[Contribution from the Research Laboratories of the Chemical Division of Merck & Co., Inc.]

Approaches to the Total Synthesis of Adrenal Steroids. XII. *dl*-$\Delta^{5,16}$-3-Ethylenedioxypregnadiene-11,20-dione

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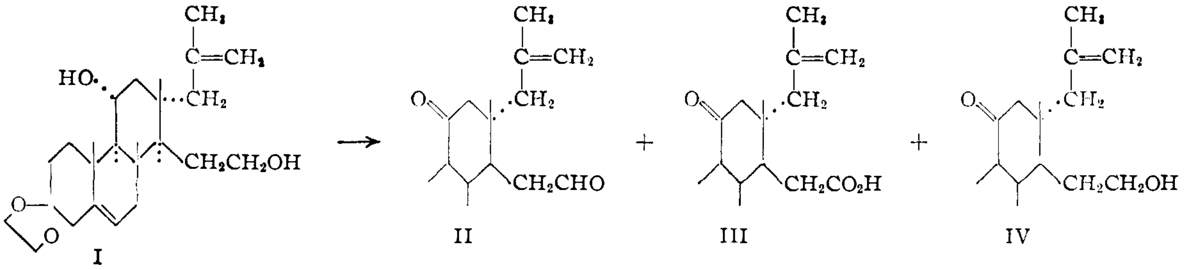
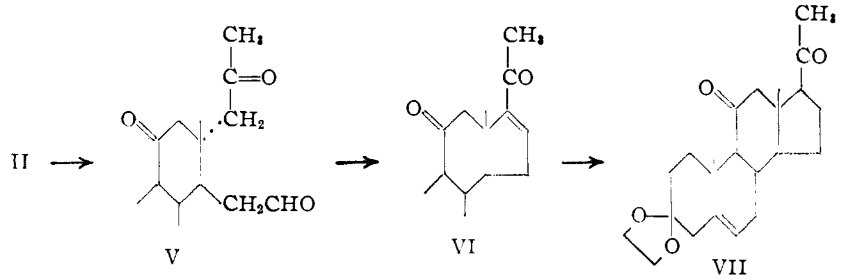
Oxidation of the tricyclic diol I with the chromic anhydride–pyridine complex converts the primary alcohol function to the corresponding aldehyde II in 68% yield. The methallyl group of II is hydroxylated and the resulting glycol is cleaved giving the acetonyl aldehyde V. The latter undergoes an intramolecular aldol condensation in the presence of potassium hydroxide to yield *dl*-$\Delta^{5,16}$-3-ethylenedioxypregnadiene-11,20-dione. The 16,17-double bond of the pregnadiene may be hydrogenated giving *dl*-11-ketoprogesterone-3-dioxolane.

The synthesis of *dl*-11-ketoprogesterone 3-dioxolane (VII) from a polyhydrophenanthrene with the C_1-side chain in the β-hydroxyethyl oxidation state[1] and the conversion of VII to *dl*-cortisone acetate[2] have been described in the two preceding papers of this series. Another method for the closure of ring D involving polyhydrophenanthrenes with the C_1-side chain at the next higher oxidation level forms the subject of the present communication.





In our program on the total synthesis of adrenal steroids, the chromic anhydride–pyridine reagent has proved valuable for the oxidation of secondary alcohols to the corresponding ketones.[1,3] It was of interest to test the effect of this reagent upon a primary alcohol such as I to determine if it would be possible to produce a reasonable yield of the corresponding aldehyde.

An application of the chromic anhydride–pyridine oxidation to the tricyclic diol I[1] resulted in the production of the keto aldehyde II as the major product (68%) along with small amounts of the keto acid III and keto alcohol IV.

Selective hydroxylation of the methallyl double bond in the keto aldehyde II with osmium tetroxide followed by cleavage of the resulting glycol with periodic acid proceeded smoothly affording the acetonyl keto aldehyde V. Cyclization of the latter with potassium hydroxide[4] led to *dl*-$\Delta^{5,16}$-3-ethylenedioxypregnadiene-11,20-dione (VI) in 73% yield.[5] Selective hydrogenation of the conjugate double bond of VI proceeded in high yield in the presence of palladium on barium carbonate giving the known 3-ethylenedioxy derivative of *dl*-11-ketoprogesterone (VII).[1]

Experimental[5a]

2β,4b-Dimethyl-7-ethylenedioxy-2-methallyl-1β-formylmethyl-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (II).—To the suspension obtained by adding 19.0 g. of chromic anhydride[6] to 190 ml. of pyridine was added a solution of 15.96 g. of 2β,4b-dimethyl-7-ethylenedioxy-2-methallyl-1β-(2-hydroxyethyl)-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (I)[1] in 160 ml. of pyridine. After standing at room temperature overnight,

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[1] W. F. Johns, R. M. Lukes and L. H. Sarett, This Journal, **76**, 5026 (1954).

[2] G. I. Poos, R. M. Lukes, G. E. Arth and L. H. Sarett, *ibid.*, **76**, 5031 (1954).

[3] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

[4] Under the conditions of A. L. Wilds, *ibid.*, **64**, 1421 (1942). See also L. H. Sarett, W. F. Johns, R. E. Beyler, R. M. Lukes, G. I. Poos and G. E. Arth, *ibid.*, **75**, 2112 (1953).

[5] The successful aldol condensation of the keto aldehyde V to a Δ^{16}-20-ketosteroid parallels the closure of ring D utilized by R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952), in their elegant total synthesis of steroids.

[5a] Melting points were determined on a Kofler micro-hotstage. Infrared spectra are of the crystalline solids in Nujol.

[6] The nature of the products was somewhat dependent upon the amount of chromic anhydride employed. Using a weight of chromic anhydride equal to that of the starting diol in twenty parts of pyridine the aldehyde, acid and alcohol were obtained in yields of 45, 20 and 5%, respectively. Decreasing the proportion of oxidizing agent further gave even lower yields of aldehyde.

the reaction mixture was poured into 500 ml. of water and extracted with three 700-ml. portions of ether. The combined ether extract was washed with water and then extracted with 100 ml. of 0.5 *N* potassium hydroxide and washed with 100 ml. of water which was added to the alkaline extract. After back extraction with ether, the alkaline solution was acidified with 8 ml. of 5 *N* sulfuric acid and excess sodium dihydrogen phosphate and the liberated acid was extracted into chloroform. From the chloroform solution there was obtained 2.20 g. (13.4%) of 2β,4b-dimethyl-7-ethylenedioxy-2-methallyl-1β-carboxymethyl-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (III), m.p. 210–216°. A sample recrystallized from ethyl acetate melted at 215–216°; $\lambda_{\max}$ 3.2–3.8, 5.82, 5.90, 6.08 μ.

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.79; H, 8.37.

Diazomethane in ether gave the methyl ester, m.p. 140–141°, from ether. The melting point was not lowered upon admixture with a sample of 2β,4b-dimethyl-7-ethylenedioxy-2-methallyl-1β-carbomethoxymethyl-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one.[1]

After washing, drying and concentration, the neutral ether solution afforded 13.9 g. of crystalline residue which was recrystallized twice from methanol to give 8.00 g. (51%) of II, m.p. 143–149°. The analytical sample melted at 148–150° after recrystallization from benzene and ether; $\lambda_{\max}$ 5.83, 5.85, 6.08 μ. It gave an immediate precipitate of a semicarbazone in ethanolic semicarbazide.

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.55; H, 8.79.

Chromatography on 150 g. of acid-washed alumina of the combined material from the mother liquors remaining after the separation of II provided an additional 2.68 g. (17%) of II, m.p. 142–149°, from the ether–petroleum ether eluate. Further elution with chloroform gave 1.56 g. (9.8%) of 2β,4b-dimethyl-7-ethylenedioxy-2-methallyl-1β-(2-hydroxyethyl)-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (IV), m.p. 110–116°, from ether. Several recrystallizations from ether gave pure IV, m.p. 119–120°; $\lambda_{\max}$ 2.82, 5.86, 6.08 μ.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.18; H, 9.34. Found: C, 74.23; H, 9.14.

This compound failed to form a semicarbazone in ethanolic semicarbazide.

2β,4b-Dimethyl-7-ethylenedioxy-2-acetonyl-1β-formylmethyl-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (V).—A solution of 10.47 g. of the methallyl keto aldehyde II in 50 ml. of benzene and 100 ml. of ether was treated with 7.50 g. of osmium tetroxide. After 1.5 hours at room temperature, the osmate ester which had precipitated was dissolved by the addition of 450 ml. of ethanol. For hydrolysis of the osmate ester a solution of 45 g. of sodium sulfite in 305 ml. of water was added and the resulting mixture was agitated vigorously for 15 minutes. An additional 500 ml. of ethanol was added and the material which had precipitated was collected on a filter and washed with ethanol. The filtrate was concentrated to a small volume under vacuum and then was diluted with water. The resulting precipitate was collected on a filter, washed with water and dried; 10.97 g., m.p. 145–172°. Recrystallization from chloroform–ether afforded 9.42 g. (83%) of glycol, m.p. 171–175°; $\lambda_{\max}$ 2.8–3.1, 5.85 μ. Chromatography of the remaining product on acid-washed alumina gave from the ether–petroleum ether eluates 945 mg. (9%) of unchanged II, m.p. 139–147°, followed by a small additional quantity of glycol eluted with chloroform.

The glycol (9.41 g., m.p. 171–175°) was dissolved in 70 ml. of tetrahydrofuran and 23 ml. of pyridine and the solution was treated with a solution of 7.15 g. of paraperiodic acid in 45 ml. of water. After 35 minutes at room temperature the reaction mixture was diluted with water and the tetrahydrofuran was distilled. The resulting crystalline precipitate was collected on a filter, washed with water and dried; 8.52 g. (98%), m.p. 121–130°. A sample recrystallized from benzene–ether and then ether melted at 131–133°; $\lambda_{\max}$ 5.83, 5.89 μ.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.48; H, 8.73.

***dl*-$\Delta^{5,16}$-3-Ethylenedioxypregnadiene-11,20-dione** (VI).—A suspension of 7.68 g. of acetonyl keto aldehyde V in 1 l. of water containing 25 g. of potassium hydroxide was freed of oxygen by distillation of 50 ml. of solvent under aspirator vacuum. The reaction mixture was then gently boiled overnight at 50–80° on the steam-bath under reduced pressure. The cooled suspension was extracted with three 200-ml. portions of chloroform and the combined chloroform extract was washed with water, dried over magnesium sulfate and concentrated to dryness. The resulting residue (7.5 g.) was dissolved in benzene and adsorbed on 225 g. of acid-washed alumina. Elution with ether–petroleum ether provided 5.62 g. (76%) of crude VI, m.p. 185–195°. Recrystallization from ethanol and methanol with combination and recrystallization of later crops gave 5.40 g. (73%) of the pure pregnadiene VI, m.p. 194–197°. A sample recrystallized from ether for analysis melted at 195–197°; $\lambda_{\max}^{\mathrm{MeOH}}$ 235 mμ, ε mol. 9,100; $\lambda_{\max}$ 5.87, 6.00, 6.24 μ.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.68; H, 7.86.

***dl*-11-Ketoprogesterone-3-dioxolane** (VII).—The pregnadiene VI (182 mg., m.p. 194–197°) in 50 ml. of benzene was shaken under three atmospheres of hydrogen over 300 mg. of 5% palladium on barium carbonate at room temperature until the uptake of hydrogen was complete (four hours). After filtration from the catalyst the solution was concentrated to dryness giving 182 mg. of crystalline residue, m.p. 175–182°. Recrystallization from ethanol afforded 157 mg. (86%) of pure VII melting at 181–183°. The melting point was not lowered on admixture with *dl*-11-ketoprogesterone-3-dioxolane described previously.[1]

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