

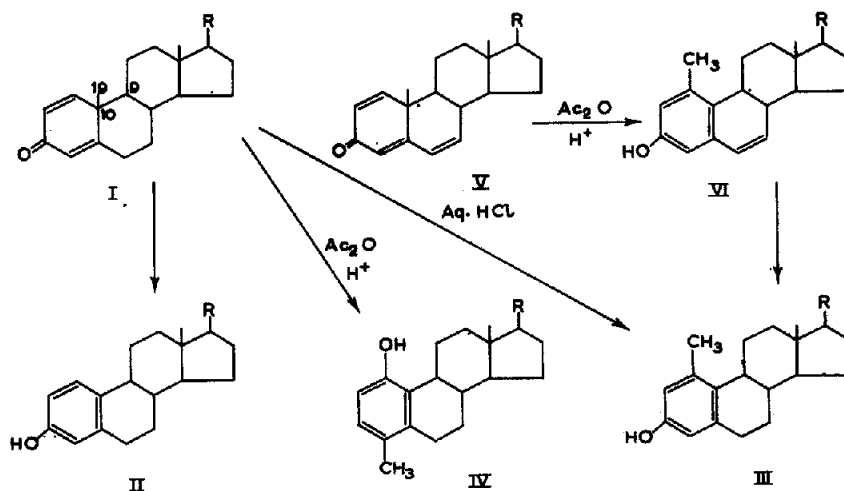
## THE SYNTHESIS OF AROMATIC A RING 9//10- SECOSTEROIDS FROM UNSATURATED 3,11-DIKETO STEROIDS

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(Received 23 July 1957)

**Abstract**—The preparation of aromatic A ring 9//10 secosteroids via the pyrolysis of unsaturated 3,11-diketosteroids is described.

THE partial synthesis of aromatic A ring steroids is based on the pioneering work of Inhoffen who showed that 3-keto-1,4-dienes could be converted to aromatic A ring steroids by two methods. In the first method the 3-keto-1,4-diene (I) was pyrolyzed in a sealed tube to give a low yield of the phenol (II).<sup>1</sup> Significantly higher yields were



reported for this reaction when the steroid, dissolved in a hydrogen-donating solvent such as mineral oil, was passed through a heated tube.<sup>2</sup> Recently this aromatization reaction was utilized for the preparation of aromatic A ring steroids containing a

<sup>1</sup> H. H. Inhoffen *Angew. Chem.* 53, 471 (1940).

<sup>2</sup> H. H. Inhoffen *Ibid.* 59, 207 (1947); C. R. Addinall Fiat Final Report 996 *The Commercial Development and Manufacture of Synthetic Hormones in Germany*. Office of the Publication Board, U.S. Dept. of Commerce; E. B. Herahberg, M. Rubin and E. Schwenk *J. Org. Chem.* 15, 292 (1950).

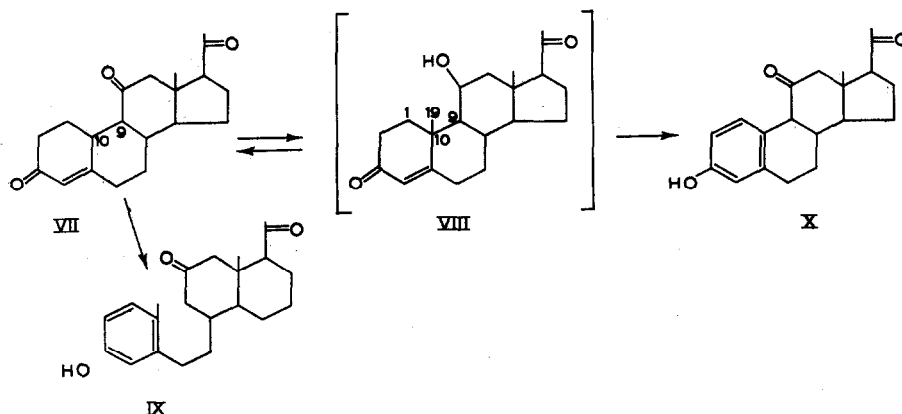
variety of functional groups.<sup>3</sup> Yields up to 40 per cent were reported in certain cases. This reaction was also successfully employed in the presence of an 11 $\alpha$ - or 11 $\beta$ -hydroxyl group and 9(11)-unsaturation.<sup>4</sup>

The second general method involved the dienone-phenol rearrangement of the 3-keto-1,4-diene in a non-aqueous acid system.<sup>2,5</sup> Originally the product of this rearrangement was thought to be the 1-methyl steroid (III), however, later work established (IV) as the correct structure.<sup>6-9</sup> Dienone-phenol rearrangement of a 3-keto-1,4,6-triene (V) afforded a true 1-methyl steroid (VI). Subsequent hydrogenation of the double bond at 6 formed the phenol (III).<sup>7</sup>

Recently the aromatization of 3-keto-1,4-dienes in the presence of aqueous mineral acid was reported to form chiefly the 1-methyl phenols (III) as well as lesser amounts of the 1-hydroxy-4-methyl phenols (IV).<sup>10</sup>

The formation of the phenol (II) by pyrolysis of a 3-keto-1,4-diene may be interpreted according to the Staudinger-Schmidt double bond rule which states that pyrolytic fission of a C-C bond in unsaturated compounds is most likely to occur at an allylic position.<sup>11</sup> Thus in structure (I) the 10,19 and the 9,10-bond both have a 1,3 relationship to two points of unsaturation ( $\Delta^1$  and  $\Delta^4$ ). The likely points of fission are therefore at 10-19 and 9-10 with the exocyclic 10,19-bond being preferred.

In the light of this rule two products are probable from the pyrolysis of a 3,11-diketo-4-ene, such as 11-ketoprogesterone (VII).



If the 11-keto group should exert its influence in the enol form (VIII), bonds 10,19 and 10,1 both would be 1,3 to two points of unsaturation and fission of the 10,19 bond again might be expected. If the effect of the 11-keto group is due to its keto form, only the 9,10-bond is 1,3 to two points of unsaturation and a 9//10 secosteroid (IX) is the likely product. The secosteroid (IX) was actually isolated, thus establishing a new type of aromatic A ring product obtainable from unsaturated 3-ketosteroids.

<sup>3</sup> *Inter alia* C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin and J. Romo *J. Amer. Chem. Soc.* **73**, 1523 (1951); C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki *Ibid.* **72**, 4534 (1950).

<sup>4</sup> B. J. Magerlein and J. A. Hogg *Ibid.* **79**, 1508 (1957).

<sup>5</sup> H. H. Inhoffen and G. Zühlsdorff *Ber. Dtsch. Chem. Ges.* **74**, 604 (1941).

<sup>6</sup> R. B. Woodward and T. Singh *J. Amer. Chem. Soc.* **72**, 494 (1950).

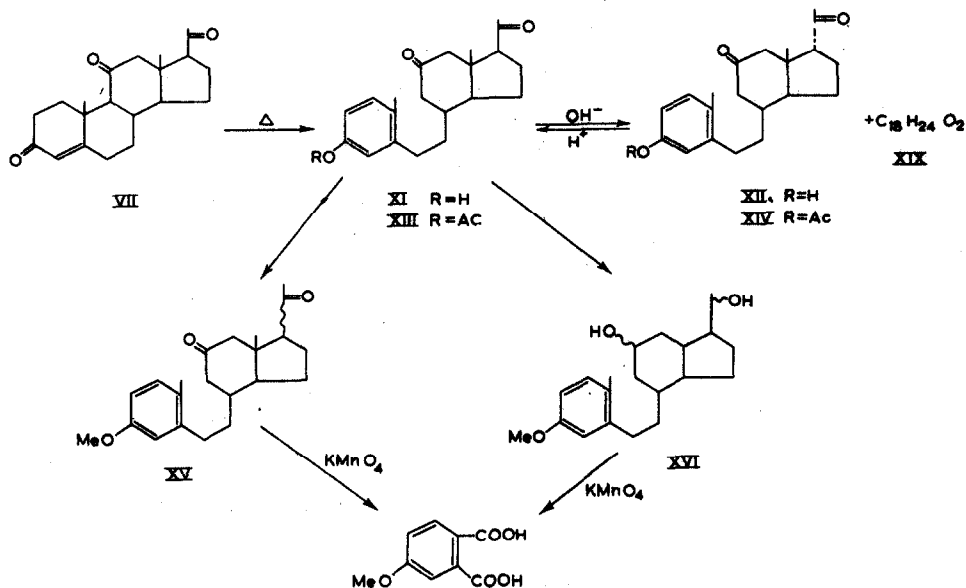
<sup>7</sup> C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki and St. Kaufmann *Ibid.* **72**, 4540 (1950).

<sup>8</sup> R. B. Woodward, H. H. Inhoffen, H. O. Larson and K. Menzel *Ber. Dtsch. Chem. Ges.* **86**, 594 (1953).

<sup>9</sup> A. S. Dreiding and A. Voltman *J. Amer. Chem. Soc.* **76**, 537 (1954).

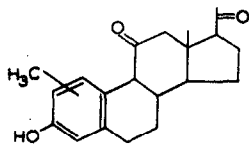
<sup>10</sup> A. S. Dreiding, W. J. Pummer and A. J. Tomaszewski *Ibid.* **75**, 3159, 3162 (1953).

<sup>11</sup> R. C. Fuson *Advanced Organic Chemistry* p. 15. John Wiley, New York (1950).



11-Ketoprogesterone was fused in an open vessel and heated to about  $350^\circ$ . A phenolic fraction, obtained in 65 per cent yield, chiefly consisted of three parts of (XI) and one part of (XII). When (XI) was treated with alkali, a mixture of (XI) and (XII) was obtained. A high yield of (XI) was obtained when (XII) was refluxed with aqueous acid. Compound (XII) is more dextrorotatory than is (XI) [(XII)  $[\alpha]_D + 43^\circ$  in acetone; (XI)  $[\alpha]_D - 35^\circ$  in acetone]. These facts suggest that (XI) and (XII) are isomeric at a carbon atom  $\alpha$  to a carbonyl. Because of the rotational change C-17 was chosen as the point of isomerization and the  $17\beta$  configuration assigned to (XII).

Before assigning the seco structure to the pyrolysis products of 11-ketoprogesterone, the phenolic formulations (X) and (XVIII) were considered.



XVIII

Structure (X) is eliminated by an accurate determination of the molecular weight as 327.7 (calcd. for  $\text{C}_{21}\text{H}_{33}\text{O}_3$ , 328.4)\* which clearly indicates that the methyl group is still present.

The physical data are insufficient to eliminate structure (XVIII). The major pyrolysis product (XI) was methylated forming the oily methyl ether (XV) which on

\* The authors are indebted to Dr. J. Shell of the Upjohn Company for the crystallographic analysis. Dr. Shell reports that the extremely high negative birefringence exhibited by these crystals is in keeping with a 9/10 seco compound, that is, the molecule is less planar and more rod shaped than the usual steroid molecule. These data are accurate to  $\pm 1$  per cent.

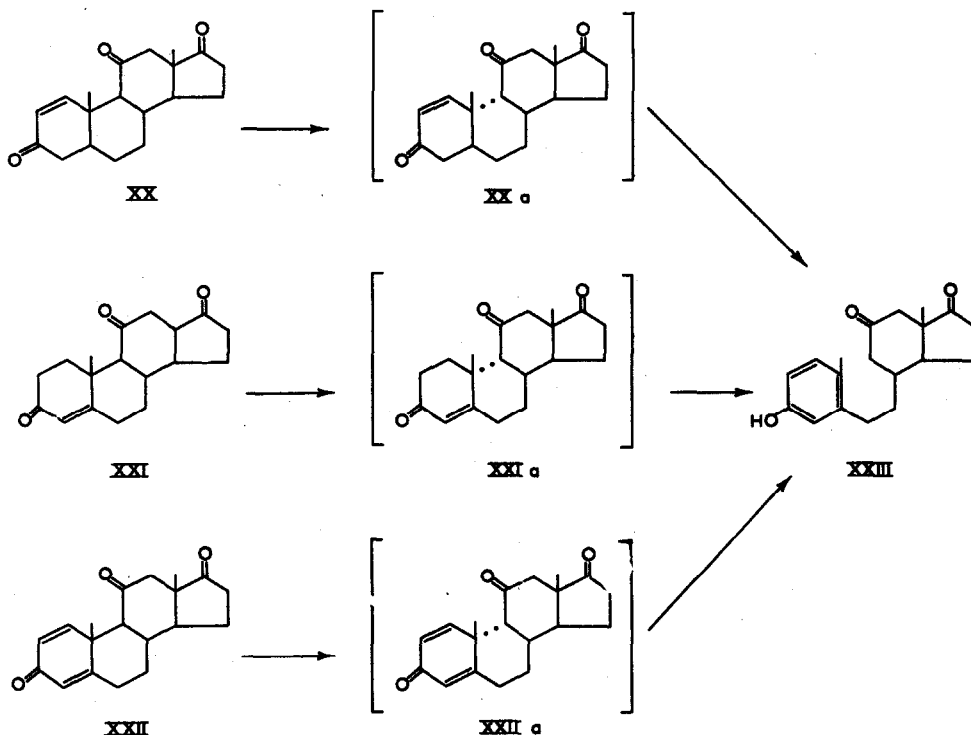
exhaustive oxidation yielded the known 4-methoxyphthalic acid. Since 4-methoxyphthalic acid could be formed only from a disubstituted phenol, structure (XVIII) is eliminated.

From these data we conclude that the seco structures (XI) and (XII) for the pyrolysis products of 11-ketoprogesterone are most consistent with the known facts.

A third crystalline product (XIX) was isolated in 0.4 per cent yield from this pyrolysis reaction. The elemental analysis for (XIX) is consistent with the empirical formula  $C_{18}H_{24}O_2$ . Infra-red data indicate phenolic hydroxyl and carbonyl.

The pyrolysis product of 4-androstene-3,11,20-trione (XXI) is assigned by analogy the seco structure (XXIII).

Having demonstrated that 9//10-secosteroids are formed in the pyrolysis of 3,11-diketo-4-enes our interest turned to 3,11-diketo steroids possessing unsaturation at 1 or at 1 and 4. In both of these cases the 9-10 bond is allylic to one more point of unsaturation than is the 10,19-bond. Therefore one might expect that the pyrolytic products from these would be formed after initial fission of the 9,10 bond. Pyrolysis of 1-androstene-3,11,17-trione (XX) or 1,4-androstadiene-3,11,17-trione (XXII) gave the same compound (XXIII) obtained by the pyrolysis of 4-androstene-3,11,17-trione (XXI).



An explanation for the formation of 9//10-secosteroids may be formulated by considering the mechanism of the aromatization reaction. Pyrolytic reactions are generally accepted to proceed by free radical mechanisms.<sup>12</sup> The pyrolysis of a 3-keto-1,4-diene therefore could first involve the loss of the 19-CH<sub>3</sub> radical leaving

<sup>12</sup> E. W. R. Steacie *Free Radical Mechanisms* p. 61. Reinhold Publishing Corporation, New York (1946).

the steroid radical which could then abstract a hydrogen atom from the solvent or from another steroid molecule to yield the phenol.

In the case of the  $\Delta^1$ ,  $\Delta^4$  or  $\Delta^{1,4}$ -3,11-diketo steroids, as previously noted, the 9,10-bond has one more 1,3 relationship to points of unsaturation than does the 10,19-bond. Therefore in the 11-keto series the presence of the 11-keto group causes the initial cleavage to occur at 9,10 to form the diradicals (XXa), (XXIa), (XXIIa), respectively. The diradicals (XXa), (XXIa), and (XXIIa) abstract the necessary hydrogen atoms to form the seco structure shown (XXIII).

#### EXPERIMENTAL\*

##### 3-Hydroxy-9//10-seco-1,3,5(10)-pregnatriene-11,20-dione (XI) and 3-Hydroxy-9//10-seco-17-iso-1,3,5(10)-pregnatriene-11,20-dione (XII)

Ten grams of 11-ketoprogesterone (I) was heated at 365–370° for 45 min, after which time gassing had noticeably decreased. About 165 ml (24 per cent of 1 mole) of gas was evolved in this reaction. Infrared analysis of this gas showed it to consist of methane, ethylene, carbon dioxide and carbon monoxide. The ratio of methane to ethylene was about 40 to 1. Benzene (25 ml) was added to the warm melt and then 100 ml of ether. The solution was separated into phenolic and neutral fractions with 5 per cent sodium hydroxide. The neutral fraction weighed 3.5 g. This dark tarry material was chromatographed over Florisil† but no definite fractions were obtained. Papergram analysis showed a small amount of 11-ketoprogesterone along with numerous unidentified materials. The phenolic fraction, 6.4 g, was dissolved in benzene and chromatographed over 500 g of Florisil. Elution with Skellysolve B‡ plus 12 per cent acetone yielded Fraction A of 2.99 g. Further elution with this solvent and also with Skellysolve B plus 20 per cent acetone gave 0.98 g of Fraction B.

Fraction A was recrystallized from 2-propanol (yield 2.13 g, 21.3 per cent). It melted 132–136°. Several recrystallizations from ethyl acetate gave an analytical sample of 3-hydroxy-9//10-seco-1,3,5(10)-pregnatriene-11,20-dione (XI) m.p. 138–139°;  $[\alpha]_D + 43^\circ$  (acetone);  $\lambda_{\max}^{\text{EtOH}}$  281 m $\mu$ ,  $a_M$  2,225; 287 m $\mu$ ,  $a_M$  1,975;  $\nu_{\max}^{\text{Nujol}}$  3205, 1705, 1675, 1618, 1583, 1497 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>21</sub>H<sub>28</sub>O<sub>3</sub>: C, 76.79; H, 8.59; Mol. wt. 327.76. Found: C, 76.53, 76.63; H, 8.38, 8.25; Mol. wt. 328.4.§

Recrystallization of Fraction B from 2-propanol yielded 780 mg of 3-hydroxy-9//10-seco-17-iso-1,3,5(10)-pregnatriene-11,20-dione (XII), m.p. 153–157°. Recrystallization from ethyl acetate-Skellysolve B gave an analytical sample m.p. 159.5–160.5°;  $[\alpha]_D - 35^\circ$  (acetone);  $\lambda_{\max}^{\text{EtOH}}$  281 m $\mu$ ,  $a_M$  2,225; 287 m $\mu$ ,  $a_M$  1,975;  $\nu_{\max}^{\text{Nujol}}$  3240, 1705, 1690, 1617, 1585, 1498 cm<sup>-1</sup>.

*Anal.* Found: C, 77.19; H, 8.73.

From the forefractions of a similar pyrolysis a crystalline compound m.p. 178–179°,  $[\alpha]_D + 15^\circ$  (acetone);  $\nu_{\max}^{\text{Nujol}}$  3230, 1687, 1675, 1618, 1585, 1502 cm<sup>-1</sup> was isolated in 0.4 per cent yield.

*Anal.* Calcd. for C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>: C, 79.37; H, 8.88. Found: C, 79.45, 79.18; H, 8.72, 8.76.

\* Melting points are uncorrected.

† A synthetic magnesia—silica gel made by the Floridin Company, Warren, Pa.

‡ A saturated hydrocarbon fraction, b.p. 60–71°.

§ See footnote on p. 82.

*Isomerization of compound (XII) to compound (XI)*

A solution of 230 mg of (XII), m.p. 153–158°, in 6 ml of ethanol and 0.6 ml of concentrated hydrochloric acid was heated under reflux for 30 min. The solvent was evaporated under vacuum and the product crystallized from ethyl acetate-Skellysolve B to give 90 mg m.p. 129–132°. Recrystallization from the same solvent gave 50 mg m.p. 133–135.5°. This material showed no m.p. depression when admixed with (XI). Its infra-red curve was identical with that of (XI).

Conversion of 17 g of crude (XII) (chromatographic fraction) to (XI) as described gave about 60 per cent of material m.p. 134–138.5°.

*Partial isomerization of compound (XI) to compound (XII)*

(A) *By alkali.* A solution of 100 mg of (XI) free from (XII), as shown by papergram, in 5 ml of 5 per cent sodium hydroxide was heated to boiling and permitted to stand for 4 hr. Acidification of the solution gave an oil which by papergram consisted of 75 per cent (XI) and 25 per cent (XII).

(B) *By heat.* Fifty milligrams of (XI) free from (XII), as shown by papergram, was heated at 360° for 15 min. Papergram showed the resulting oil to be 64 per cent (XI) and 36 per cent (XII).

*3-Acetoxy-9//10-seco-1,3,5(10)-pregnatriene-11,20-dione (XIII)*

A solution of 200 mg of (XI) in 1.5 ml of acetic anhydride and 1.5 ml of pyridine was warmed on a steam bath for ninety minutes. The cooled reaction mixture was poured into water with vigorous stirring. The crude product obtained by filtration was dried and recrystallized from ethyl acetate-Skellysolve B to give 200 mg (87.5 per cent) of (XIII) m.p. 138–139°. Further crystallization yielded an analytical sample m.p. 139–140°,  $\lambda_{\max}^{\text{EtOH}}$  268 m $\mu$ ,  $a_M$  558; 274.5 m $\mu$ ;  $a_M$  548.  $\nu_{\max}^{\text{Nujol}}$  1745, 1692, 1612, 1585, 1500, 1219 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>23</sub>H<sub>30</sub>O<sub>4</sub>: C, 74.56; H, 8.16. Found: C, 74.53, 74.71; H, 8.31, 8.08.

*3-Acetoxy-9//10-seco-17-iso-1,3,5(10)-pregnatriene-11,20-dione (XIV)*

In the manner described above (XII) was acylated to give 54 per cent yield of (XIV) m.p. 90–94°. Chromatography over Florisil was necessary to purify the crude material. The analytical sample melted 91–93°;  $\lambda_{\max}^{\text{EtOH}}$  268 m $\mu$ ,  $a_M$  555; 274.5 m $\mu$ ,  $a_M$  540.  $\nu_{\max}^{\text{Nujol}}$  1748, 1694, 1605, 1584, 1494, 1214 cm<sup>-1</sup>.

*Anal.* Found: C, 74.69, 74.55; H, 8.10, 8.20.

*3-Methoxy-9//10-seco-1,3,5(10)-pregnatriene-11,20-dione (XV)*

To a solution of 2.0 g of (XI) in 15 ml of ethanol warmed to 70° there was added at 5-min intervals 1 ml of sodium hydroxide (10 g NaOH/25 ml H<sub>2</sub>O) and 1 ml of dimethyl sulfate. Five additions were made. The solution was poured into water and the methyl ether extracted with methylene dichloride. After washing with water and drying, evaporation of the solvent gave 2.10 g of oily methyl ether (XV) which resisted crystallization.

*Oxidation of 3-methoxy-9//10-seco-1,3,5(10)-pregnatriene-11,20-dione (XV)*

A solution of 5.0 g sodium hydroxide in 100 ml of water was heated to 90° and 1.0 g of (XV) added. A solution of 4.0 g of potassium permanganate in 80 ml of

water was added in 20 ml portions. Each addition was made when the permanganate color of the previous addition was discharged. Finally 1.0 g portions of potassium permanganate were added until the purple color persisted at 90° for 1 hr. A total of 9.0 g of potassium permanganate was added. Five milliliters of ethanol was added to destroy the excess oxidizing agent. The solution was filtered after 10 g of Celite 545 was added to aid in the filtration. The clear solution was acidified and concentrated to dryness. The residue was triturated three times with 50 ml portions of hot ethyl acetate. The extract was concentrated to dryness. The extraction with ethyl acetate was repeated to give 0.49 g of solids. By alternate recrystallization from ethyl acetate and water a total of 90 mg of 4-methoxyphthalic acid was obtained m.p. 172–174°. The infra-red absorption of this compound was identical with that of a known sample of this acid.\*

### 3-Methoxy-9//10-*seco*-1,3,5(10)-pregnatriene-11 $\xi$ ,20 $\xi$ -diol (XVI)

Five grams of (XI) was dissolved in 150 ml of benzene and added to 300 ml of ether containing 3.0 g of lithium aluminum hydride. After heating under reflux for 1.5 hr the reaction mix was hydrolyzed and worked up in the usual fashion. The oily residue was methylated as described for the preparation of (XV) to give 4.5 g of oily (XVI).

### Dehydration studies with compound (XVI)

Three 100 mg samples of methyl ether (XVI) were treated with thionyl chloride-pyridine, sodium bisulfate and BF<sub>3</sub>-etherate, respectively. The ultra-violet absorption curves of the crude products were essentially identical with that of the starting compound.

### Dehydrogenation studies with compound (XI)

Treatment of 100 mg samples of (XI) with 5 per cent Pd-C at 250–350° for 10–20 min gave oily products whose ultra-violet absorption showed no bands characteristic of naphthalenic compounds.

### 3-Hydroxy-9//10-*seco*-1,3,5(10)-androstriene-11,17-dione (XXIII)

(A) *From adrenosterone*. Ten grams of adrenosterone was pyrolyzed at a bath temperature of 350–360° for 50 min. The melt, when cooled, was dissolved in a mixture of benzene and methylene dichloride and chromatographed over 800 g of Florisil. The fraction eluted with Skellysolve B—4 per cent acetone weighed 814 mg (8.1 per cent yield). Recrystallization from ethyl acetate gave 750 mg m.p. 208–211°;  $[\alpha]_D + 85^\circ$ ;  $\lambda_{\text{max}}^{\text{EtOH}}$  281 m $\mu$ ,  $a_M$  2,250, flex 286 m $\mu$ ;  $\nu_{\text{max}}^{\text{Nujol}}$  3250, 1735, 1690, 1620, 1590, 1500 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>19</sub>H<sub>24</sub>O<sub>3</sub>: C, 75.97; H, 8.05. Found: C, 75.86, 75.88; H, 7.77, 7.66.

(B) *From 1-androstene-3,11,17-trione*. Pyrolysis of 1.0 g of 1-androstene-3,11,17-trione as described above yielded 135 mg of crude (XXIII) which when recrystallized from ethyl acetate melted 209–212°. The infra-red absorption curve of this material was identical with that from A above.

\* We are indebted to Dr. H. Shechter of the Ohio State University for an authentic sample of 4-methoxyphthalic acid.

(C) *From 1,4-androstadiene-3,11,17-trione.* In a similar manner pyrolysis of 0.5 g of 1,4-androstadiene-3,11,17-trione yielded 100 mg of the seco steroid (XXIII) m.p. 210–214°.

*Acknowledgements*—The authors are indebted to L. M. Rejneke and associates for papergram analyses; to Dr. J. L. Johnson, J. E. Stafford and Mrs. G. S. Fonken for spectroscopic studies; to W. A. Struck and associates for microanalyses and optical rotations; to V. R. Shellman for technical assistance; and to Professor M. S. Newman for valuable suggestions in the course of this work.