydroxy acid and its lactone (Vc). Extraction with 200 ml. of boiling ethyl acetate left 10 g. of the insoluble 3-methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-ylpropanoic acid, melting at 150–152° with decomposition.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.71; H, 8.44.

Heating this acid at 160° for a few minutes resulted in loss of water and quantitative conversion to the lactone (Va). Lactonization may also be achieved by treating a concentrated solution of the hydroxy acid in alcohol with a small amount of 3*N* hydrochloric acid, letting the solution stand for 5 min. and then recovering the product by dilution with water.

3-(3-Oxo-17β-hydroxy-19-nor-4-androsten-17α-yl)-propanoic acid lactone (Xa) *by reduction of sodium salt* (VIIa). Procedure D was used on 114 g. of the sodium salt VIIa. The reaction mixture was diluted to a volume of 3 l. with water and acidified by the addition of 600 ml. of acetic acid. After 2 hr. the finely divided white solid was collected on a filter, rinsed well with water, and pressed as dry as possible on the funnel. This crude enol ether (VIIIa) was hydrolyzed and rearranged by stirring it with 200 ml. of hydrochloric acid and 360 ml. of water in 2 l. of methanol for 2 hr. The resulting solution was treated with Darco, filtered, poured into 8 l. of water, and the mixture was allowed to stand overnight. The white crystals were collected, rinsed free of acid, and dried to give 79.1 g. of crude (Xa). Crystallization

(10) This hydrogenation was carried out by Mr. W. M. Selby.

from 237 ml. of ethyl acetate and 553 ml. of isopropyl ether yielded 52 g. of the lactone melting at 134–135°. Concentration of the mother liquor gave 14 g. of material which was chromatographed to furnish an additional 6 g. of pure product.

3-[3-Oxo-17β-hydroxy-19-nor-5(10)-androsten-17α-yl]propanoic acid lactone (IXa). Procedure D was followed on 3.7 g. of VIIa to the point where excess ammonia was evaporated. Addition of 250 ml. of water at this point produced a two-phase solution. The upper solvent layer was separated, carefully acidified with hydrochloric acid, and diluted with several volumes of water. The precipitate was collected on a funnel and washed free of acid with water. The product was dried and crystallized twice from ethyl acetate to yield 0.470 g. of lactone (IXa), m.p. 173–177°.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.65; H, 8.14.

4-(3-Oxo-17β-hydroxy-19-nor-4-androsten-17α-yl)butanoic acid lactone (Xb). Procedure D was used on 6.9 g. of 4-[3-methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]butanoic acid (VIIb). The dilute aqueous solution containing the crude lithium salt was carefully acidified with dilute hydrochloric acid and the precipitate collected on a funnel and washed free of acid with water. Two crystallizations from ethyl acetate yielded 1.45 g. of 4-[3-oxo-17β-hydroxy-19-nor-5(10)-androsten-17α-yl]butanoic acid as the semihydrate, m.p. 108–111°, after vacuum drying at 80°.

Anal. Calcd. for $C_{22}H_{32}O_4 \cdot {}^1/_2H_2O$: C, 71.51; H, 9.00. Found: C, 71.09; H, 9.03.

The ethyl acetate mother liquors were evaporated to dryness and dissolved in 500 ml. of benzene. After adding 150 mg. of *p*-toluene sulfonic acid the solution was distilled to a residual volume of 100 ml. which was washed twice with water and then dried over sodium sulfate. After evaporation of the solvent the crude residue was chromatographed over silica gel. Elution with 15% ethyl acetate–85% benzene produced a fraction which was crystallized from ethyl acetate with isopropyl ether to yield 84 mg. of Xb, m.p. 143–145°, ϵ^{240} 17,700, infrared ($CHCl_3$) 5.75μ (six-membered lactone).

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.77; H, 8.82.

3-(3-Oxo-17β-hydroxy-5α-androstan-17α-yl)propanoic acid lactone (XIIa) *and 3-(3-oxo-17β-hydroxy-5β-androstan-17α-yl)propanoic acid lactone* (XIIIa). A solution of 1.0 g. of VIa in 25 ml. of ethyl acetate was treated with hydrogen at atmospheric pressure at 30° in the presence of 0.2 g. of 5% palladium on carbon. When the uptake of hydrogen ceased, the catalyst was filtered off and the filtrate evaporated to dryness. The residue was chromatographed over silica and the products were eluted with 10% ethyl acetate–90% benzene. The early fractions gave 0.50 g. of the *trans* isomer (XIIa), which on recrystallization from ethyl acetate yielded 0.45 g. of XIIa, m.p. 178–179°, $[\alpha]_D$ +5.2° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.41; H, 9.12.

The later eluates yielded on recrystallization from ethyl acetate 0.14 g. of the *cis* isomer (XIIIa), m.p. 183–185°, $[\alpha]_D$ +6.8° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.62; H, 9.17.

4-(3-Oxo-17β-hydroxy-5α-androstan-17α-yl)butanoic acid lactone (XIIb) *and 4-(3-oxo-17β-hydroxy-5β-androstan-17α-yl)butanoic acid lactone* (XIIIb). Seven and one-half g. of the crude lactone (VIb), which assayed 80% by ultraviolet, was dissolved in 100 ml. of ethanol and hydrogenated at atmospheric pressure in the presence of 1.5 g. of 5% palladium on carbon until absorption ceased (8.0 hr.). The catalyst and the solvent were removed, leaving 7.3 g. of a viscous product which could not be crystallized. The mixture was chromatographed over silica and eluted with ethyl acetate–benzene solution. Early in the 10% ethyl acetate eluate there was obtained 720 mg. of solid product which was crystallized from ethyl acetate–isopropyl ether to furnish 260 mg. of the *trans* isomer (XIIb) as fine white needles, m.p. 191–193°, $[\alpha]_D$ +30° ($CHCl_3$). Infrared (KBr) 5.78μ.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.02; H, 9.24.

Late in the 10% ethyl acetate eluate, 1.7 g. of solid fractions were collected, which, after crystallization from ethyl acetate–isopropyl ether, weighed 800 mg. and melted at 196–197°, (*cis* isomer, XIIIb), $[\alpha]_D$ +28.6° ($CHCl_3$). Infrared (KBr) 5.78μ.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.90; H, 9.43.

A mixture of the *cis* and *trans* isomers melted at 175°.

3-(3-Oxo-17β-hydroxy-19-nor-5α-androstan-17α-yl)propanoic acid lactone (XIIc) *and 3-(3-oxo-17β-hydroxy-19-nor-5β-androstan-17α-yl)propanoic acid lactone* (XIIIc). A solution of 6.0 g. of Xa in 100 ml. of ethyl acetate at 30° was treated with hydrogen at atmospheric pressure in the presence of 1.0 g. of 5% palladium on carbon. After hydrogen uptake ceased, the solution was filtered and the filtrate evaporated to dryness. The residue was chromatographed over silica and the products were eluted with 15% ethyl acetate–85% benzene. The early fractions were recrystallized from ethyl acetate to give 0.45 g. of XIIc, m.p. 198–201° (also obtained as a polymorph melting 168–170°), $[\alpha]_D$ +9.7° (diox.).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.41; H, 9.27.

The middle fractions of this eluate contained a mixture of XIIc and XIIIc. However, pure XIIIc could be obtained from the later 15% ethyl acetate eluates by crystallization from ethyl acetate. In this fashion 1.63 g. of XIIIc, m.p. 218–222°, $[\alpha]_D$ 0.0° (diox.), was obtained.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.36; H, 9.50.

3-(3β,17β-Dihydroxy-5α-androstan-17α-yl)propanoic acid lactone (XIV). A solution of 0.60 g. of Va in 20 ml. of absolute ethanol was treated with hydrogen at atmospheric pressure and 24° in the presence of 0.1 g. of 5% palladium on charcoal. After 7 hr., hydrogen uptake ceased and the mixture was filtered and the filtrate evaporated to dryness. Recrystallization from ethyl acetate yielded 0.40 g. of product, m.p. 196–199°. An analytical sample of the product, XIV, prepared by recrystallization from ethyl acetate, melted 199–201° and showed an $[\alpha]_D$ of −20.0° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.29; H, 9.91.

3-(3-Oxo-17β-hydroxy-5α-androstan-17α-yl)propanoic acid lactone (XIIa) *from* XIV. Procedure C was used on 10 g. of XIV. The crude product was recrystallized from ethyl acetate to give 7.1 g. of XIIa, m.p. 177–179°. This was shown to be identical with XIIa, obtained above by hydrogenation, by determination of mixture melting points, and comparison of infrared spectra.

3-(3-Oxo-17β-hydroxy-19-nor-5α-androstan-17α-yl)propanoic acid lactone (XIIc) *from* Xa. To a solution of 1.5 g. of Xa in 50 ml. of *t*-butyl alcohol, 50 ml. of tetrahydrofuran, and 150 ml. of ammonia was added 1.0 g. of lithium. After the blue color disappeared the solvents were removed by distillation. The residue was treated with water and made strongly acid with hydrochloric acid. The precipitate was collected, washed with water, and dried. Then it was suspended in 150 ml. of acetone and treated with 3.5 ml. of 6*N* chromic acid–sulfuric acid solution. The excess chromium was destroyed with isopropyl alcohol and the solution filtered and evaporated to dryness. The residue was crystallized from ethyl acetate (Darco) to give a total of 0.65 g. of material m.p. 195–197°. This was shown to be identical with XIIc, obtained by hydrogenation, by mixture melting point determination and comparison of infrared spectra.

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