recrystallisation from MeOH gave 180 mg. of (XXII) as leaflets, m.p. 160~161°. *Anal.* Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.00; H, 11.74. $[\alpha]_D^{15}$ +9°(c=0.54). I.R. λ_{max}^{Nujol} cm^{-1}: 1717, 1200, 970.

Summary

By consecutive formylation, methylation, and deformylation, 4,22-stigmastadien-3-one (IV) affords 2α-methyl-4,22-stigmastadien-3-one (VII), while the same treatment of the 5α-dihydro compound (VIII) of (IV) gives the 2α-methyl derivative (XI), which agrees with the reduction product of (VII) with lithium in liquid ammonia. The same treatment of the 5β-dihydro compound (XIIIa) of (IV) forms the 4β-methyl derivative (XXa). These experimental results are consistent with the general rule that the 2-position in 3-oxo-5α-steroids and 4-position of 3-oxo-5β-steroids are active.

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47. Kyosuke Tsuda and Shigeo Nozoe: Steroid Studies. XII.[1] On the Methylation of 3-Oxosteroids. (2).

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Formylation of progesterone series is more complicated than the formylation of 4,22-stigmastadien-3-one and 4,22-ergostadien-3-one series described in the preceding paper,[1] because in progesterone series, carbonyl group is present not only in 3- but also in 20-position.

Application of equimolar amount of ethyl formate to progesterone (I) affords 2,21-bis(hydroxymethylene)-4-pregnene-3,20-dione (II), sparingly soluble in benzene, and a monohydroxymethylene compound melting at 160°, which shows ultraviolet absorption maxima at 250 and 304 mμ (in MeOH), agreeing with the absorption maxima of 2-hydroxymethylene-4,22-stigmastadien-3-one.[1] The absorption of 20-ketone at 1704 cm^{-1} in the infrared spectrum of this substance remains the same but the absorption of its 3-ketone (1639 cm^{-1}) shows a marked shift to a smaller frequency region. These facts indicate that this monohydroxymethylene compound is the 2-substituted compound (III).

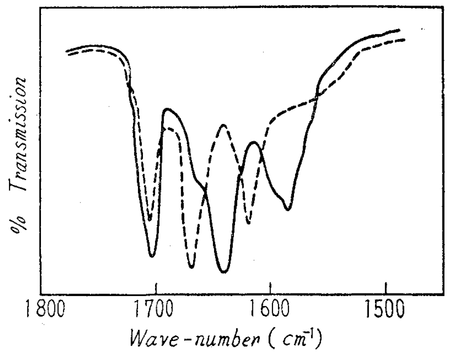

Fig. 1.
Infrared Spectra (in Nujol)

—— 2-Hydroxymethylene-4-pregnene-3,20-dione (III)
------ Progesterone (I)

Methylation of (III) with methyl iodide followed by deformylation of (IV) so formed gives 2α-methyl-4-pregnene-3,20-dione (2α-methylprogesterone) (V) of m.p. 146~147°, whose ultraviolet and infrared spectra are both very similar to those of (I).

Catalytic hydrogenation of (V) over palladium-carbon in ethanol gives the dihydro

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[1] Part XI: This Bulletin, 7, 232(1959).

compound whose fractional recrystallization separates it into a sparingly soluble compound of m.p. 178° and an easily soluble compound of m.p. 112°. The fact that the former compound is 2α-methyl-5α-pregnane-3,20-dione (VI) and the latter, 2β-methyl-5β-pregnane-3,20-dione (VII), was proved in the following manner.

Catalytic hydrogenation of (I) results in the formation of 5α-dihydro compound (VIII) and 5β-dihydro compound (X).[2] Formylation of (VIII) gives only one kind of a hydroxymethylene compound whose ultraviolet absorption maximum of 282.5 mμ agrees with that of 2-hydroxymethylene-5α-22-stigmasten-3-one.[1] From the experimental results to be described below, this formylation product is 2-hydroxymethylene compound (IX). The methyl derivative of m.p. 178°, obtained by methylation of (IX) followed by deformylation, is entirely identical with (VI) described above, and this confirms the fact that (VI) and (VII) are respectively 5α- and 5β-dihydro series. On the other hand, the 2-methyl should naturally take the stable equatorial conformation since it has undergone deformylation reaction, and the configuration of 2α is assigned to (VI) and 2β to (VII).

Formylation of 5β-pregnane-3,20-dione (X) invariably gives the dihydroxymethylene compound (XI). Since the compounds of 5β-series are active in 4-position,[1] this compound must be 4,21-bis(hydroxymethylene)-5β-pregnane-3,20-dione.

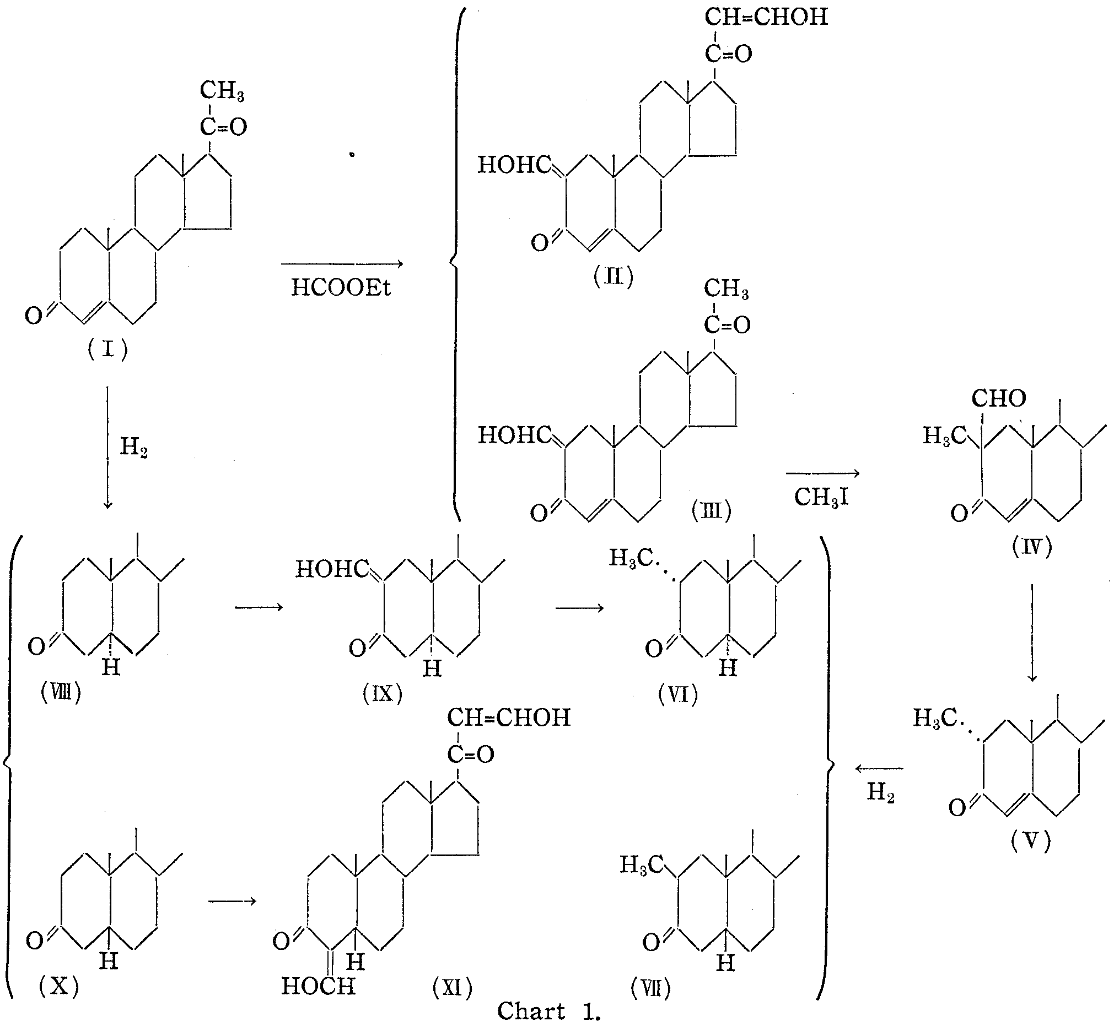

Chart 1.

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2) N. J. Antia, Y. Mazur, F. S. Spring: J. Chem. Soc., **1954**, 1218.

Experimental

2,21-Bis(hydroxymethylene)-4-pregnene-3,20-dione (II) and 2-Hydroxymethylene-4-pregnene-3,20-dione (III)—540 mg. of NaOMe was suspended in 20 cc. of dry benzene and 740 mg. of ethyl formate was added to the stirred mixture at room temperature. This solution was added to a solution of 3.14 g. of progesterone (I) in 20 cc. of dehyd. benzene with vigorous stirring. The mixture was stirred until a gelatinous orange precipitate separated and the mixture was allowed to stand over night. After usual processing, the syrup obtained was dissolved in 5 cc. of benzene to give 300 mg. of crystalline product melting at 200°. Recrystallization from MeOH gave (II) as pale yellow needles, m.p. 203~204°. *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found : C, 74.46; H, 7.96. $[\alpha]_D^{15}$ +97° (c=1.84). U.V. λ_{max}^{MeOH} mμ(log ε) : 267(3.96), 297(3.95).

The filtrate, diluted with 50 cc. of benzene, was chromatographed on silica gel and elution with benzene afforded 740 mg. of crystalline material melting at 155~159°. Recrystallization from MeOH gave (III), m.p. 160~161°. *Anal.* Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found : C, 76.99; H, 8.84. $[\alpha]_D^{15}$ +137°(c=1.44). U.V. λ_{max}^{MeOH} mμ(log ε) : 250(4.16), 304(3.82).

2α-Methyl-4-pregnene-3,20-dione (V) via 2-Methyl-2-formyl Derivative (IV)—A mixture of 1.71 g. of (III), 1.38 g. of K_2CO_3, and 4.14 g. of MeI in 15 cc. of acetone was heated under reflux for 24 hr. After the usual processing, recrystallization from MeOH gave crude (IV) as needles, m.p. 164~165°.

Without further purification, the crude material was treated with 30 cc. of MeOH and 3 cc. of 10% HCl in the usual way, resulting oily product was dissloved in 40 cc. of benzene, and the solution was chromatographed on alumina. Elution with benzene and recrystallization from MeOH afforded 400 mg. of (V) as needles, m.p. 146~147°. *Anal.* Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found : C, 80.59; H, 9.92. $[\alpha]_D^{15}$ +222°(c=0.96). U.V. λ_{max}^{MeOH} : 241.5 mμ(log ε 4.20).

Catalytic Hydrogenation of 2α-Methyl-4-pregnene-3,20-dione (V)—A solution of 180 mg. of (V) dissolved in 10 cc. of EtOH was hydrogenated over 10 mg. of 10% Pd-C. Hydrogenation was stopped when 1.1 moles of H_2 had been absorbed. The reaction mixture was separated from the catalyst, which was washed with a small amount of AcOEt, and the filtrate was evaporated under a reduced pressure to remove the solvent. Trituration of the residue with MeOH and recrystallization from AcOEt gave 70 mg. of 2α-methyl-5α-pregnane-3,20-dione (VI), m.p. 177~178°. *Anal.* Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found : C, 79.72; H, 10.32. $[\alpha]_D^{15}$ +126°(c=0.80).

Material recovered from the filtrate, when crystallized from light petr. ether, yielded 60 mg. of 2β-methyl-5β-pregnane-3, 20-dione (VII), m.p. 111~112°. *Anal.* Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found : C, 80.28; H, 10.51. $[\alpha]_D^{15}$ +92°(c=0.37).

2-Hydroxymethylene-5α-pregnane-3,20-dione (IX)—2.72 g. of (VIII) was treated with NaOMe (from 400 mg. of Na) and 1.28 g. of ethyl formate in 20 cc. of benzene in the usual way. After the usual processing, 2 g. of crude (IX) was obtained. Recrystallization from ligroine gave (IX), m.p. 200~201°. *Anal.* Calcd, for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.74; H, 9.42. $[\alpha]_D^{15}$ +132° (c=1.55). U.V. λ_{max}^{MeOH} : 285.5 mμ (log ε 4.11).

2α-Methyl-5α-pregnane-3,20-dione (VI)—Methylation of 570 mg. of (IX) was accomplished by heating under reflux for 24 hr. with 455 mg. of K_2CO_3 and 1.42 g. of MeI in 10 cc. of acetone. Treated in the usual way, pale yellow crude crystals, m.p. 182~184°(decomp.), were obtained. Without further purification of this product, successive deformylation was carried out in the usual way. Resulting crude oily material was purified by chromatography on alumina and the fraction eluted first with benzene was recrystallized from MeOH to yield 400 mg. of (VI) as needles, m.p. 177~178°, undepressed on admixture with a sample prepared from (V) by catalytic hydrogenation.

4,21-Bis(hydroxymethylene)pregnane-3,20-dione(XI)—A solution of 2.9 g. of (X) in 20 cc. of benzene was added to a solution of NaOMe (from 426 mg. of Na) and 1.37 g. of ethyl formate in 20 cc. of benzene. Resulting solution was treated in the usual way. Recrystallization from light petr. ether gave 700 mg. of (XI), m.p. 150~151°. *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found : C, 74.43; H, 8.88. U.V. λ_{max}^{MeOH} : 280.5 mμ(log ε 4.14).

Summary

Formylation of progesterone (I) gives the 2,21-bis(hydroxymethylene) compound (II) and 2-hydroxymethylene compound (III). Methylation of (III) and subsequent deformylation affords 2α-methylprogesterone (V). Formylation of the 5α-dihydro compound (VIII) of (I) results in the sole formation of the 2-hydroxymethylene compound (IX), and its methylation followed by deformylation gives the 2α-methyl derivative (VI). On the contrary, the 5β-dihydro compound (X) of (I) affords only the 4,21-bis(hydroxymethylene) compound (XI).

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