Summary

The structures of substance B-III and B-III′, newly isolated from digitalis seeds,[2] were examined. It was found that enzymatic hydrolysis of substance B-III afforded gitoroside, and a mild acid hydrolysis afforded gitoxigenin and new trisaccharide which consists of cellobiose and digitoxose. This sugar was named digilanidotriose. Therefore, substance B-III is formulated as gitoxigenin cellobiosido-digitoxoside, and was designated as gitorocellobioside. The partial decomposition of gitorocellobioside with a snail enzyme afforded a new diglycoside which is gitoxigenin glucosido-digitoxoside and this was designated as glucogitoroside.

Substance B-III′ was examined by the same method and was shown to be a new cardiotonic pentaglycoside which has a structure of gitoxigenin cellobiosido-tridigitoxoside, and was named gitoxin cellobioside.

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46. **Kyosuke Tsuda and Shigeo Nozoe**: Steroid Studies. XI.[1] On the Methylation of 3-Oxosteroids. (1).

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2-Substituted analogs of steroidal hormones possess glucocorticoidal activity[2] and 4-substituted analogs of testosterone show anabolic activity.[3] The present paper deals with the synthesis of 3-oxosteroids possessing a methyl group in 2- or 4-position.

Methyl group can be introduced into the 2-position of 3-oxosteroids by ethoxyoxalylation with ethyl oxalate, followed by methylation and deoxalylation,[2,4] while methyl derivative of testosterone is obtained by its direct methylation.[3]

The methylation of 3-oxosteroid carried out in the present series of work consisted of introduction of a hydroxymethylene group with ethyl formate, followed by methylation of its product and deformylation. Shortly before this work was completed, Quartey[5] published reports on the methylation of 2-position of cholest-4-en-3-one according to the same principle.

Formylation of 4,6,22-ergostatrien-3-one (I) affords a hydroxymethylene compound (II) of m.p. 138°, which shows ultraviolet absorption maxima at 292 and 331 mμ (in MeOH) and an absorption for α,β-unsaturated β-hydroxy ketone at 1637 cm^{-1} in its infrared absorption spectrum.[6] (II) easily undergoes conversion by hydrochloric acid to a formyl compound (III) of m.p. 169°, which shows ultraviolet absorption maxima (in MeOH) at 294 and 323 mμ, and an absorption for α,β-unsaturated β-hydroxy aldehyde at 1667 cm^{-1} in its infrared spectrum[6] (Fig. 1).

The infrared spectra of (II) and (III) are entirely devoid of free O-H stretching absorption in the fundamental region. This is a characteristic of enolic β-diketone

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1) Part X: J. Am. Chem. Soc., in press.
2) J.A. Hogg, F.H. Lincoln, R.W. Jackson, W.P. Schneider: J. Am. Chem. Soc., **77**, 6401(1955).
3) B. Camerino, B. Patelli, A. Vercollone: *Ibid.*, **78**, 3540(1956).
4) S. Bernstein: *Ibid.*, **79**, 4555(1957).
5) J.A.K. Quartey: J. Chem. Soc., **1958**, 1710.
6) L.J. Bellamy: "The Infra-red Spectra of Complex Molecules," 114(1954). John Wiley & Sons, Inc., New York.

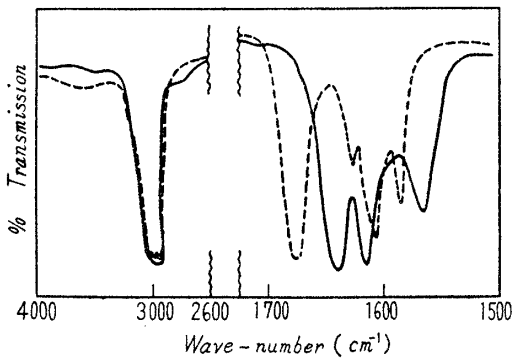
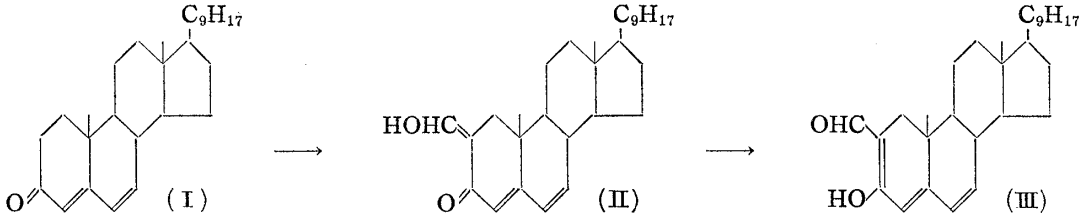


Fig. 1.
Infrared Spectra (in Nujol)

—— 2-Hydroxymethylene-4,6,22-ergostatrien-3-one (II)

------ 2-Formyl-2,4,6,22-ergosta-tetraën-3-ol (III)



having a strong hydrogen bonding[7] and it is assumed that its associated O–H absorption cannot be discriminated by overlapping with the C–H stretching absorption in the region of 2800~3000 cm^{-1} (Fig. 1). Such a marked shift of CO absorption and lack of free OH absorption support the structures of (II) and (III), and the shift of their ultraviolet absorption maxima to a longer wave-length region also support the enolic chromophor structure of (II) and (III).[8] Both (II) and (III) color brownish green to ferric chloride solution and the copper inner-complex salt of (II) is obtained as green crystals from chloroform.

Formylation of 4,22-stigmastadien-3-one (IV) gives a 2-hydroxymethylene compound (V) of m.p. 162°, which shows infrared spectra analogous to (II) and colors similarly with ferric chloride solution. When heated with methyl iodide in acetone, in the presence of potassium carbonate, (II) changes to 2-methyl compound (VI), which undergoes deformylation when heated with ethanolic hydrochloric acid to form 2α-methyl-4,22-stigmastadien-3-one (VII). The configuration of the 2-methyl group in (VII) is α-oriented since it takes the stable equatorial configuration by deformylation with an acid.

Reduction of (VII) with lithium in liquid ammonia[9] affords the 5α-dihydro compound (XI) of m.p. 177~178° in a good yield, while catalytic hydrogenation of (VII) in ethanol over palladium-carbon, in the presence of a trace of alkali, chiefly gives the 5α-dihydro compound (XI), accompanied by the formation of a small amount of the 5β-dihydro compound (XII) of m.p. 142°.

The methyl derivative, obtained by formylation, methylation, and subsequent deformylation of the 5α-dihydro compound (VIII), obtained by reduction of (IV) with lithium in liquid ammonia, agrees with (XI). This fact has shown that in 5α-3-oxosteroids, C-2 is active to formylation reaction. The same position is reported to be active to formylation in *trans*-β-decalone.[10]

A substance of m.p. 156° is obtained as a by-product during preparation of (VII) from (V) through (VI). Since its ultraviolet absorption maximum appears at 241 mμ, it is known to be an α,β-unsaturated ketone and, from its analytical values and for-

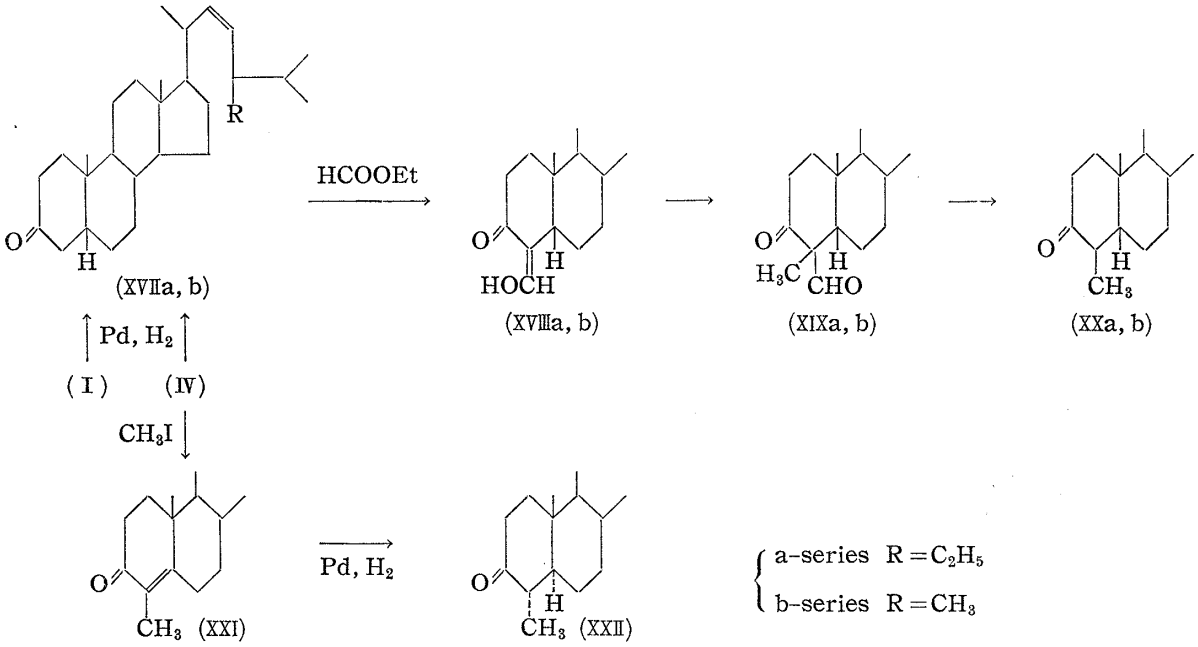
7) *Idem.* : *Ibid.*, 91.
8) J.S.E. Holker, A.D.G. Powell, A. Robertson, J.J.H. Simes, R.S. Wright : J. Chem. Soc., **1953**, 2414.
9) D.H.R. Barton, D.A. Ires : J. Chem. Soc., **1954**, 903.
10) R.B. Woodward, *et al.* : J. Am. Chem. Soc., **74**, 4227(1952); du Feu, McQuillin, Robinson : J. Chem. Soc., **1937**, 53.

mation of (V) with alkali, it may be assumed as the O-methyl ether of (V). When heated in hydrochloric acid, (XIII) changes into the 2-formyl compound (XIV), which is analogous to (III). (XIV) shows ultraviolet absorption maxima (in MeOH) at 255 and 299 mμ, and colors with ferric chloride solution.

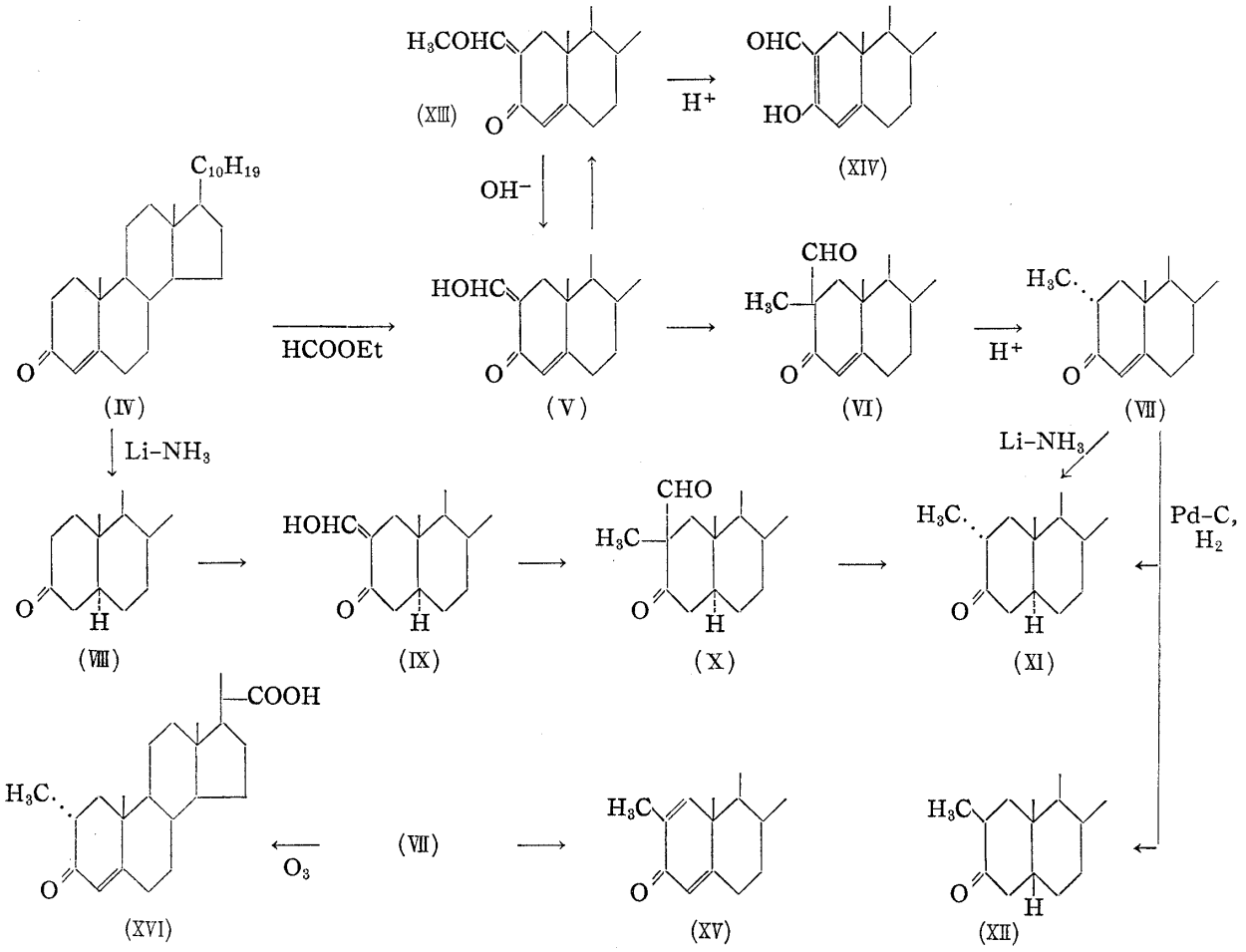
(VII) forms the 1-dehydro compound (XV) when refluxed with chloranil in xylene, while ozonolysis of (VII) affords 2α-methyl-3-oxo-bisnor-4-cholenic acid (XVI).

Formylation of 5β-22-stigmasten-3-one[11] (XVIIa), obtained by catalytic hydrogenation of (IV) over palladium-carbon, gives the hydroxymethylene compound (XVIIIa), whose methylation changes it to (XIXa), and its deformylation affords the monomethyl derivative (XXa) of (XVIIa). (XXa) is clearly different from 2α-methyl compound (XII) of the 5β-series and the methyl group introduced into it must take an equatorial conformation, so that this compound is determined as formula (XXa), or 4β-methyl-5β-22-stigmasten-3-one. It is known that steroids of A/B-*cis* series are active in the 4-position[12] and the present observation also agrees with this view. In exactly the same manner, 4β-methyl-5β-22-ergosten-3-one (XXb) is obtained from 5β-22-ergosten-3-one[13] (XVIIb) via (XVIIIb) and (XIXb).

General method for the methylation of 4-position in Δ^4-3-oxosteroids calls for the use of potassium *tert*-butoxide and methyl iodide.[14] Methylation of (IV) by this method and catalytic hydrogenation of its product gives the dihydro compound (XXII) of m.p. 160~162° in a good yield. (XXII) is different from (XXa) and, since its 4-methyl group does not undergo inversion by treatment with acid or alkali, it takes the equatorial conformation, justifying the formula of (XXII) as 4α-methyl-5α-22-stigmasten-3-one. Hydrogenation of Δ^4-3-oxosteroids chiefly affords the 5β-dihydro compound but the present series of work has confirmed the formation of 5α-dihydro compound mainly in (XXI) which is a 4-methyl-Δ^4-3-oxosteroid. The same observation was affirmed by Yanagita and others in octalone series.[15]



11) D. H. R. Barton, C. J. W. Brooks: J. Am. Chem. Soc., **72**, 1633(1950).
12) A. Butenandt, A. Wolff: Ber., **68**, 2093(1935); C. Djerassi, C. R. Scholz: Experientia, **3**, 107 (1954); L. Ruzicka, W. Bosshard, W. H. Fischer, H. Wirz: Helv. Chim. Acta, **19**, 1147(1936).
13) A. F. Daglish: J. Chem. Soc., **1954**, 2627.
14) F. Sondheimer, Y. Mazur: J. Am. Chem. Soc., **79**, 2906(1957); N. W. Atwarter: *Ibid.*, **79**, 5315 (1957); Y. Mazur, A. Weizman, F. Sondheimer: *Ibid.*, **80**, 1007(1958).
15) S. Yanagita, R. Futaki: J. Org. Chem., **21**, 949(1956).



After completion of the present series of experiments, a report of Sondheimer and others[16] appeared, in which was described 2- and 4-methylation of cholestanone and coprostanone.

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Experimental

All melting points are uncorrected. Infrared spectra were obtained in Nujol with Koken Model DS 301 Spectrophotometer and ultraviolet spectra were measured with Beckman Model DK-2 Spectrophotometer. Rotations were determined in $CHCl_3$ solution with Rudolf Model 200 Polarimeter.

2-Hydroxymethylene-4,6,22-ergostatrien-3-one (II) and 2-Formyl-2,4,6,22-ergostatetraën-3-ol (III)—4 g. of (I) in 20 cc. of dehyd. benzene was added dropwise to the solution of NaOMe (from 460 mg. of Na) in 20 cc. of dehyd. benzene and 1.45 g. of ethyl formate at room temperature. The cloudy mixture was heated for 5 min., excluding moisture. The reaction mixture was cooled, Na salt was filtered, which was washed with ether and dried. It was suspended in 20 cc. of H_2O, neutralized with 10% HCl, which was filtered and washed with H_2O. Recrystallisation from AcOEt gave 2 g. of (II) as yellow needles, m.p. 137~138°, which gave immediate brownish green color reaction with $FeCl_3$ in EtOH. *Anal.* Calcd. for $C_{29}H_{42}O_2$: C, 82.41; H, 10.02. Found: C, 82.67; H, 10.02. $[\alpha]_D^{15}$ −275° (c=1.05). U.V. λ_{max}^{MeOH} mμ(log ε): 292(4.38), 331(4.11). I.R. λ_{max}^{Nujol} cm^{-1}: 1637, 1616, 1567.

The Cu complex of (II) was obtained when the $CHCl_3$ solution of (II) was shaken with saturated solution of $CuSO_4$.

On the other hand the filtrate obtained after removal of Na salt was acidified with 10% HCl and allowed to stand over night, by which pale yellow crystals appeared. Filtered crystals were washed with a small amount of petr. ether and recrystallisation from petr. ether gave 1 g. of (III),

16) Y. Mazur, F. Sondheimer: J. Am. Chem. Soc., **80**, 5220(1958).

m.p. 168~169°. *Anal.* Calcd. for $C_{29}H_{42}O_2$: C, 82.41; H, 10.02. Found: C. 82.11; H. 10.22. $[\alpha]_D^{15}$ −368°(c=0.74). U.V. λ_{max}^{MeOH} mμ(log ε): 294(4.42), 323(shoulder). I.R. λ_{max}^{Nujol} cm^{-1}: 1667, 1610, 1590.

2-Hydroxymethylene-4,22-stigmastadien-3-one (V)—To a solution of NaOMe, prepared from 230 mg. of Na and 740 mg. of ethyl formate in 10 cc. of benzene, 2 g. of (IV) in 10 cc. of benzene was added and the reaction mixture was heated under reflux for 10 min. The solution was cooled and filtered, and the collected precipitate was washed with ether and dried. The yellow Na salt was suspended in 20 cc. of ether, neutralized with 10% HCl, and the mixture was shaken until the precipitate dissolved in ether completely. Evaporation of ether to dryness and recrystallisation of the precipitate from AcOEt gave 2 g. of (V), m.p. 162~163°. *Anal.* Calcd. for $C_{30}H_{46}O_2$: C, 82.13; H, 10.57. Found: C, 82.05; H, 10.53. $[\alpha]_D^{15}$ +3°(c=1.49). U.V. λ_{max}^{MeOH} mμ(log ε): 253(4.16), 306(3.87). I.R. λ_{max}^{Nujol} cm^{-1}: 1670, 1640, 1587, 1568.

2α-Methyl-4,22-stigmastadien-3-one (VII) via 2-Methyl-2-formyl Derivative (VI)—i) 880 mg. of (V) in 10 cc. of dehyd. acetone was heated under reflux for 24 hr. with 570 mg. of MeI and 550 mg. of K_2CO_3. After cooling of the reaction mixture, inorganic materials were removed by filtration, the filtrate was evaporated to dryness, and trituration of residue with MeOH gave pale yellow crude crystals, m.p. 96~100°, which was used for the next step without further purification. Analytical sample, m.p. 102~106°. *Anal.* Calcd. for $C_{31}H_{48}O_2$: C, 82.24; H, 10.69. Found: C, 82.00; H, 10.66. U.V. λ_{max}^{MeOH}: 241 mμ(log ε 4.17).

Deformylation of crude 2-methyl-2-formyl compound was carried out by refluxing for 2 hr. with 10 cc. of 10% HCl in 20 cc. of EtOH. The cooled acid solution was neutralized with satd. $NaHCO_3$ solution and concentrated to about 5 cc. Dilution with H_2O and extraction with ether furnished an oily product which crystallised in a refrigerator after 10 hr. The resultant product was dissolved in 50 cc. of benzene and passed over 20 g. of alumina, which was eluted with benzene, and recrystallisation of the residue from MeOH gave 400 mg. of (VII), m.p. 130~131°. *Anal.* Calcd. for $C_{30}H_{48}O$: C, 84.84; H, 11.39. Found: C, 84.60; H, 11.26. $[\alpha]_D^{15}$ +51°(c=1.35). U.V. λ_{max}^{MeOH}: 241 mμ(log ε 4.21).

ii) To a suspension of 54 mg. of NaOMe in 10 cc. of benzene, 400 mg. of (V) in 10 cc. of benzene was added. After refluxing for 30 min., the solution was cooled and 4 g. of MeI was added. Further refluxing for 3 hr. and evaporation to dryness afforded an oily material. This was dissolved in 20 cc. of benzene, inorganic material was filtered off, and the solution was dried over Na_2SO_4. Purification by chromatography over alumina gave colorless needles of (VII), which showed no depression by admixture with the product obtained by the first procedure.

Lithium-Liquid Ammonia Reduction of (VII)—A solution of 200 mg. of (VII) in 40 cc. of dehyd. ether was added rapidly, with stirring, to a solution of 100 mg. of Li in 100 cc. of liquid NH_3 under chilling with dry ice-acetone. The blue solution was stirred for 5 min. and ethereal solution of *tert*-BuOH was added to decompose the excess of Li. Liquid ammonia was allowed to evaporate at room temperature, the solvent was removed under a reduced pressure, the residue was dissolved in 100 cc. of MeOH, and allowed to stand over night. The undissolved material was collected and recrystallised from MeOH to 20 mg. of needles, which showed a high m.p. of over 260°.

The filtrate was evaporated and the residue was triturated with MeOH. Recrystallisation from MeOH gave 140 mg. of (XI), m.p. 177°, which was undepressed on admixture with a sample prepared by catalytic hydrogenation of (VII).

Catalytic Hydrogenation of (VII)—A solution of 14 mg. of KOH in 10 cc. of dehyd. MeOH was added to a solution of 210 mg. of (VII) in 20 cc. of dehyd. MeOH and the solution was shaken in H_2 over 20 mg. of Pd-C catalyst. Hydrogenation was stopped when ca. 1 mole (13 cc.) of H_2 was absorbed during 25 min. The catalyst was removed by addition of ether and filtration, the filtrate was evaporated to dryness under a reduced pressure, and recrystallisation of the residue from MeOH gave 40 mg. of 2α-methyl-5α-22-stigmasten-3-one (XI) as needles, m.p. 177~178°. *Anal.* Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.43; H, 11.68. $[\alpha]_D^{15}$ +20°(c=1.06). I.R. λ_{max}^{Nujol} cm^{-1}: 1717, 970.

A small amount of AcOH was added to the filtrate, MeOH was evaporated under a reduced pressure to dryness, and petr. ether was added. After removing the inorganic salt, this solution was chromatographed over 30 g. of alumina. Colorless amorphous material eluted with petr. ether-benzene (9:1). Recrystallisation from MeOH gave 60 mg. of 2β-methyl-5β-22-stigmasten-3-one (XII) as silky needles, m.p. 135~136°. *Anal.* Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.35; H, 11.72. $[\alpha]_D^{15}$ +29°(c=0.36). I.R. λ_{max}^{Nujol} cm^{-1}: 1725, 1190, 972.

20 mg. of (XI) was obtained by elution with petr. ether-benzene (2:8).

Methylation of 5α-22-Stigmasten-3-one (VIII)—200 mg. of (VIII) in 3 cc. of benzene was added to a suspension of 54 mg. of NaOMe and 74 mg. of ethyl formate in 5 cc. of benzene. The mixture was heated on a water bath for 20 min. After the usual treatment including acidification, extraction and recrystallisation from AcOEt gave 180 mg. of 2-hydroxymethylene-5α-22-stigmasten-3-one (IX) as crystals of m.p. 194~195°. *Anal.* Calcd. for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.41; H, 10.92. $[\alpha]_D^{15}$ +35°(c=0.36). U.V. λ_{max}^{MeOH}: 283 mμ(log ε 4.08). I.R. λ_{max}^{Nujol} cm^{-1}: 3140, 2700, 1560, 1200.

Methylation of (IX) was accomplished by heating under reflux for 20 hr. with 150 mg. of MeI and

140 mg. of K_2CO_3 in 20 cc. of acetone. The reaction mixture was treated by usual processing. Without isolation of 2-methyl-2-formyl derivative, the crude (X) was treated with dil. H_2SO_4 and EtOH under reflux for 2 hr. Recrystallisation from MeOH gave needles, m.p. 177~178°, which showed no depression on admixture with the samples obtained from (VII) by catalytic hydrogenation or Li-liq. NH_3 reduction.

Methyl Ether of (V) and 2-Formyl-2,4,22-stigmastatrien-3-ol (XIV)—During the formation of (VII) from (V) by the above-mentioned procedure (i), a methyl ether of (V), m.p. 156~157°, was obtained as a by-product. *Anal.* Calcd. for $C_{31}H_{48}O_2 \cdot H_2O$: C, 78.89; H, 10.59. Found : C, 78.83; H, 10.60. $[\alpha]_D^{15}$ −12°(c=1.15).

50 mg. of (XIII) was dissolved in 5 cc. of acetone, 0.5 cc. of conc. HCl was added and the mixture was heated for 5 min. Filtration and recrystallisation from acetone gave 45 mg. of (XIV), m.p. 166~167°. *Anal.* Calcd. for $C_{30}H_{46}O_2$: C, 82.13; H, 10.57. Found : C, 81.85; H, 10.61. $[\alpha]_D^{15}$ −156°(c=0.62). U.V. λ_{max}^{MeOH} mμ(log ε) : 254.5(4.18), 299(3.89).

50 mg. of (XIII) was dissolved in 10 cc. of EtOH, 50 mg. of NaOMe was added and the mixture was heated under reflux for 4 hr. Neutralization, extraction, and recrystallisation from MeOH gave (V).

2-Methyl-1,4,22-stigmastatrien-3-one (XV)—A solution of 425 mg. of (VII) in 10 cc. of xylene was heated under reflux for 8 hr. with 245 mg. of chloranil, during which color of the solution changed to reddish brown. The solution was evaporated *in vacuo*, benzene was added, and the solution was washed with 10% KOH and H_2O. Dried benzene solution was chromatographed on alumina, oily product eluted first with petr. ether was dissolved in 10 cc. of MeOH and allowed to stand for 2 days in a refrigerator. Filtration and recrystallisation from MeOH gave (XV) as needles, m.p. 98~100°. *Anal.* Calcd. for $C_{30}H_{46}O$: C, 85.24; H, 10.97. Found : C, 84.93; H, 10.78. U.V. λ_{max}^{MeOH} : 251 mμ (log ε 4.00). I.R. λ_{max}^{Nujol} cm^{-1} : 1667, 1634, 1618, 904.

2α-Methyl-3-oxo-bisnor-4-cholenic Acid (XVI)—A solution of 1.9 g. of (VII) in 88 cc. of CH_2Cl_2 was chilled in dry ice-acetone bath and a stream of ozone-rich air (0.3 millimole O_3/min.) was passed for 15 min. To a suspension of 2.3 g. of Zn in this reaction mixture, 10 cc. of AcOH was added with stirring and the mixture was stirred for additional 30 min. at 5°. After removing Zn, CH_2Cl_2 was evaporated under a reduced pressure and recrystallisation from *iso*-PrOH afforded (XVI), m.p. 232~240°(decomp.); yield, 1.5 g. *Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found : C, 77.17; H, 9.45. $[\alpha]_D^{15}$ +64°(c=1.25). U.V. λ_{max}^{MeOH} : 241.5 mμ(log ε 4.22). I.R. λ_{max}^{Nujol} cm^{-1} : 3160, 1730, 1660, 1618.

4-Hydroxymethylene-5β-22-stigmasten-3-one (XVIIIa) and 4-Hydroxymethylene-5β-22-ergosten-3-one (XVIIIb)—To a solution of 1.05 g. of ethyl formate and NaOMe (from 326 mg. of Na) in 20 cc. of benzene, a solution of 4.7 g. of (XVIIa) in 20 cc. of benzene was added and resultant gelatinous solution was allowed to stand over night. The filtered precipitate was treated in the usual manner and recrystallisation from MeOH and petr. ether-ether afforded 4 g. of (XVIIIa) as leaflets, m.p. 150~151°. *Anal.* Calcd. for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found : C, 81.79; H, 10.99. U.V. λ_{max}^{MeOH} : 291 mμ (log ε 3.91). $[\alpha]_D^{15}$ +15.2°(c=1.24).

In accordance with the above procedure, (XVIIIb) was obtained from (XVIIb); m.p. 154~155°. *Anal.* Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found : C, 81.97; H, 10.91. U.V. λ_{max}^{MeOH} : 287 mμ (log ε 3.88).

4β-Methyl-5β-22-stigmasten-3-one (XXa) and 4β-Methyl-5β-22-ergosten-3-one (XXb) via the corresponding 4-Methyl-4-formyl Derivatives (XIXa and XIXb)—A mixture of 747 mg. of (XVIIIa), 484 mg. of K_2CO_3, and 1.5 g. of MeI in 10 cc. of acetone was heated under reflux for 24 hr. The usual processing gave 620 mg. of crude (XIXa), which was used for deformylation without further purification. The crude compound was treated in the usual way. The resulting material was chromatographed on alumina, eluted with benzene, and recrystallisation from MeOH yielded 350 mg. of (XXa) as silky needles, m.p. 136~137°. *Anal.* Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found : C, 84.35; H, 11.72. $[\alpha]_D^{15}$ −33°(c=0.78). I.R. λ_{max}^{Nujol} cm^{-1} : 1718, 1200, 972.

In accordance with the above procedure, (XXb) was obtained from (XVIIIb); m.p. 115~117°. *Anal.* Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found : C, 84.05; H, 11.67.

4-Methyl-4,22-stigmastadien-3-one (XXI)—Direct monomethylation was carried out by the same procedure for preparation of 4-methyltestosterone[14]. 4.6 g. of (IV) in 92 cc. of boiling *tert*-BuOH was added to a boiling solution of 0.75 g. of K in 50 cc. of *tert*-BuOH. 1.8 g. of MeI in the same solvent was added dropwise during a 4-hr. period to boiling solution with efficient stirring. The resultant solution was cooled, the solvent was evaporated *in vacuo*, the residue was diluted with 200 cc. of H_2O, and extracted with benzene. The residue from the benzene solution was chromatographed over 200 g. of alumina, eluted with benzene, and recrystallisation from MeOH afforded (XXI), m.p. 154~155°. *Anal.* Calcd. for $C_{30}H_{48}O$: C, 84.84; H, 11.39. Found : C, 84.64; H, 11.38. $[\alpha]_D^{15}$ +61°(c=0.55). U.V. λ_{max}^{MeOH} : 251 mμ(log ε 4.19).

4α-Methyl-5α-22-stigmasten-3-one (XXII)—A solution of 14 mg. of KOH and 210 mg. of (XXI) dissolved in 30 cc. of dehyd. MeOH was shaken in H_2 over 20 mg. of 5% Pd-C, until 1 mole of H_2 was absorbed. The catalyst was removed by filtration, the filtrate was evaporated to dryness, and

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).

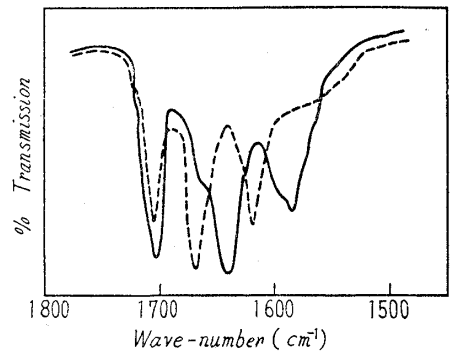

Fig. 1.
Infrared Spectra (in Nujol)

—— 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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