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107. Hiroshi Mitsuhashi and Masamichi Fukuoka : Synthesis of 14β-Pregnanes and Selenium Dehydrogenation of 3β,14β-Dihydroxy-5α,17α-pregnane-15,20-dione 3-Acetate. Studies on C-Nor-D-homosteroids. VI.*1

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Selenium dehydrogenation has been widely used to establish the carbon skeleton of steroids and other alicyclic systems. Recently, the formation of Jacobs' hydrocarbon from 12β-hydroxysteroids, *i.e.* sarcostin,[1] cynanchogenin,[2] desisovaleryl-tetrahydrodrevogenin A[3] and 3β,12β,20β-trihydroxy-5α-pregnane[4] has been reported. In view of these results it was of interest to examine possible skeletal rearrangements further during dehydrogenation. Geiger,[5] *et al.* have studied the selenium dehydrogenation of usharidin and isolated 3′-isopropylcyclopentenophenanthrene and a hydrocarbon which was presumed to be a benzofluorene derivative. This report suggested that 14β-hydroxysteroids might rearrange to benzofluorene type hydrocarbons through a cyclopropanium cation or its equivalent. To examine this problem, Reichstein and coworkers[6,7] attempted the dehydrogenation of strophanthidin and usharidin but obtained only alkylcyclopentenophenanthrenes and alkylchrysenes. In this paper the preparation of 14,15,20-oxygenated steroids and the selenium dehydrogenation of 3β,14β-dihydroxy-5α,17α-pregnane-15,20-dione 3-acetate is described. Hecogenin (I) was converted to pregn-16-en-20-one (II) according to Cameron's method,[8] and this product was oxidized with N-bromosuccinimide followed by epoxidation with monoperphthalic acid to give 3β-acetoxy-14β,15β-epoxy-5α-pregn-16-en-20-one[9] (III). The cleavage of the epoxide at the 14,15-position furnished several isomeric diols.[10] Treatment of III with 2*N* sulfuric acid in dioxane[11] furnished 14β,15α-dihydroxy-pregn-16-en-20-one 3-acetate (IVa) and its deacetylated compound (IVb) (evidences for the configurational assignments

*1 Part V : Tetrahedron, **22**, 1033 (1966). A part of this work was reported at the Hokkaido Branch Meeting of the Pharmaceutical Society of Japan. August 22, 1964 and May 29, 1965 Sapporo.

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2) H. Mitsuhashi, Y. Shimizu : This Bulletin, **8**, 738 (1960).
3) R. E. Winkler, T. Reichstein : Helv. Chim. Acta, **37**, 722 (1954).
4) H. Mitsuhashi, Y. Shimizu : Tetrahedron Letters, **20**, 902 (1962).
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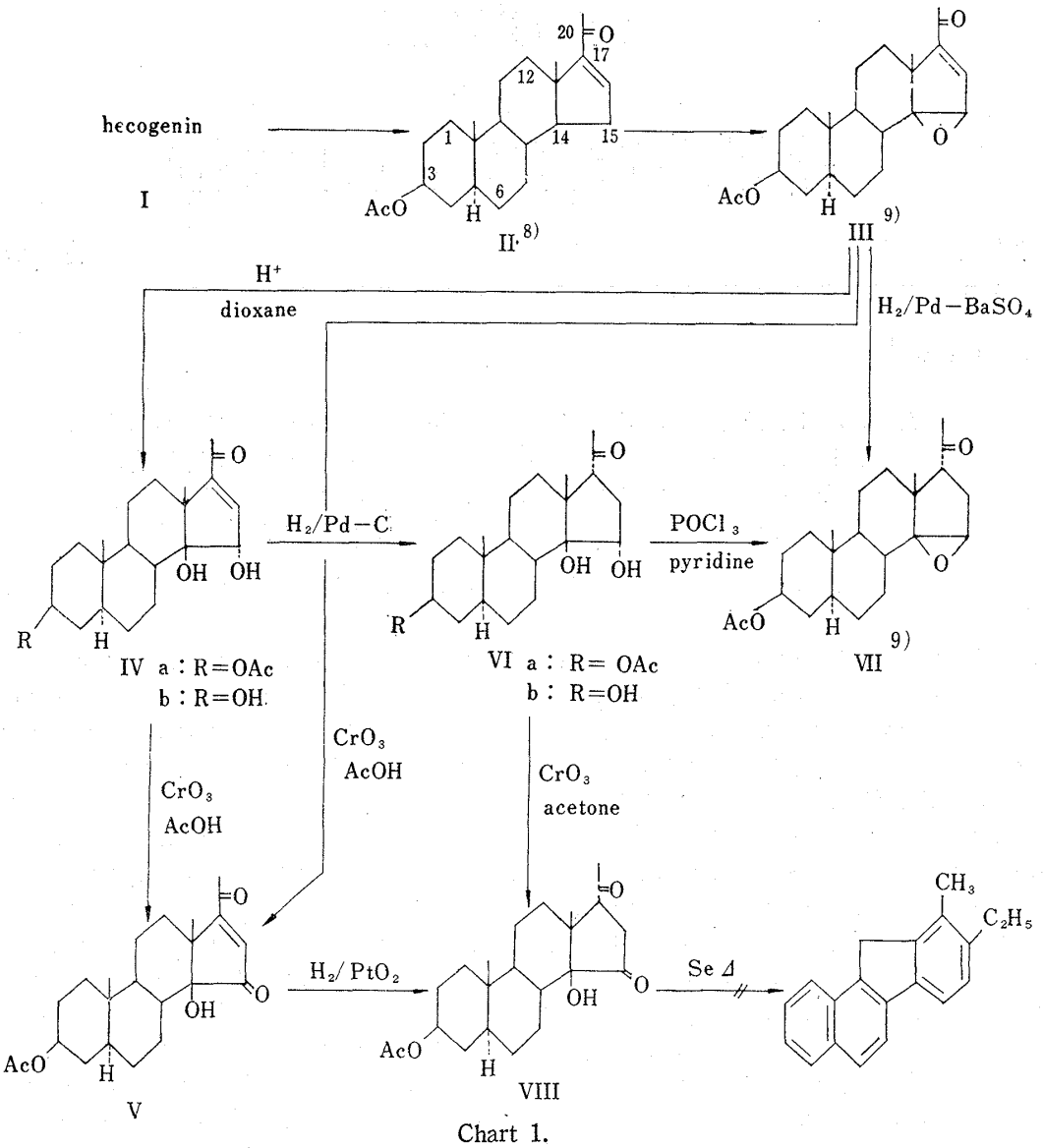

Chart 1.

at the 14- and 15-positions are discussed latter) in high yield. Ⅳa was oxidized with chromium trioxide in acetic acid to 3β,14β-dihydroxy-pregn-16-ene-15,20-dione 3-acetate (Ⅴ). This product (Ⅴ) was also prepared from Ⅲ in 90% yield by oxidation with the same reagent. The IR (infrared) spectrum of Ⅳa showed bands at 3540, 1724, 1250 (acetate), 1647 (α,β-unsaturated ketone) and 1610 cm^{-1} (C=C) and the UV (ultraviolet) spectrum showed a maximum at 231 mμ (log ϵ 3.83) due to the α,β-unsaturated ketone system. The structure of Ⅴ was shown from its IR spectrum 3575 (OH), 1720 (conj. five membered ring ketone) and 1680 cm^{-1} (conj. open-chain ketone), its UV spectrum 247 mμ (log ϵ 3.95) and its NMR (nuclear magnetic resonance) spectrum τ, 7.73 (3H) due to a methylketone, and 3.38 (1H) due to a vinyl proton. Catalytic hydrogenation of Ⅳa furnished the saturated diol (Ⅵa) which contained an additional carbonyl band at 1695 cm^{-1}. The two hydroxyl groups and side chain in the saturated diol (Ⅵa) were assigned the 14β-,15α- and 17α-orientation by the following two experiments. (i) Dehydration of Ⅵa with phosphorus oxychloride in pyridine furnished 3β-acetoxy-14β,15β-epoxy-5α,17α-pregnan-20-one*[3] (Ⅶ). (ii) The diol (Ⅵa) which had a negative ORD

*3 3β-acetoxy-14β,15β-epoxy-5α,17α-pregnan-20-one (Ⅶ) was prepared from 3β-acetoxy-14β,15β-epoxy-5α-pregn-16-en-20-one (Ⅲ) by hydrogenation according to known methods.[9]

(optical rotatory dispersion) Cotton effect, furnished the saturated triol (VIb) in high yield by alkaline hydrolysis which also showed a negative Cotton effect.[12] Support for this second explanation has been presented very recently when it was observed that the treatment of C/D *cis* pregnan-20-one with methanol in the presence of alkali furnished the 17α-side chain compound as a main product and had shown negative Cotton effect.[12] Catalytic hydrogenation of pregn-16-ene-15,20-dione (V) with 5% palladium-charcoal or 5% palladium-barium sulfate furnished five compounds (VIII to XII in Table I). VIII showed IR absorption at 3600 (OH), 1745 (five membered ring ketone), 1725 (acetate) and 1710 cm^{-1} (open-chain ketone) and a negative ORD Cotton effect $[\alpha]_{266}$ (peak) +1902°, $[\alpha]_{333}$ (trough) −2875°. VIII was also derived from the ketodiol (XI) and VIa by oxidation. By hydrogenolysis with 5% palladium-charcoal in ethylacetate, VIII afforded the saturated diketone (IX).

Hydrogenation of pregn-16-ene-15,20-dione (V) was considered to proceed by two pathways, one; V→VIII→IX, another; V→X→XI→XII (from Table I).

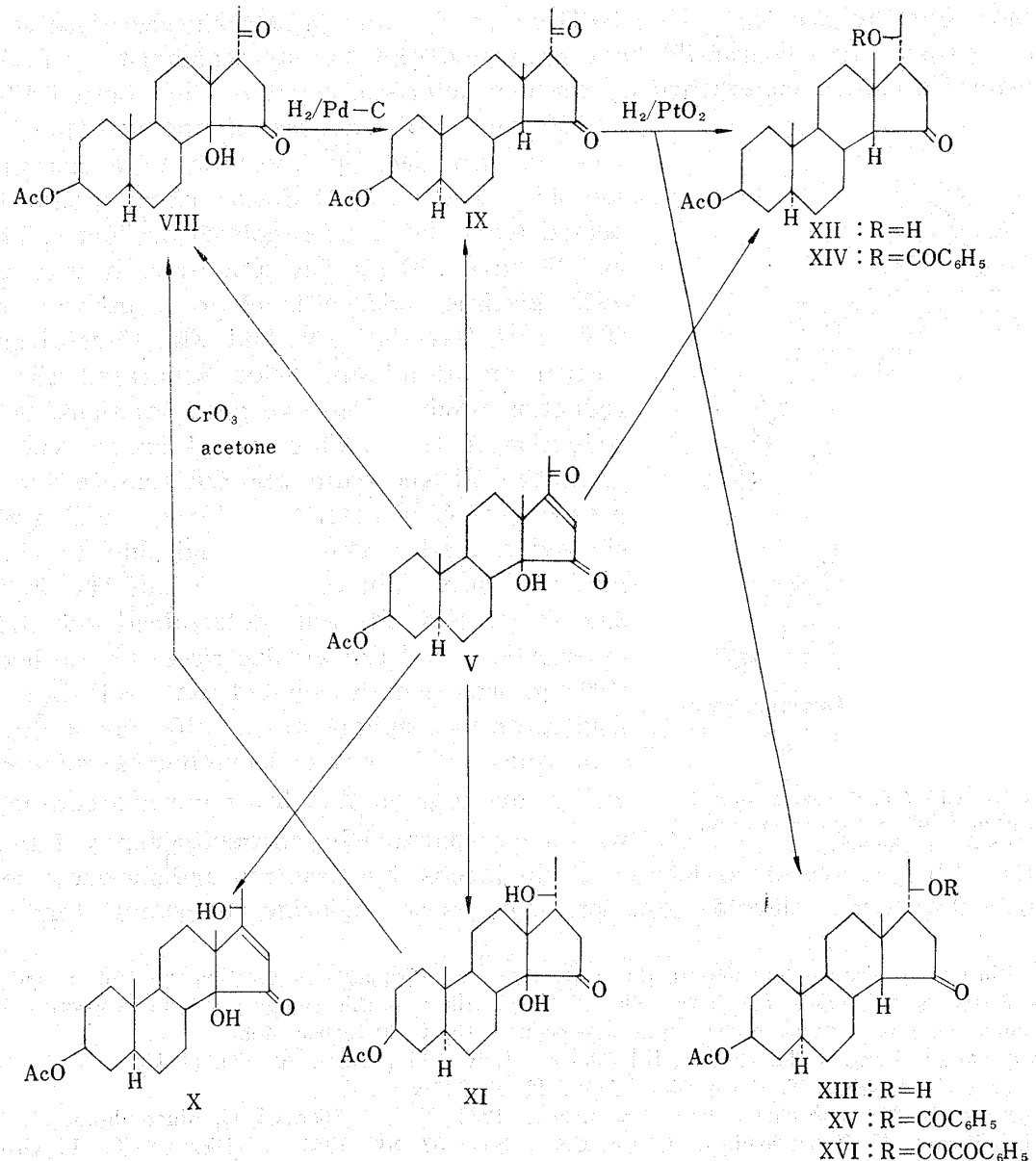

Chart 2.

12) H. Mitsuhashi, T. Nomura, M. Fukuoka : Steroids, **4**, 483 (1964).

Table I. The Reduction Products of 3β,14β-Dihydroxy-5α-pregn-16-ene-15,20-dione 3-Acetate

Condition	Absorp. H_2 (mole)	V (%)	X (%)	Ⅷ (%)	Ⅺ (%)	Ⅸ (%)	Ⅻ (%)
Pd-C in EtOH	1.3	12	28.2	20	10	27.9	trace
Pd-$BaSO_4$ in EtOH	1.5	6.4	28.2	28.5	5.4	5.2	—
Pd-C in AcOEt	2.25	—	trace	trace	trace	90.5	8.6
PtO_2	1	—	—	99	trace	—	—
Zn-AcOH 1.5 hr. reflux		—	trace	trace	trace	86.5	—

The configuration of Ⅺ was also considered to be 14β,17α type since the compound (Ⅷ) was also derived by oxidation of 3β,14β,15α-trihydroxy-5α,17α-pregnan-20-one 3-acetate (Ⅵa) which had a stable configuration of the 17-side chain with a C/D *cis* juncture, and hydrogenation of the double bond between the 16- and 17-positions had to take place from the β-side.[13] The ORD curve of Ⅸ and Ⅻ both showed negative Cotton effects. Lardon[14] and Djerassi[15] have suggested that the stereochemistry of C/D *cis* 15-ketosteroids can be established by the characteristic negative ORD Cotton effect.

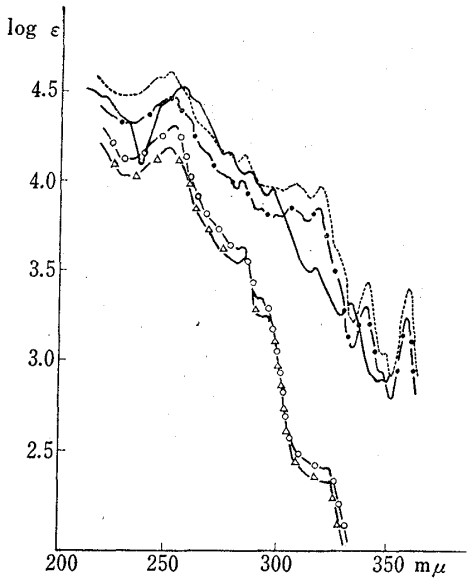

Fig. 1. Ultraviolet Absorption Spectra of Compound A, B, C, D and E

The intensity (log ε) was calculated for $C_{17}H_{14}$. ——A, ------B, ——●——C, ——○——D, ——△——E.

If the hydrogenolysis of the α-ketols (Ⅷ, Ⅺ) was accompanied by inversion to a normal 14α-steroid a positive ORD Cotton effect would be expected from the hydrogenolysis-product. Thus Ⅸ and Ⅻ have C/D *cis* ring junctures. Ⅸ was reduced with platinic oxide-ethanol to a mixture of the 20β- and 20α-ols*4 (Ⅻ and XIII). Careful gradient elution on aluminum oxide separated the crude reduction product into two pure fractions. Selective reduction of the C-20 carbonyl group was shown from the IR spectrum and ORD curve due to the presence of C-15-ketone, and the NMR spectrum showed a methyl doublet signal due to the C-21 methyl group. The configuration of the 20β- and 20α-ols (Ⅻ and XIII) was determined by the benzoate rule[16] and the atrolactric ester method.[17] Ⅷ (100 mg.) was dehydrogenated with selenium under a nitrogen atmosphere at ca. 310° for 24 hr. The *n*-hexane soluble part of the ether extract consisted of 5 compounds on thin-layer chromatography, and was then separated by chromatography into 5 oily fractions. All fractions were different from Jacobs' hydrocarbon and showed a negative test with 2% ferric chloride solution and ferric chloride-potassium ferricyanide

*4 In writing the projection formulas in the present group of paper, a suggestion by Fieser and Fieser, Experientia, **4**, 285 (1948), has been followed. According to this suggestion the respective 20β- or 20α-substituent is written on the left or the right of the C-20 carbon atom.

13) L. Ruzicka, A. Plattner, H. Heuser, Kd. Meier : Helv. Chim. Acta, **30**, 1342 (1947).
14) A. Lardon, H. P. Sigg, T. Reichstein : *Ibid.*, **42**, 1457 (1959).
15) C. Djerassi, G. Mutzenbecher : Proc. Chem. Soc., **1963**, 377; C. Djerassi, G. Mutzenbecher, J. Fajikos, D. H. Williams, H. Budzikiewicz : J. Am. Chem. Soc., **87**, 817 (1965); C. Djerassi, T. T. Grossnikle, L. B. High : *Ibid.*, **78**, 3163 (1956); C. Djerassi, R. Riniker, B. Riniker : *Ibid.*, **78**, 6362 (1956).
16) J. H. Brewster : Tetrahedron, **13**, 106 (1961).
17) V. Prelog, G. Tsatsas : Helv. Chim. Acta, **36**, 1178 (1953). J. C. Danilewicg, D. C. F. Garbutt, A. Horeau, W. Klyne : J. Chem. Soc., **1964**, 2254.

reagents.[18] The ultraviolet absorption maximum of these fractions show long wavelength absorption suggesting the presence of a highly conjugated system. The UV spectra suggested that all of the fractions consisted of cyclopentenophenanthrene-, chrysene-, and phenanthrene derivatives (Fig. 1). These results indicate that 14β-hydroxy-15-ketosteroids do not form Jacobs' hydrocarbon on selenium dehydrogenation.

Experimental

All melting points were measured with a Kofler Hot Stage Microscope and are uncorrected. Optical rotations were measured with a Hitachi Photoelectric Polarimeter Model PO-B. UV spectra were measured on a Hitachi Photoelectric spectrophotometer Model EPU-2A or a Hitachi Recording Spectrophotometer EPS-2U. IR spectra were measured on a Koken model DS-301 spectrophotometer equipped with NaCl optics, or a Shimadzu Recording Infrared Spectrophotometer Model IR-27. Opitical rotatory dispersion (ORD) curves were run in methanol with a JASCO Model ORD/UV-5. NMR spectra were determined at 60 Mc. in $CDCl_3$ solutions containing tetramethylsilane as an internal reference using a Nihon Denshi JNMC-60.

3β,14β,15α-Trihydroxy-5α-pregn-16-en-20-one (IVb) and its 3-Acetate (IVa)——2*N* H_2SO_4 (2.5 ml.) was added to a solution of 3β-acetoxy-14β,15β-epoxy-5α-pregn-16-en-20-one (III, 219 mg.) in dioxane (17 ml.). After standing at 25° for 90 hr., the solution was poured into H_2O, and the product extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4, and solvent removed. The residue was recrystallized from MeOH to give IVa (24.9 mg.), m.p. 251~256° $[\alpha]_D^{24}$ +40.9° (c=0.48, $CHCl_3$) UV: λ_{max}^{EtOH} 231 mμ (log ε 3.83): IR ν_{max}^{Nujol} cm^{-1}: 3540, 3320, 1724, 1647, 1610, 1250. *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.97; H, 8.68. The mother liquors from recrystallization of IVa, contained three compounds on thin-layer chromatography in the MeOH-$CHCl_3$ (7:100) system, and was chromatographed on silica gel (10 g.) (Mallincrodt Chemical Works, for chromatographic analysis, 100 mesh). Elution with benzene-ether (4:1) gave the starting material (18.2 mg.) (III), benzene-ether (3:2, 1:1) gave IVa (67.4 mg.).

Elution with benzene-ether (1:1) gave IVb, which was recrystallized from AcOEt, m.p. 243~245° (77.1 mg.). $[\alpha]_D^{22}$ +97.7° (c=0.532, MeOH). UV λ_{max}^{EtOH} mμ (log ε): 231.5 (3.87). IR ν_{max}^{Nujol} cm^{-1}: 3450~3350, 1671, 1660, 1610. *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.35; H, 9.13.

3β,14β-Dihydroxy-5α-pregn-16-ene-15,20-dione (V)——a) From IVa: A mixture of IVa (25 mg.) and CrO_3 (7 mg.) in 90% AcOH (10 ml.) was allowed to stand at 25° for 17 hr., and after destruction of the excess CrO_3, was concentrated under reduced pressure to give a solid mass which was extracted with CH_2Cl_2. The organic layer was washed with 5% $NaHCO_3$ and H_2O, dried over Na_2SO_4 and solvent removed to dryness. The residue was recrystallized from ether-hexane to give a yellow product (V), m.p. 168~169°. b) From III: A solution of III (1 g.) in AcOH (30 ml.) was treated with CrO_3 (350 mg.) in 90% AcOH (15 ml.) at room temperature for 24 hr., and worked up as described above. The product was purified by repeated recrystallization to obtain V (700 mg.). $[\alpha]_D^{17}$ +25.96° (c=1.033, $CHCl_3$). UV mμ (log ε): λ_{max}^{EtOH} 247 (3.95). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3575 (OH), 1725 (oAc), 1720 (conj. five membered ketone), 1680 (conj. open chain-ketone), 1255 (oAc). NMR (τ): 9.24 (singlet, C_{19}-CH_3), 8.79 (singlet, C_{18}-CH_3), 8.00 (singlet, acetate-CH_3), 7.73 (hydroxy-proton). The product was identical with that prepared from IVa by mixed melting point and identical IR spectra. *Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.29; H, 8.31.

3β,14β,15α-Trihydroxy-5α,17α-pregnan-20-one 3-Acetate (VIa)——A solution of IVa (260 mg.) in MeOH (30 ml.) was shaken with previously reduced 5% palladium-charcoal (100 mg.) in a hydrogen atmosphere. Hydrogen uptake ceased after 2 hr., absorbing 1.3 moles. The catalyst was removed, the solvent was evaporated *in vacuo* and the residue was chromatographed on Al_2O_3 (10 g.).

Elution with benzene-methanol (100:0.5) gave VIa (213 mg.), which was recrystallized from ether, m.p. 186~188°. $[\alpha]_D^{17}$ −48.07° (c=1.165, $CHCl_3$). RD: (c=0.1375, MeOH), $[\alpha]_{263}^{25}$ (peak) +1483.6°, $[\alpha]_{305}^{25}$ (trough) −1287.2°. IR ν_{max}^{Nujol} cm^{-1}: 3540, 1720, 1695, 1270. *Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.55; H, 9.27. A solution of VIa (50 mg.) in 5% methanol-potassium hydroxide (10 ml.) was refluxed for 5 hr., and after cooling, the reaction mixture was poured into H_2O followed extraction continuously with ether. The extract (40 mg.) gave VIb (5 mg.) which was purified by repeated recrystallization from AcOEt, m.p. 198~200°. RD: (c=0.185, MeOH), $[\alpha]_{263}$ (peak) +2027°, $[\alpha]_{304.5}$ (trough) −1351.3°, $[\alpha]_{589}$ −82°. IR ν_{max}^{Nujol} cm^{-1}: 3540 (broad), 1700. *Anal.* Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.00; H, 10.01

3β-Acetoxy-14β,15β-epoxy-5α,17α-pregnan-20-one (VII)——$POCl_3$ (0.5 ml.) was added to an ice-cold solution of VIa (60 mg.) in dry pyridine (2 ml.), and after storage at −5° for 15 hr., the solution was poured into ice-water. The resulting precipitate was extracted continuously with ether, and the ether soluble material was chromatographed on Al_2O_3 (1 g.). Elution with benzene gave III, which was recrystallized from ether-hexane, m.p. 147~149°, RD: (c=0.208, MeOH). $[\alpha]_{259}$ (peak) +1038.4°, $[\alpha]_{302}$ (trough) −461.5°, $[\alpha]_{589}$ −2°, IR ν_{max}^{Nujol} cm^{-1}: 1727, 1698, 1240. NMR (τ): 9.18 (19-CH_3), 8.70 (18-CH_3), 8.02 (acetate-CH_3), 7.89 (21-CH_3), 6.63 (15-H). *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.70; H, 9.12.

18) G. M. Barton, R. S. Evans, J. A. F. Gardner: Nature, **170**, 249 (1952).

Hydrogenation of 3β,14β-Dihydroxy-5α-pregn-16-ene-15,20-dione 3-Acetate (V)——a) With palladium-charcoal catalyst. A solution of V (165 mg.) in EtOH (20 ml.) was shaken with previously reduced 5% Pd-C (78 mg.) in a hydrogen atmosphere. Hydrogenation ceased after 1 hr. with the uptake of 1.3 mol. equivalents of H_2. The catalyst was removed by filtration and the solvent removed *in vacuo*. The residue was composed of 6 compounds by thin-layer chromatography in a 2% or 3% methanol in benzene system, and was chromatographed on silica gel (15 g.). Elution with benzene gave starting material (V, 20 mg.). Elution with benzene-ether (4:1) gave crystals (46 mg.) and oily substances. The former crystals (IX) were purified by repeated recrystallization from hexane, m.p. 121.5~123°, $[\alpha]_D^{20}$ −63.1° (c=1.38, $CHCl_3$). RD: (c=0.175, MeOH), $[\alpha]_{270}$ (peak) +3142.8°, $[\alpha]_{317}$ (trough) −2742.8°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (15-ketone), 1725 (shoulder, acetate), 1712 (20-ketone), 1252. NMR (τ): 9.24 (19-CH_3), 8.60 (18-CH_3), 8.00 (acetate-CH_3), 7.77 (21-CH_3). *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.80; H, 9.05. The latter oil (67.9 mg.) was rechromatographed on Al_2O_3 (2 g.) and elution with benzene gave a crystalline compound (VIII) (33 mg.), which was recrystallized from ether-hexane, m.p. 179.5~181.5°, $[\alpha]_D^{16}$ −83.7° (c=0.75, $CHCl_3$). RD: (c=0.16, MeOH), $[\alpha]_{266}$ (peak) +1902°, $[\alpha]_{333}$ (trough) −2875°.IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1745, 1725, 1710, 1220. *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.81; H, 8.66. Elution of the oil with benzene-ether (4:1) gave XI (17 mg.) which was recrystallized from hexane, m.p. 141~143°, RD: (c=0.1, MeOH), $[\alpha]_{265}$ (peak) +1680°, $[\alpha]_{332}$ (trough) −1500°, $[\alpha]_{589}$ −40°. IR ν_{max}^{Nujol} cm^{-1}: 3600, 1745, 1720, 1275. *Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.77; H, 9.32. Elution of the previous chromatogram with benzene-ether (3:2) gave X (46.6 mg.), which was recrystallized from hexane, m.p. 155~165°. UV mμ (logε): λ_{max}^{EtOH} 235 (3.73). RD: (c=0.25, MeOH), $[\alpha]_{280}$ (peak) +672°. $[\alpha]_{334}$ (trough) −512°, $[\alpha]_{589}$ −80°. IR ν_{max}^{Nujol} cm^{-1}: 3580, 1732, 1715, 1610, 1270. *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.90; H, 9.05.

b) Hydrogenation of V (884 mg.) in AcOEt (40 ml.) over 5% Pd-C (500 mg.) was carried out with the uptake of 2.25 mol. equivalents of H_2. The crude product was composed of 5 compounds and separated by chromatography on Al_2O_3 (20 g.) to give VIII, X, XI and other 2 crystalline compounds. Elution with benzene gave IX (800 mg.). Elution with benzene and benzene-ether (4:1, 1:1) gave XII (75 mg.), which was recrystallized from ether-hexane, m.p. 149~151°. RD: (c=0.23, MeOH). $[\alpha]_{276}$ (peak) +2173.9°, $[\alpha]_{324}$ (trough) −1717.3°, $[\alpha]_{589}$ −54.3°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1735 (shoulder), 1727, 1250. NMR (τ): 9.25 (singlet, 19-CH_3), 8.90 (singlet, 18-CH_3), 8.75 (doublet, J=7.0 c.p.s., 21-CH_3), 8.58*5 (singlet, 20-hydroxyl-H), 8.00 (singlet, acetate-CH_3). *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.29; H, 9.70.

c) With palladium-barium sulfate catalyst. Hydrogenation of V (186 mg.) in EtOH (30 ml.) over 5% Pd-$BaSO_4$ (100 mg.) was carried out with the uptake 1.5 mol. equivalents of H_2. The crude product was composed of 5 compounds by thin-layer chromatography and separated by repeated chromatography on Al_2O_3 to give V (11.19 mg.), VIII (54 mg.), IX (9.6 mg.), X (54.1 mg.) and XI (10 mg.).

d) With Adams' catalyst. A suspension of $PtO_2 \cdot H_2O$ (24.75 mg.) in 95% EtOH (2 ml.) was stirred in an atmosphere of H_2. A solution of V (250 mg.) in 95% EtOH (20 ml.) was added to the above catalyst and the mixture was stirred in a hydrogen atmosphere. Hydrogenation ceased after 10 min. with absorption of 14 ml. of H_2 (1 mol.). The catalyst was removed by filtration and the solvent evaporated leaving a semi-solid material. Recrystallization from ether-hexane afford VIII (200 mg.). m.p. 179.5~182°.

e) With Zn-acetic acid. Zn granules (200 mg.) were added to a solution of V (20 mg.) in AcOH (4 ml.), and after refluxing for 1.5 hr., and removal of the solvent, the residual product was chromatographed on Al_2O_3 (2 g.). Elution with benzene gave IX (17.3 mg.). The presence of VIII, X and XI in trace amounts was indicated by thin-layer chromatography.

3β,14β-Dihydroxy-5α,17α-pregnane-15,20-dione 3-Acetate (VIII)——a) From 3β,14β,20β-trihydroxy-5α,17α-pregnan-20-one 3-acetate (XI). Kiliani reagent[10] was added to a solution of XI (30 mg.) in acetone (5 ml.). After storage at the room temperature for 6 hr., and destruction of the excess oxidant with MeOH, the reaction solution was poured into H_2O and extracted with ether. The ether layer washed with 5% $NaHCO_3$, H_2O and dried over Na_2SO_4. Removal of solvent gave a crystalline mass. Recrystallization of this product from ether-hexane afforded VIII.

b) From 3β,14β,15α-trihydroxy-5α,17α-pregnan-20-one 3-acetate (VIa). A solution of VIa (50 mg.) in acetone (10 ml.) was oxidized with the Kiliani reagent[10] (0.2 ml.) and after work up as in a), gave VIII. This product was identical with VIII obtained from XI by mixed melting point and identical infrared spectra.

3β-Acetoxy-5α,14β,17α-pregnane-15,20-dione (IX) from 3β,14β-Dihydroxy-5α,17α-pregnane-15,20-dione (VIII)——A solution of VIII (10 mg.) in AcOEt (10 ml.) was shaken with previously reduced 5% Pd-C (5 mg.) in a hydrogen atmosphere for 30 min. The catalyst was removed by filtration, and the solvent was evaporated *in vacuo*. The residual product was passed through Al_2O_3 column and recrystallized from ether-hexane to give IX.

Hydrogenation of 3β-Acetoxy-5α,14β,17α-pregnane-15,20-dione (IX)——Hydrogenation of IX (211 mg.) in EtOH (12 ml.) over $PtO_2 \cdot H_2O$ (101 mg.) was carried out with the uptake 1.0 mol equivalents of H_2. The crude product was composed of 4 compounds by TLC, and was chromatographed on Al_2O_3 (40 g.). Elution with benzene gave the starting material (IX, 3.25 mg.). Elution with benzene-ether (9:1) gave XIII (156 mg.),

*5 The signal at τ 8.58 disappeared upon adding CF_3COOH.

which was recrystallized from methanol, m.p. 212~213°, $[\alpha]_D^{25}$ 0° (c=1.747, $CHCl_3$), RD: $[\alpha]_{278}$ (peak) + 1818.2°, $[\alpha]_{325}$ (trough) −134.5, $[\alpha]_{589}$ 0°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3640, 1730, 1725 (shoulder), 1255. NMR (τ): 9.23 (19-CH_3), 8.78 (doublet, J=7.0, 21-CH_3), 8.65 (18-CH_3), 8.40 (OH-H), 7.98 (acetate-CH_3). *Anal.* Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.06; H, 9.66. Elution with benzene–ether (1:1) gave the mixed product (52 mg. XII, XIII and an unknown product).

3β,20β-Dihydroxy-5α,14β,17α-pregnan-15-one 3-Acetate 20-Benzoate (XIV)——Benzoyl chloride (0.05 ml.) was added to a solution of XII (84 mg.) in pyridine (1 ml.) under cooling and the mixture was set aside at 37° for 20 hr. The remaining benzoyl chloride was decomposed by adding ice-water and the solid mass extracted with ether. The ethereal portion was chromatographed on Al_2O_3 (5.5 g.). Elution with hexane-benzene (4:1) gave XIV, which was rechromatographed on Al_2O_3, amorph. RD: (c=0.339, MeOH), $[\alpha]_{589}$ −75.6°, $[\alpha]_{283}$ (peak) +1311°, $[\alpha]_{325}$ (trough) −1689°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (shoulder), 1725 (shoulder), 1720, 1605, 1275. *Anal.* Calcd. for $C_{30}H_{40}O_5$: C, 74.97; H, 8.39. Found: C, 74.82; H, 8.35.

3β,20α-Dihydroxy-5α,14β,17α-pregnan-15-one 3-Acetate 20-Benzoate (XV)——Benzoyl chloride (0.05 ml.) was added to a solution of XIII (75 mg.) in pyridine (1 ml.) under cooling and the mixture was set aside at 37° for 20 hr. The remaining benzoyl chloride was decomposed by adding ice-water and the solid mass, extracted with ether, was chromatographed on Al_2O_3 (5 g.). Elution with benzene gave XV (26 mg.), which was rechromatographed on Al_2O_3, and further purified by preparative thin-layer chromatography (using Aluminiumoxid G nach Stahl für Dünnschichtchromatographie), amorph. RD: (c=0.354, MeOH), $[\alpha]_{589}$ +82.03, $[\alpha]_{284}$ (peak)+2079°, $[\alpha]_{325}$ (trough) −413°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735, 1720, 1605, 1275. *Anal.* Calcd. for $C_{30}H_{40}O_5$: C, 74.97; H, 8.39. Found: C, 75.02; H, 8.64.

3β,20α-Dihydroxy-5α,14β,17α-pregnan-15-one 3-Acetate 20-Phenylglyoxylate (XVI)——Phenylglyoxyloyl chloride (40 mg.) was added to a solution of XIII (70 mg.) in dry benzene (1.5 ml.) and pyridine (1 ml.). The mixture was set aside at 37° for 20 hr., poured into ice-water, and extracted with ether. The ether extract was washed with 2% aqueous acetic acid and water, dried over Na_2SO_4 and evaporated to dryness. The residue afforded by recrystallization from CH_2Cl_2–MeOH to give XVI (61 mg.), m.p. 237~238°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1742 (shoulder), 1735, 1693, 1602, 1255. RD: (c=0.200, dioxane), $[\alpha]_{289}$ (peak) +650°, $[\alpha]_{298}$ + 460°, $[\alpha]_{313}$ (shoulder) −400°, $[\alpha]_{326}$ (trough) −800°, $[\alpha]_{589}$ +10.0°. *Anal.* Calcd. for $C_{31}H_{40}O_6$: C, 73.20; H, 7.93. Found: C, 73.24; H, 8.14.

Atrolactic Acid from 3β,20α-Dihydroxy-5α,14β,17α-pregnan-15-one 3-Acetate 20-Phenylglyoxylate (XVI) ——A solution of XVI (48.2 mg.) in tetrahydrofuran (5 ml.) was added dropwise to an ice-cold solution of methylmagnesium iodide prepaped from magnesium (21 mg.), methyl iodide (1.5 ml.) and dry ether (1.5 ml). The mixture was set aside at room temperature for 4 hr., refluxed for 1 hr., and cooled. The solvent was removed *in vacuo*, and a few drops of water and then 2% aqueous acetic acid were added, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with 0.1*N* sodium thiosulfate and water, dried over Na_2SO_4, and evaporated to dryness. The residue was hydrolyzed by refluxing with potassium hydroxide (50 mg.) in 10% aqueous methanol (5 ml.) for 5 hr. The solvent was removed *in vacuo* and the residue taken up in water and extracted with AcOEt to remove neutral material. The aqueous layer was acidified with 5% HCl and extracted with ether. The ether extract was washed with water, dried over Na_2SO_4, and evaporated to dryness, affording atrolactic acid (11.2 mg.) as a crystalline, m.p. 87.5~90°. RD: (c=0.556, $CHCl_3$), (positive plane curve) $[\alpha]_{589}$ +7.01°, $[\alpha]_{500}$ +14.0°, $[\alpha]_{400}$ +23.3°.

Dehydrogenation of 3β,14β-Dihydroxy-5α,17α-pregnane-15,20-dione 3-Acetate (VIII)——3β,14β-Dihydroxy-5α,17α-pregnane-15,20-dione 3-acetate (VIII) (107 mg.) was dehydogenated with twice the amount of selenium powder under a nitrogen atmosphere at 310~315° for 24 hr. The product was extracted with *n*-hexane. The *n*-hexane soluble part (24.4 mg.) was chromatographed on Al_2O_3 (2 g.) and separated into five oily fractions, A, B, C, D and E. All fractions were purified by the rechromatography and preparative thin-layer chromatography. All fractions from A to E showed a negative test with 2% $FeCl_3$ solution and $FeCl_3$–$K_3Fe(CN)_6$ reagent. Fraction A (0.3 mg.) was less poler than the compound A,[4] m.p. 95~99°, showed a yellow color for the $SbCl_3$–$CHCl_3$ solution, and its UV spectrum was similar to that of cyclopentenophenanthrene. Fractions B (0.9 mg.) and C (2.1 mg.) were more polar than Jacobs' hydrocarbon, showed an orange and a green color with $SbCl_3$–$CHCl_3$ solution, respectively, and the UV spectra of B and C were similar to that of chrysene derivatives, although the material were not sufficiently pure (Fig. 1). Fraction D (1.45 mg.) and E (8 mg.) were also more polar than Jacobs' hydrocarbon, showed a green-yellow and a blue color with $SbCl_3$–$CHCl_3$ solution, respectively, and the UV spectra of D and E were similar to that of phenanthrene derivatives (Fig. 1).

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Summary

The synthesis of some C/D *cis*-15-ketopregnane derivatives from hecogenin is described. Hecogenin was degraded to II which in turn was converted to V *via* III. Catalytic hydrogenation of V affords the five reduction products, VIII to XIII. VIII was dehydrogenated with selenium but Jacobs' hydrocarbon was not obtained.

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108. Ikuo Suzuki, Toshiaki Nakashima, and Natsuko Nagasawa : Studies on Cinnolines. IV.*1 On Nitration of Cinnoline 2-Oxide.

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In a previous communication,[1] it was reported that cinnoline 2-oxide gave 5-, 6-, and 8-nitrocinnoline 2-oxides on warming with a mixture of nitric and sulfuric acids, and gave 5-nitrocinnoline 2-oxide by treatment with benzoyl nitrate. The present paper describes a detail of the experiments for nitration of cinnoline 2-oxide and deals with the relationship between the product ratio of nitro compounds, the concentration of sulfuric acid, and the reaction temperature.

Morley[2] obtained 5-nitrocinnoline and 8-nitrocinnoline in approximately equal proportions by nitration of cinnoline using fuming nitric acid and concentrated sulfuric acid at 20° for one hour. Ochiai and Ikehara[3] reported that isoquinoline N-oxide gave on warming with potassium nitrate and sulfuric acid at 60° for 3 hours 5-nitroisoquinoline N-oxide in 90% yield and 8-nitroisoquinoline N-oxide in 2% yield.

When cinnoline 2-oxide (I) was warmed with a mixture of nitric and sulfuric acids at 90° for 2.5 hours, three kinds of mononitro cinnoline 2-oxide were produced : yellow needles (II), m.p. 215~217° (in 3% yield), pale yellow needles (III), m.p. 212~213° (in 15% yield), pale yellow needles (IV), m.p. 228° (decomp.) (in 23% yield). In this reaction, I was recovered in 31% yield. When this reaction was carried out at 70° for 3 hours, II, III and IV were obtained in 1.1, 15, and 13% yields with 42% recovery of I.

Catalytic hydrogenation of III and IV over Adams platinum catalyst gave monoaminocinnolines and monoaminocinnoline 2-oxides. The former compounds were found to be identical with 6-[4] and 8-aminocinnoline[5] (VI and VII), obtained by hydrogenation of 6-[2] and 8-nitrocinnoline[6] over palladium-charcoal, by comparing their spectra and by determining the mixed melting point, respectively, hence the structures of III and IV

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