Tetrahedron 1967. Vol. 23, pp. 2145 to 2152. Pergamon Press Ltd. Printed in Northern Ireland

SYNTHESIS OF CHIOGRALACTONE*[1]

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(*Received in Japan* 1 *August* 1966; *accepted for publication* 19 *September* 1966)

Abstract—Chiogralactone, $C_{23}H_{34}O_4$ was isolated from *Chionographis japonica* MAXIM. (Liliaceae). This compound, assumed to have structure I on the basis of the physical data and chemical degradation is identical with 3β,16β-dihydroxy-6-oxo-24-nor-5α-cholan-23-oic acid lactone (I) synthesized from diosgenin.

IN THE previous paper,[1] chiogralactone isolated from *Chionographis japonica* MAXIM. was assumed to have structure I on the basis of the physical data and chemical degradation to 3β,6β-dihydroxy-5α-pregn-16-en-20-one (IV) through the dihydroxy

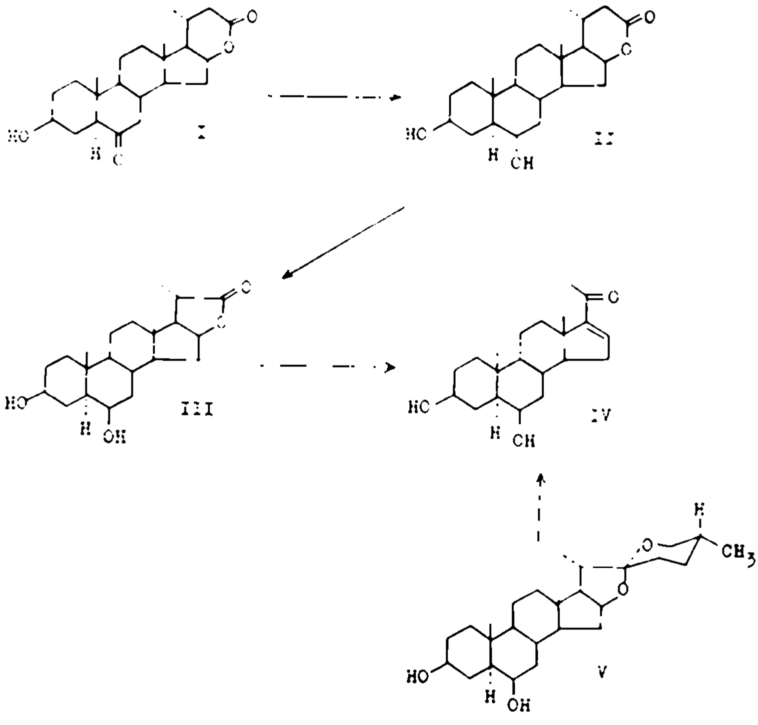

Chart 1

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* Studies on the Steroidal Components of Domestic Plants L. Compounds of *Chionographis japonica* MAXIM. (3).

[1] Part XLIX: K. Takeda, M. Iwasaki, A. Shimaoka and H. Minato, *Tetrahedron*, Suppl. 8, Part I, 123 (1966).

compound (II) and the γ-lactone (III). Although Marker *et al.*[2] obtained 3β,6β-dihydroxy-5α-pregn-16-en-20-one of m.p. 214–216° by degradation of β-chlorogenin (V), the compound IV derived from chiogralactone showed m.p. 255–257°.*

It was decided, therefore, to synthesize chiogralactone for the confirmation of the suggested structure (I). Although a γ-lactone corresponding to III was obtained from 3β,6α-dihydroxy-5α-androstan-17-one by Sondheimer's method,[3] this attempt† failed in conversion of the γ-lactone function into the δ-lactone. Therefore, diosgenin acetate (VI) was taken as the starting material, the double bond of which could be utilized for the introduction of an oxygen function into the 6 position. Hydroboration of VI with diborane followed by oxidation with an alkaline hydrogen peroxide and acetylation gave chlorogenin diacetate[4] (VII), m.p. 153–155°, in 83% yield.

Chlorogenin diacetate (VII) was subjected to hydrogenation in glacial acetic acid containing a small amount of 60% perchloric acid with Adams' catalyst followed by acetylation to afford dihydrochlorogenin triacetate (VIII), of which chromium trioxide oxidation in glacial acetic acid at 90–95° gave 6α-hydroxy-dihydrokryptogenin triacetate (IX), m.p. 149–150°, in 49% yield.

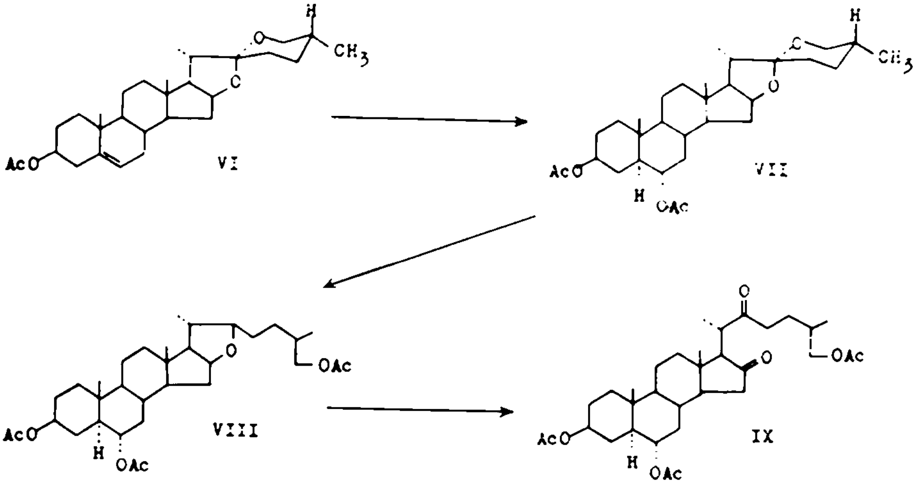

Chart 2

Ring-closure of IX with potassium hydroxide in methanol gave a 1 : 1 mixture of two glassy ketonic products (X and XI), which were separated by alumina chromatography. 6α-Hydroxydihydrofesogenin (X) had frequencies at 3630, 3460, 1690 and 1649 cm^{-1} in the IR spectrum, and a max at 247 mμ (ε 9800) in the UV spectrum. Another product was assumed to have the structure XI, since (i) it showed absorption

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* As the structure of chiogralactone (I) has now been confirmed, the m.p. of IV should correctly be 255–257°.

† This attempt will be described in the following paper of this series.

[2] R. E. Marker, D. L. Turner and E. L. Wittbecker, *J. Am. Chem. Soc.* 64, 809 (1942).

[3] Y. Mazur, N. Danieli and F. Sondheimer, *J. Am. Chem. Soc.* 82, 5889 (1960).

[4] P. Liang and C. R. Noller, *J. Am. Chem. Soc.* 57, 525 (1935).

bands at 3640, 3480 and 1743 cm^{-1} and no absorption max corresponding to the α,β-unsaturated ketone in UV region, (ii) its less polarity on a TLC in comparison with X suggested a dihydroxy compound and (iii) it afforded a 1 : 1 mixture of X and XI when refluxed in a solution of potassium hydroxide in methanol.

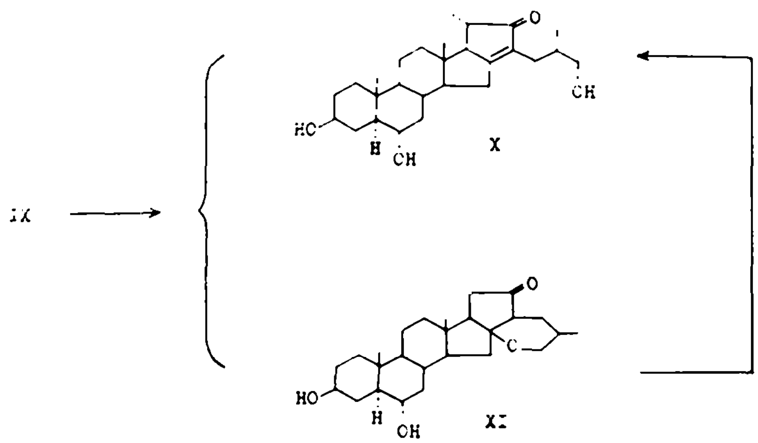

Chart 3

The elimination of the CO group of X, by either Huang-Minlon reduction or thio-ketalization followed by reduction with lithium-liquid ammonia was unsuccessful. Moreover, sodium borohydride reduction of the triacetate of X caused hydrogenation of the double bond. Finally, the triacetate of X was treated with LAH to afford the unsaturated tetraol (XII), m.p. 204–206°, the tetraacetate of which was subjected to hydrogenolysis with Adams' catalyst in a 1 : 1 mixture of glacial acetic acid and ethanol. The resultant reaction mixture consisting of the unsaturated triacetate (XIII) and the saturated by-products was treated with osmium tetroxide, and the chromatography on alumina gave the diol XIV. The overall yield from XII was 17%.

The diol XIV was oxidized with sodium periodate, affording the diketone XV, m.p. 248·5–249°, and the diketone XV was subjected to ring-closure with potassium hydroxide in methanol to give the α,β-unsaturated ketone XVI, which had frequencies at 3620, 3430 and 1645 cm^{-1} in the IR spectrum, and a max at 253 mμ (ε 12,000) in the UV spectrum. No formation of a saturated ketone such as the XI was observed, and the α,β-unsaturated ketone XVI was obtained in more than 81% yield. The triacetate of XVI was subjected to ozonolysis followed by treatment with hydrogen peroxide in aqueous sodium carbonate solution to afford the triketone XVII, m.p. 110–111°, which was further oxidized with hydrogen peroxide in methanolic potassium hydroxide solution to give the keto-carboxylic acid XVIII, m.p. 240–241°. Oxidation of XVIII with Jones' reagent gave the triketo-carboxylic acid XIX, m.p. 226–228°, ν_{max} 1742 and 1710 cm^{-1}, in 82% yield, being identical with 3,6,16-trioxo-24-nor-5α-cholan-23-oic acid[1] derived from chiogralactone.

Since fesogenin which can be produced from kryptogenin by the same procedure

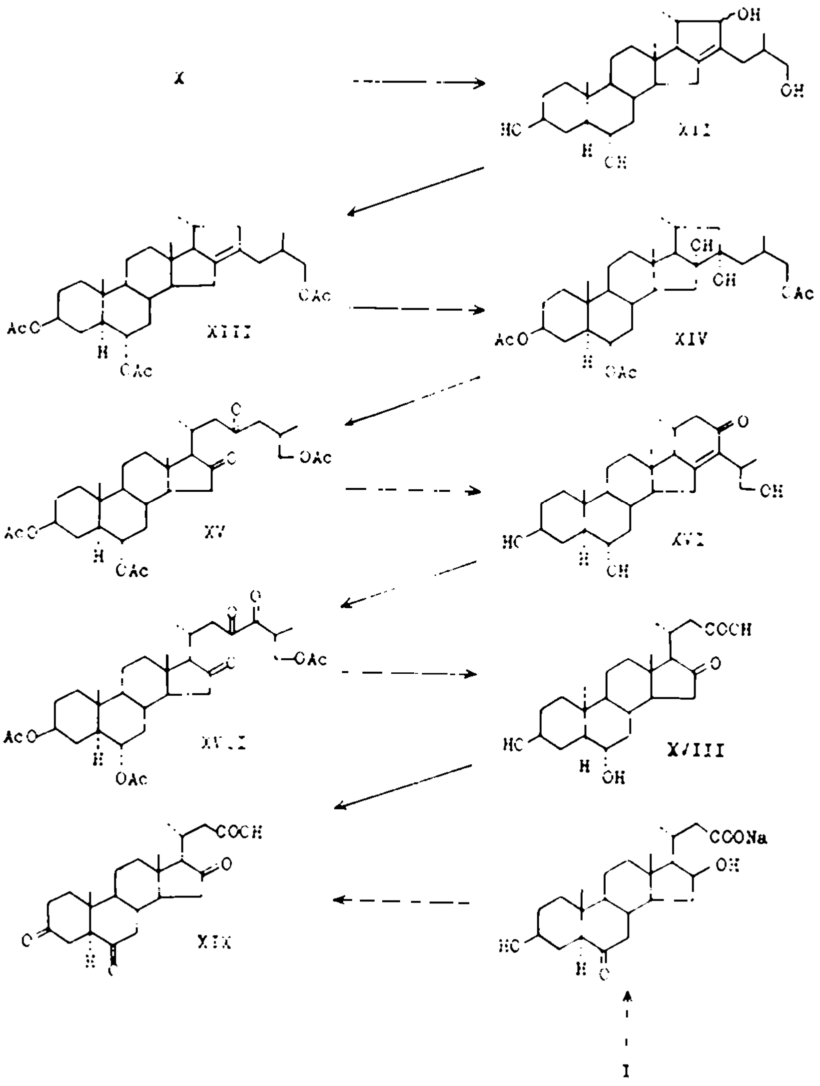

Chart 4

as 6α-hydroxy-dihydrofesogenin (X) has the 20-normal configuration[5] and the isomerization at the 20 position can not take place during the conversion from X to XIX, the triketo-carboxylic acid (XIX) should belong to the 20-normal series, that is, the C_{20}-Me group of I has the α-configuration.

Subsequently, the triketo-carboxylic acid XIX was esterified with diazomethane and the ester formed was reduced with sodium borohydride to give the diol-lactone XX, m.p. 280–283°. The two OH groups at the 3 and 6 positions and the lactonic oxygen at the 16 position should each have the β-configuration.[5,6] The compound XX

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[5] C. W. Shoppee, *Chemistry of the Steroids* (2nd Edition) p. 408. Butterworth, London (1964).

[6] C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.* 3361 (1952).

is identical with $3\beta,6\beta,16\beta$-trihydroxy-24-nor-5α-cholan-23-oic acid lactone[1] derived from chiogralactone.

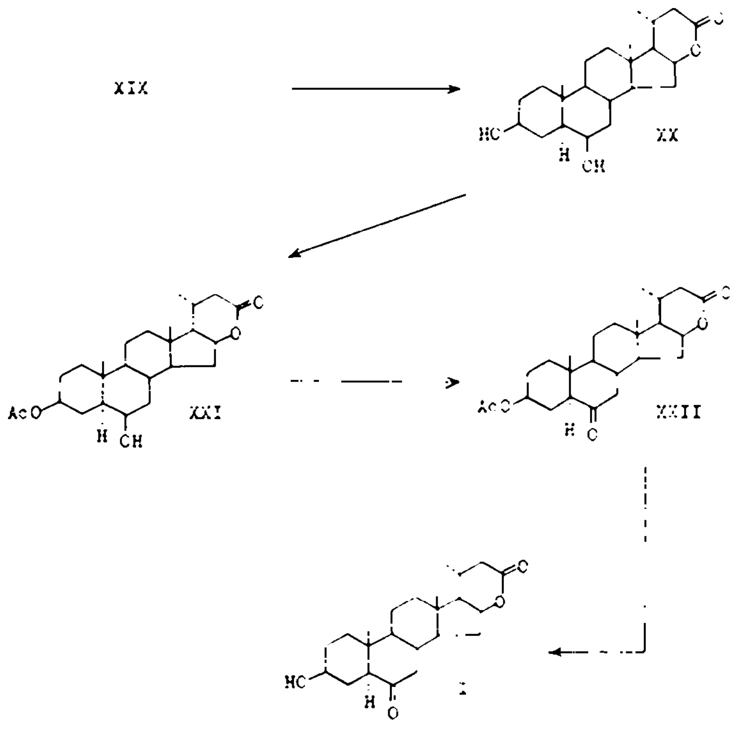


Chart 5

Partial acetylation of the equatorial OH group at the 3 position of XX was achieved with about one molar equivalent of acetic anhydride in pyridine to give the monoacetate XXI. Oxidation of XXI with Jones' reagent gave 3β-acetoxy-6-oxo-16β-hydroxy-24-nor-5α-cholan-23-oic acid lactone (XXII), m.p. 228–230°, which had frequencies at 1734, 1725 and 1716 cm^{-1} in the IR spectrum. The compound XXII was saponified with a solution of potassium carbonate in methanol to give $3\beta,16\beta$-dihydroxy-6-oxo-24-nor-5α-cholan-23-oic acid lactone (I), m.p. 238–240°, $[\alpha]_D$ $-112°$, ν_{max} 3730, 3540, 1733 and 1712 cm^{-1}, being identical with chiogralactone by mixed m.p. and comparisons of the IR spectra and $[\alpha]_D$ values.

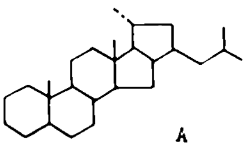
EXPERIMENTAL

All m.ps were taken on a Kofler hot stage apparatus and corrected. UV spectra were taken in 95% EtOH and IR spectra in chf.

Chlorogenin diacetate (VIII). Diborane was generated by dropwise addition of a soln of $NaBH_4$ (1·5 g) in dry diglyme (50 ml) to a stirred soln of freshly distilled BF_3-etherate (10 g) in dry diglyme (10 ml). The gas was passed into a soln of VI (8 g) in dry THF (80 ml) with a slight flow of dry N at 20–23° over a period of 1 hr. After stirring the mixture at the same temp for 2 hr, water (5 ml), 2N NaOH (6 ml) and 30% H_2O_2 (6 ml) were successively added and the mixture stirred for an additional hr. A large vol of water was added and the mixture extracted with chf. The extract was washed well with water, dried over Na_2SO_4, and evaporated, leaving a crystalline residue, which was acetylated with Ac_2O–pyridine at room temp. The product was recrystallized from MeOH to give VII (7·5 g, 83% yield) as colourless prisms, m.p. 153–155°, ν_{max} 1727, 980, 917, 895 and 863 cm^{-1}, identical with an authentic sample of chlorogenin diacetate (mixed m.p. and IR spectra).

3β,6α,27-Triacetoxy-5α-cholestane-16,22-dione (6α-hydroxy-5,6-dihydrokryptogenin triacetate, IX). A soln of VII (7·5 g) in glacial AcOH (50 ml) containing a drop of 60% perchloric acid was shaken with H over a pre-reduced Adams' catalyst (750 mg) at 23°. After 18 hr, 1·07 molar equivs of H had been absorbed and uptake stopped. The catalyst was removed and the filtrate was concentrated under reduced press. The residue was poured into water and extracted with ether. The extract was washed with 5% $NaHCO_3$aq and water, dried over Na_2SO_4, and evaporated. The residue was acetylated with Ac_2O–pyridine at room temp, affording VIII (8 g), a glassy substance. The IR spectrum showed no absorption band attributable to the spiroketal group. To a soln of VII (8 g) in glacial AcOH (130 ml) a soln of CrO_3 (5 g) in 80% AcOH (50 ml) was added dropwise during 1·5 hr with stirring at 94–97°. The mixture was stirred at the same temp for 2·5 hr and the excess CrO_3 was destroyed by addition of MeOH (35 ml). After concentration to 1/3 vol under reduced press, water was added and the mixture extracted with ether. The extract was washed with 5% $NaHCO_3$aq and water, dried over Na_2SO_4, and evaporated. Recrystallization from MeOH gave IX (4·1 g, 49% yield) as colourless prisms, m.p. 149–150°, ν_{max} 1731 cm^{-1} (superimposed three esters and two ketones). (Found: C, 69·05; H, 8·95. $C_{33}H_{50}O_8$ requires: C, 68·95; H, 8·75%.)

3β,6α,27-Trihydroxy-5α-fes-16(23)-en-22-one‡ (*6α-hydroxy-5,6-dihydrofesogenin*, X). A mixture of IX (4·1 g), KOH (20 g), MeOH (100 ml) and water (100 ml) was refluxed for 3 hr in N atm. After concentration to 1/2 vol under reduced press, water was added and the mixture extracted with chf. The extract was washed with water, dried over Na_2SO_4, and evaporated. The resulted residue was chromatographed on alumina (Woelm II, 150 g).



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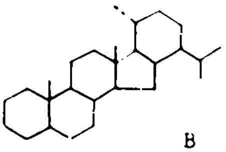

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Chf eluted XI (1·4 g, 46% yield) as a glassy substance, R_f = 0·47,§ ν_{max} 3640, 3480 and 1743 cm^{-1}.

Chf–MeOH (95:5) eluted X (1·6 g, 52% yield) as a glassy substance, R_f = 0·33,§ ν_{max} 3630, 3460, 1690 and 1649 cm^{-1}, λ_{max} 247 mμ (ε 9800). Treatment with Brady's reagent gave a 2,4-dinitrophenylhydrazone as red fine prisms, m.p. 256–257° (dec) (recrystallized from AcOEt–EtOH). (Found: C, 64·7; H, 7·7; N, 8·9. $C_{33}H_{46}O_7N_4$ requires: C, 64·9; H, 7·6; N, 9·15%.)

When XI was treated with KOH as above, a 1:1 mixture of X and XI was obtained.

5α-Fes-16(23)-ene-3β,6α,22,27-tetraol‡ (XII). Compound X (2·1 g) was acetylated with Ac_2O–pyridine at room temp, affording the triacetate (2·6 g) as a glassy substance. A soln of the triacetate (2·6 g) in dry ether (25 ml) was added dropwise to another soln of LAH (0·5 g) in dry ether (25 ml) during 30 min with stirring and ice-cooling. The mixture was stirred at room temp for 2·5 hr, and decomposed by addition of water (2·5 ml). The resulted mixture was acidified with 2N H_2SO_4, and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated. Recrystallization from chf–MeOH gave XII (1·5 g, 71% yield) as colourless fine prisms, m.p. 204–206°. The IR spectrum showed no absorption band in the CO region. (Found: C, 75·1; H, 10·25. $C_{27}H_{44}O_4$ requires: C, 74·95; H, 10·15%.)

3β,6α,27-Triacetoxy-5α-fes-16(23)-ene-16α,23α-diol‡ (XIV). The tetraol XII (1·5 g) was acetylated with Ac_2O–pyridine at room temp affording the tetraacetate (2·1 g) as a glassy substance. A soln of the tetraacetate (2·1 g) in glacial AcOH (20 ml) and 99% EtOH (20 ml) was shaken with H over a pre-reduced Adams' catalyst (100 mg) at 23°. After 12·5 hr, 1·2 molar equivs of H had been absorbed and uptake stopped. The catalyst was removed and the filtrate was concentrated under reduced press. The residue was poured into water and extracted with ether. The extract was washed with 5%

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‡ Nomenclatures are based on the hypothetical substances, fesan (A) and isofesan (B) according to Djerassi's proposal, G. Diaz, A. Zaffaroni, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.* 17, 747 (1952).

§ TLC was carried out with "Merck", Kieselgel G and benzene-acetone (1:3).

$NaHCO_3$aq and water, dried over Na_2SO_4, and evaporated. To a soln of the residue in dry dioxan (20 ml), another soln of OsO_4 (500 mg) in dry dioxan (10 ml), was added and the mixture left for 60 hr at room temp. Dioxan (50 ml) was added, and the mixture was saturated with H_2S. The black ppt was filtered off, and washed with dioxan. The filtrate and washings were evaporated, and the residue (1·9 g) was chromatographed on alumina (Woelm II, 50 g), to give XIV (340 mg, 17% yield), as a glassy substance, ν_{max} 3530 and 1731 cm^{-1}. Hydrolysis of XIV with 10% K_2CO_3–MeOH gave the pentaol, as colourless needles, m.p. 152–154° (recrystallized from MeOH). (Found: C, 68·85; H, 10·3 $C_{27}H_{44}O_6{\cdot}H_2O$ requires: C, 69·15; H, 10·3%.)

3*β*,6*α*,27-*Triacetoxy-5α-cholestane*-16,23-*dione* (XV). A soln of sodium periodate (240 mg) in water (8 ml) was added to another soln of XIV (320 mg) in MeOH (19 ml). The mixture was left for 6 days at room temp and evaporated. Water was added to the residue and extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated. Recrystallization from MeOH gave XV (290 mg, 91% yield) as colourless prisms, m.p. 148·5–149°, ν_{max} 1732 cm^{-1} (superimposed three esters and two ketones). (Found: C, 68·8; H, 9·0. $C_{33}H_{50}O_8$ requires: C, 68·95; H, 8·75%.)

3*β*,6*α*,27-*Trihydroxy-5α-isofes*-16(24)-*en*-23-*one*‡ (XVI). A mixture of XV (280 mg), KOH (4 g), MeOH (20 ml) and water (20 ml) was refluxed for 3 hr in N atm. After concentration to 1/2 vol under reduced press, water was added and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated. The residue (210 mg) was chromatographed on alumina (Woelm II, 6 g) to give XVI (170 mg, 81% yield) as a glassy substance, ν_{max} 3620, 3430 and 1645 cm^{-1}, λ_{max} 253 mμ (ε 12,000).

3*β*,6*α*,27-*Triacetoxy-5α-cholestane*-16,23,24-*trione* (XVII). Compound XVI (170 mg) was acetylated with Ac_2O–pyridine at room temp, affording the triacetate (220 mg) as a glassy substance. A soln of the triacetate (220 mg) in AcOEt (20 ml) was treated at −75° with 3% O_3. After 1·5 molar equivs of O_3 was absorbed, the soln coloured blue was left at −75° for 30 min. The solvent was removed in high vacuum at room temp to afford an oily residue. To this residue were added 2N Na_2CO_3 (10 ml) and 30% H_2O_2 (6 ml), and the mixture was stirred for 4 hr at room temp. The mixture was poured into water, made negative to colour-test with ZnI_2–starch paper by addition of $NaHSO_3$, and extracted with ether. The extract was washed with water, dried over Na_2SO_4 and evaporated. Recrystallization from MeOH gave XVII (150 mg, 63% yield) as colourless needles, m.p. 110–111°, ν_{max} 1732 cm^{-1} (superimposed 3 esters and 3 ketones). (Found: C, 65·7; H, 8·1. $C_{33}H_{48}O_9{\cdot}H_2O$ requires: C, 65·3; H, 8·3%.)

3*β*,6*α*-*Dihydroxy-16-oxo-24-nor-5α-cholan-23-oic acid* (XVIII). To a soln of XVII (140 mg) in 0·5N methanolic KOH (24 ml) was added dropwise 30% H_2O_2 (1·5 ml) with stirring and ice-cooling, and the mixture was stirred for 1 hr at room temp. The mixture was concentrated under reduced press, poured into water and extracted with AcOEt. The aqueous layer was made negative to colour-test with ZnI_2–starch paper by addition of $NaHSO_3$, acidified to Congo Red with 2N H_2SO_4, and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated. Recrystallization from acetone gave XVIII (78 mg, 86% yield) as colourless prisms, m.p. 240–241°, ν_{max} 1739 and 1720 cm^{-1}. (Found: C, 70·25; H, 9·25. $C_{23}H_{36}O_5$ requires: C, 70·35; H, 9·25%.)

3,6,16-*Trioxo-24-nor-5α-cholan-23-oic acid* (XIX). To a soln of XVIII (76 mg) in acetone (5 ml) and dimethylformamide (0·5 ml) was added Jones' reagent (0·3 ml), and the mixture was stirred vigorously for 5 min with ice-cooling. The mixture was poured into ice-water and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated. Recrystallization from acetone gave XIX (62 mg, 82% yield) as colourless prisms, m.p. 226–228°, ν_{max} 1742 and 1710 cm^{-1}. (Found: C, 70·85; H, 8·2. $C_{23}H_{32}O_5$ requires: C, 71·1; H, 8·3%.) The product (XIX) was identical with 3,6,16-trioxo-24-nor-5α-cholan-23-oic acid derived from the natural chiogralactone (mixed m.p. and infrared spectra).

3*β*,6*β*,16*β*-*Trihydroxy-24-nor-5α-cholan-23-oic acid lactone* (XX). Compound XIX (59 mg) was treated with diazomethane affording the Me ester (60 mg). A soln of $NaBH_4$ (300 mg) in MeOH (4 ml) was added to another soln of the Me ester (60 mg) in MeOH (6 ml), and the mixture was left for 3 hr at room temp. The mixture was poured into water, acidified to Congo Red with 2N H_2SO_4, and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated. The residue was dissolved in a soln of K_2CO_3 (500 mg) in MeOH (3 ml) and water (2 ml), and refluxed for 1 hr. After removal of the solvent, water was added and extracted with AcOEt. The aqueous layer was acidified to Congo Red and extracted with AcOEt. The extract was washed with 5%

$NaHCO_3$aq and water, dried over Na_2SO_4, and evaporated. Recrystallization from chf–MeOH gave XX (33 mg, 58% yield) as colourless prisms, m.p. 280–283°. (Found: C, 73·2; H, 9·6. $C_{23}H_{36}O_4$ requires: C, 73·35; H, 9·65%.) The m.p. was not depressed on admixture with 3β,6β,16β-trihydroxy-24-nor-5α-cholan-23-oic acid lactone derived from the natural chiogralactone.

3β-Acetoxy-6-oxo-16β-hydroxy-24-nor-5α-cholan-23-oic acid lactone (XXII). Compound XX (32 mg) was dissolved in a soln of Ac_2O (10 mg) in dry pyridine (1·5 ml) and the mixture was left for 17 hr at room temp. Working up in the usual way, the resulted mixture was purified by preparative TLC ("Merck" Kieselgel G) to give XXI (11 mg, 31% yield) as a glassy substance, ν_{max} 3620, 3510, 1738 and 1729 cm^{-1}.

To a soln of XXI (15 mg) in acetone (3 ml) was added Jones' reagent (0·9 ml), and the mixture was stirred vigorously for 5 min with ice-cooling. The mixture was poured into ice-water and extracted with AcOEt. The extract was washed with 5% $NaHCO_3$aq and water, dried over Na_2SO_4, and evaporated. Recrystallization from acetone–hexane gave XXII (12 mg, 80% yield) as colourless plates, m.p. 228–230°, ν_{max} 1734, 1725 and 1716 cm^{-1}. (Found: C, 72·3; H, 8·85. $C_{25}H_{36}O_5$ requires: C, 72·1; H, 8·7%.) The product (XXII) was identical with 3β-acetoxy-6-oxo-16β-hydroxy-24-nor-5α-cholan-23-oic acid lactone derived from the natural chiogralactone (mixed m.p. and IR spectra).

3β,16β-Dihydroxy-6-oxo-24-nor-5α-cholan-23-oic acid lactone (I). Compound XXII (10 mg) was dissolved in a soln of K_2CO_3 (300 mg) in MeOH (2·5 ml) and water (0·5 ml), and the mixture was refluxed for 1 hr in N atm. After removal of the solvent, water was added, acidified to Congo Red with 2N H_2SO_4, and extracted with AcOEt. The extract was washed with 5% $NaHCO_3$aq and water, dried over Na_2SO_4, and evaporated. Recrystallization from acetone–hexane gave I (7 mg, 78% yield) as colourless prisms, m.p. 238–240°, $[\alpha]_D^{28}$ $-111{\cdot}6°$ ($\pm 2{\cdot}6°$) (*c*, 0·155 in chf), ν_{max} 3730, 3540, 1733 and 1712 cm^{-1}. (Found: C, 73·5; H, 9·1. $C_{23}H_{34}O_4$ requires: C, 73·75; H, 9·15%.) This product was identical with the natural chiogralactone (mixed m.p., IR spectra and optical rotations).

Acknowledgement—The author wishes to express sincere thanks to Dr. Ken'ichi Takeda, Director of this laboratory, for his encouragement and guidance throughout this work. The author is also indebted to Dr. Hitoshi Minato for his helpful advices and suggestions.