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STUDIES ON C-NOR-D-HOMOSTEROIDS—V[1]

SYNTHESIS OF C-NOR-D-HOMOCHOLANIC ACID

H. MITSUHASHI and S. HARADA
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

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Abstract—The conversion of desoxycholic acid to the corresponding C-nor-D-homo system has been studied. One of the major products of the Bamford-Stevens rearrangement in this series has been shown to possess the C-nor-D-homostructure, IV.

THERE have been several reports concerning the preparation of C-nor-D-homosteroids by pyrolytic decomposition of 12-tosylhydrazones of normal steroids.[2–5] Chang[6] recently studied the rearrangement of 12α-methanesulphonyloxycholane but could find little direct evidence for its conversion into the C-nor-D-homosystem. Migration of the C-18 methyl group to the 12-position appeared to account for the major product. Johnson *et al.* have prepared an A/B *cis* C-nor-D-homosteroid by a C-ring contraction.[7] The work reported here is part of a programme in our laboratories on the preparation and hormonal effects of C-nor-D-homosteroids. This paper describes the rearrangement of the 12-tosylhydrazone of desoxycholic acid to a C-nor-D-homosystem and its structure determination.

Desoxycholic acid (I) can be readily converted to tosylhydrazone of 3α-hydroxy-12-ketocholanic acid (II), in five steps.[8,9] Heating II with sodium ethyleneglycolate at 150–170° for 1 hr afforded an oily substance, which was converted to the C-24-acid methyl ester. The methyl ester, so obtained, was chromatographed on neutral alumina and afforded two compounds, III and IV. Reduction of III with LAH gave a diol (Va). Treatment of Va with *p*-nitrobenzoylchloride in pyridine afforded *p*-nitrobenzoate (Vb). Its NMR spectrum showed bands at $\tau(CDCl_3)$, 4·19 (quartet, vinyl proton, J = 10 c/s),[10] 9·06 and 9·24 (singlets, C-19, C-18 methyl groups).[11] The physical and chemical properties found for V are consistent with those reported by Bladon *et al.*[12] The predominant product compound IV took up 1 mole of hydrogen to give a dihydro

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[1] H. Mitsuhashi and N. Kawahara, *Tetrahedron* **21**, 1215 (1965).

[2] R. Hirschmann, C. S. Snoddy, C. F. Hiskey and N. L. Wendler, *J. Amer. Chem. Soc.* **76**, 4013 (1954).

[3] J. Elks, G. H. Phillips, D. A. H. Taylor and L. J. Wyman., *J. Chem. Soc.* 1739 (1954).

[4] H. Mitsuhashi and Y. Shimizu, *Tetrahedron* **19**, 1027 (1963).

[5] D. N. Kirk, *Tetrahedron Letters* 119 (1965).

[6] F. C. Chang, *Tetrahedron Letters* 2075 (1963).

[7] P. W. Schieess, D. M. Bailey and W. S. Johnson, *Tetrahedron Letters* 549 (1963).

[8] E. C. Kendall, B. F. McKenzie, V. R. Mattox and L. L. Engel, *J. Biol. Chem.* **173**, 271 (1948); **162**, 555 (1946).

[9] T. Reichstein und M. Sorkin, *Helv. Chim. Acta* **25**, 797 (1942).

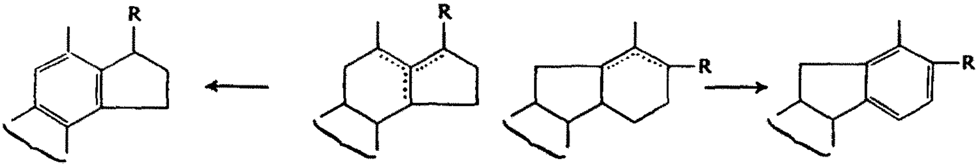
[10] J. N. Schoolery, *J. Amer. Chem. Soc.* **80**, 5121 (1958).

[11] R. F. Zürcher, *Helv. Chim. Acta* **44**, 1380 (1961); **46**, 2054 (1963).

[12] P. Bladon, H. B. Henbest and G. W. Wood, *J. Chem. Soc.* 2737 (1952).

derivative, (VI). Several attempts to make crystalline derivatives of IV were unsuccessful, but IV proved to be chromatographically homogeneous. Reduction of IV with LAH gave a diol (VII) and treatment of this diol (VII) with *p*-nitrobenzoylchloride in pyridine furnished a di-*p*-nitrobenzoate (VIII). The NMR spectrum of VIII showed bands at $\tau(CDCl_3)$, 1·71 (singlet, equivalent to 2 aromatic protons). 4·95 (multiplet, for C-3 proton), 5·62 (triplet, C-24 2 protons), 8·41 (singlet, C-18 methyl), 9·00 (doublet, C-21 methyl, $J = 7$ c/s) and 9·12 (singlet, C-19 methyl).

A consideration of the possible products and their physical and chemical properties resulting from a Bamford-Stevens rearrangement of the 12-tosylhydrazone (II) with the physical data described above lead to (a) and (b) as the most probable structure for IV.



(c) (a) (b) (d)

Compound VII was converted to a diacetate (IX) under mild acetylation conditions. Bromination with N-bromosuccinimide in carbon tetrachloride solution followed by dehydrobromination with collidine gave, after chromatography on alumina, a chromatographically homogeneous oil (X), $\nu_{max}^{CS_2}$ 820 cm^{-1}(aromatic), λ_{max}^{MeOH} 259, 264, 267 mμ. The NMR spectrum of X showed a multiplet centered at 2·88 which integrated for two aromatic protons. The reaction from IX to X can be expressed either as (a) → (c) or (b) → (D). The NMR spectra of X and the following compounds were compared; 22,23-dibromo-12-methyl-18-nor-ergosta-8,11,13trien-3β-olacetate[13]: 3·22 τ(one aromatic proton at C-11), 7·77 τ(C-12-methyl), veratramine triacetate: 3·00 τ(2 aromatic protons in ring D)[14] and verarine: 3·00 τ(2 aromatic protons in ring D).[15] Thus, the occurrence of two aromatic protons in the NMR spectrum of X clearly shows that X has structure (D) derived from (b). Osmium tetroxide hydroxylation of IV gave, after processing, XIV, whose NMR spectrum showed C-18 methyl as singlet at 8·52τ. Lead tetra-acetate oxidation of XIV in 90% acetic acid consumed 1 mole of reagent and gave a diketone (XV). The IR spectrum of XIV showed bands at 1710 and 1730 cm^{-1}, and its potassium salt had bands at 1730, (5-membered ring ketone) and 1705 cm^{-1} (methylketone). The NMR spectrum of XV showed a singlet at 7·80 τ(methyl ketone), thus indicated that the original double bond in IV was between carbons 12 and 13.

EXPERIMENTAL

All m.p. were measured on the Kofler Hot Stage Microscope and are uncorrected. For identification, homogenity test, and in order to follow the course of reactions, use was made of TLC on alumina (Aluminumoxide G nach Stahl). The UV spectra were obtained with a Shimadzu Recording UV-Spectrophotometer RS-27. The IR spectra were measured with a Shimadzu IR Spectrophotometer type IR, NMR spectra were taken on a Nihon Denshi JNMC-60 in the indicated solvents using tetramethylsilane as internal reference and reported in τ units. Column chromatography was carried out on neutral alumina.

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[13] C. F. Hammer, D. S. Savage, J. B. Thomson and R. Stevenson, *Tetrahedron* **20**, 929 (1964).

[14] Private communication Prof. Masamune, Kokkaido University.

[15] T. Tomko and S. Bauer, *Coll. Czech. Chem. Commun.* **29**, 2570 (1964).

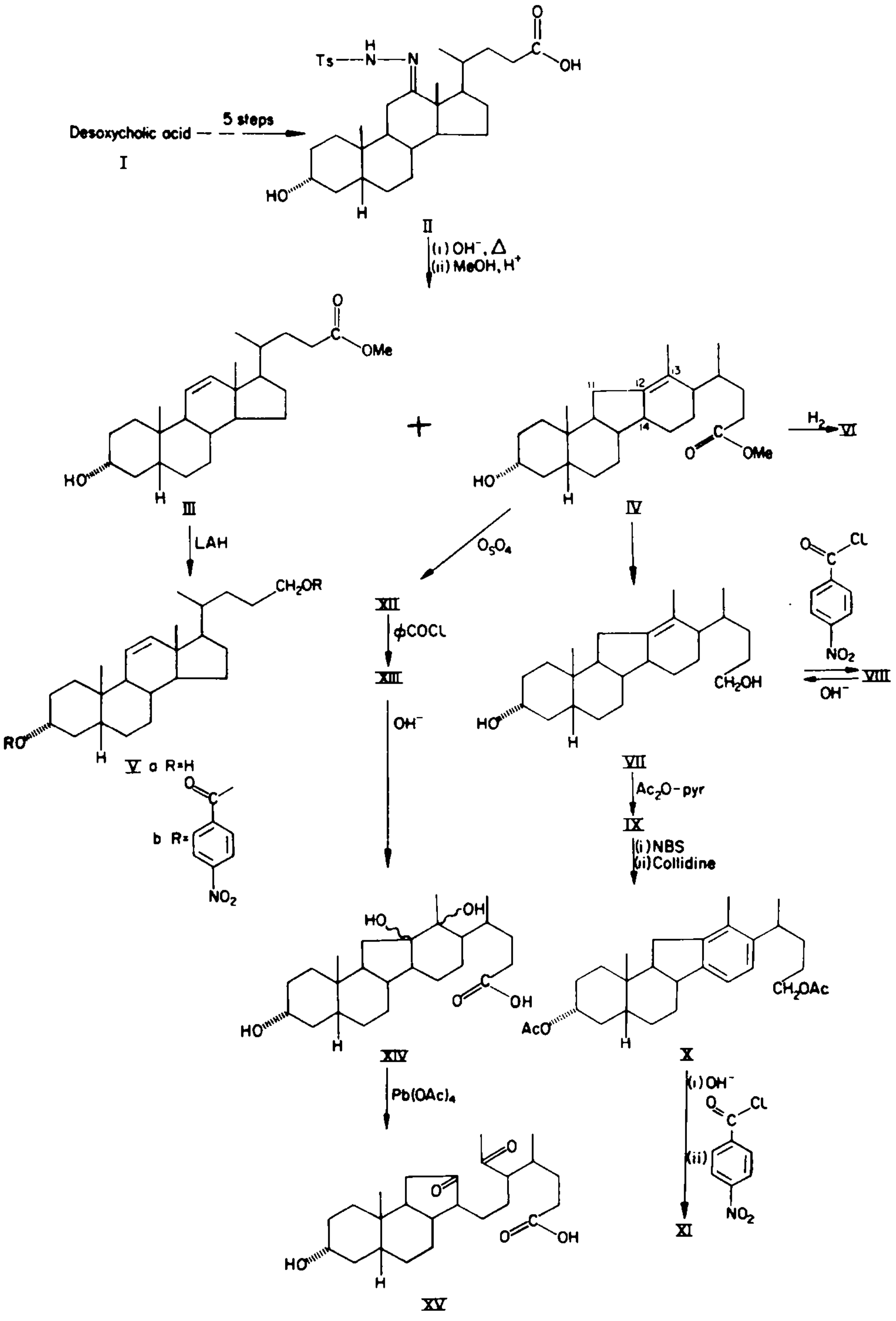
Desoxycholic acid
I
5 steps
Ts—N—N
H
OH
O
HO
H
II
(i) OH⁻, Δ
(ii) MeOH, H⁺
OMe
III
+
11
12
13
14
OMe
IV
H₂
VI
LAH
CH₂OR
RO
V a R=H
b R=
NO₂
OsO₄
XII
φCOCl
XIII
OH⁻
Cl
NO₂
CH₂OH
VIII
OH⁻
VII
Ac₂O-pyr
IX
(i) NBS
(ii) Collidine
HO
OH
XIV
CH₂OAc
AcO
X
Pb(OAc)₄
(i) OH⁻
(ii)
Cl
NO₂
XI
XV

Chart 1

Starting materials. Desoxycholic acid (I 45·0 g) purified by Kendall's method,[8] m.p. 148°/168–170° (from MeOH), was esterified with 135 ml of 1·5% HCl in MeOH at 20° overnight to give 43·0 g of desoxycholic acid methyl ester m.p. 90–105°. This was monobenzoylated with 14·0 ml dist. benzoyl chloride in 43·0 ml absolute benzene and 11·4 ml dried pyridine at 20° for 2 hr to give 42·7 g 3α-benzoxy-12α-hydroxy-cholanic acid methyl ester m.p. 83–93°. A mixture of the above ester, acetic acid (39 ml) chromic acid (8·3 g) and water (8·3 ml) was vigorously stirred for 45 min at 20°, then conc. H_2SO_4 (4·5 ml) was added and stirring continued for 45 min. Upon processing, 33·8 g 3α-benzoxy-12-keto-cholanic acid methyl ester m.p. 105° was obtained. This was refluxed in 1 l. 5% methanolic KOH for 10 hr to give 21·2 g of 3α-hydroxy-12-keto-cholanic acid, m.p. 120°/161–162°. Total yield of 4 steps was 47%.

Tosylhydrazone of 3α-*hydroxy*-12-*keto-cholanic acid* (II). Hydroxy-12-keto-cholanic acid (21·2 g) was dissolved in 120 ml glacial acetic acid, in which 21·2 g tosylhydrazine, m.p. 111–113°, was added. The solution was held at 30° for 16 hr. After addition of water, the reaction mixture was cooled at 0° for several hr and then filtered. Recrystallization from MeOH afforded white needles (27·1 g) m.p. 228–229° (dec.), $[\alpha]^{21}_{589}$ −9·04° (*c*, 0·66, MeOH) $\nu^{\mathrm{Nujol}}_{\mathrm{max}}$ 3500, 2900, 1735, 1500, 1180, 820 cm^{-1}, (Found: C, 66·47; H, 8·41; N, 5·20. Calc. for $C_{31}H_{46}O_5N_2S$: C, 66·64; H, 8·30; N, 5·01%.)

Rearranged products III *and* IV. To a solution of Na (5·8 g) in ethylene glycol (250 ml), II (10·5 g) was added, and the mixture was gradually heated under N_2 at 150–170° for 1 hr. After cooling, the reaction mixture was acidified with dil. HCl and filtered, to give 6·5 g product. The substance (5·0 g) was dissolved in 17 ml 5% methanolic HCl and held overnight at 30°. After neutralization by iced Na_2CO_3aq, the reaction mixture was extracted with ether and the extract washed, dried (Na_2SO_4) and solvent removed, 4·53 g of an oily methyl esters was obtained and chromatographed on 180 g alumina. The main product (IV) was eluted with benzene (1·94 g), and III was obtained by elution with benzene–ether (0·4 g). Further elution gave three minor products; IV $\nu^{\mathrm{CHCl_3}}_{\mathrm{max}}$ 3500, 1730, 1040 cm^{-1}, NMR τ (in $CDCl_3$) 6·40 (singlet, methyl ester), 8·48 (C-18 methyl), 9·15 (C-19 and C-21 methyl). (Found: C, 76·81; H, 9·99. $C_{25}H_{40}O_3$ requires: C, 77·27; H, 10·3%.)

5β-*Chol*-11-*ene*-3α, 24-*diol* (Va),[12] Compound III (320 mg) was refluxed with LAH (300 mg) in absolute tetrahydrofuran (30 ml) for 3 hr under anhydrous conditions. The lithium aluminum complex was then hydrolysed with ether saturated with water, acidified, and extracted with ether. The extract was washed with water, Na_2CO_3aq and water, dried (Na_2SO_4) overnight and solvent removed. The residue was recrystallized from MeOH and gave 116 mg of white needles (Va), m.p. 190–194°, $[\alpha]^{19\cdot0}_{589}$ +47·0° (*c* 0·61, MeOH), $\nu^{\mathrm{Nujol}}_{\mathrm{max}}$ 3250, 1060, 723 cm^{-1}. (Found: C, 80·08; H, 11·24; Calc. for $C_{24}H_{40}O_2$: C, 79·94; H, 11·18%.)

5β-*Chol*-11-*ene*-3α, 24-*diol di*-(p-*nitro*)-*benzoate* (Vb). 5β-Chol-11-ene-3α, 24-diol (Va; 174 ml) was dissolved in 2 ml pyridine, to which 220 mg (2·5 mole) *p*-nitrobenzoyl chloride was added, and the mixture shaken vigorously, and held at 30° overnight. After pouring into ice water, the reaction mixture was extracted with benzene and the extract washed with dil. HCl, Na_2CO_3aq and water, dried and solvent removed. Recrystallization from acetone afforded pale yellow plates (Vb), m.p. 178–182°, $[\alpha]^{125}_{D}$ +46·3° (*c*, 1·84 $CHCl_3$), yield 180 mg $\nu^{\mathrm{Nujol}}_{\mathrm{max}}$ 1715, 1603, 1525, 1280, 1103, 1020, 985, 715 cm^{-1}, $\lambda^{\mathrm{dioxane}}_{\mathrm{max}}$ 260 mμ (ε 24,000). (Found: 69·29; H, 6·72; N, 4·23. $C_{38}H_{46}O_8N_2$ requires: C, 69·28; H, 7·04; N, 4·25%.)

C-*Nor*-D-*homo*-5β-*cholan*-3α-*olic acid* (VI). Rechromatographed IV (133 mg) was dissolved in 15 ml glacial acetic acid and shaken with PtO_2, under an H_2 atm. for 8 hr. Exactly 1 mole H_2 was consumed. The catalyst was filtered off and the solvent evaporated to dryness. The residue was extracted with ether. After the ethereal solution was dried (Na_2SO_4), evaporation of the solvent gave a colourless oil, and the product (120 mg) chromatographed on alumina (4·8 g). Elution with benzene gave 68·2 mg of an oily substance (VI), $\nu^{\mathrm{CHCl_3}}_{\mathrm{max}}$, 3500, 1730, 1240, 1040 cm^{-1}. (Found: C, 76·63; H, 10·77. $C_{25}H_{42}O_3$ requires: C, 76·87; H, 10·84%.)

C-*Nor*-D-*homo*-5β-*chol*-12-*ene*-3α, 24-*diol* (VII). Compound IV (1·42 g) was dissolved in 30 ml dry tetrahydrofuran, and added dropwise to LAH 0·9 g in dry tetrahydrofuran (60 ml). The mixture was refluxed for 3 hr. The reaction mixture was treated as for Va, 1·09 g of oily product was purified by chromatography on alumina (40 g). Elution with hexane–ether (5:1) furnished VII (876 mg). (Found: C, 79·50; H, 11·15. $C_{24}H_{40}O_2$ requires: C, 79·94; H. 11·18%.)

C-*Nor*-D-*homo*-5β-*chol*-12-*ene*-3α, 24-*diol di*-(p-*nitro*)-*benzoate* (VIII). Compound VII (664 mg) was dissolved in pyridine (6 ml), to which 860 mg *p*-nitrobenzoyl chloride was added. This solution was shaken well and allowed to stand at 30° overnight. The reaction mixture was poured into ice water, and extracted with benzene. The benzene extract was washed with dil HCl water, Na_2CO_3aq and water, dried by Na_2SO_4 and solvent removed. The residue was recrystallized from acetone, m.p. 175–184°, $[\alpha]_D^{19.5}$ +7·98 (*c*, 0·977, $CHCl_3$). (Found: C, 69·38; H, 6·97; N, 4·02. $C_{38}H_{46}O_8N_2$ requires: C, 69·28; H, 7·04; N, 4·25%.) Compound VIII was hydrolysed to VII in good yield.

C-*Nor*-D-*homo-5β-chol*-12-*ene*-3α, 24-*diol diacetate* (IX). Compound VII (1·03 g) was dissolved in Ac_2O (5 ml) and pyridine (10 ml), and allowed to stand at 30° overnight. After treatment in the usual way 1·2 g oil was obtained, and chromatographed over alumina (48 g). Elution with hexane gave pure IX (650 mg). $\nu_{max}^{CS_2}$ 1740, 1240 cm^{-1}, NMR, τ (in $CDCl_3$) 5·24 (C-3 proton), 5·93 (C-24-2-protons), 7·96 (2-OAc), 8·39 (C-18 methyl), 9·06 (C-19 and C-21 methyl). (Found: C, 75·91; H, 9·96. $C_{28}H_{44}O_4$ requires: C, 75·63; H, 9·97%.)

C-*Nor*-D-*homo-5β-chola*-12,14,16-*triene*-3α, 24-*diol diacetate* (X). Compound IX (200 mg) was dissolved in 1·17 ml abs. CCl_4 and refluxed for 12 min with 220 mg (2·5 mole) N-bromosuccinimide. After filtration of the succinimide the organic solvent was evaporated and the residue dissolved in pure collidine (1 ml) and xylene (10 ml), and refluxed for 1·5 hr. The brownish-black reaction solution was extracted with ether and the extract washed well by acid, base and water, and dried. The product (174 mg) was chromatographed on alumina (8·7 g) and eluted with benzene, fractions 1–5 (94 mg) were rechromatographed, to give pure X (64 mg), $\nu_{max}^{CS_2}$ 1730, 1230 (ester), 1603, 820 cm^{-1} (aromatic). NMR τ (in $CDCl_3$); 2·88 (multiplet, 2 aromatic protons) 7·96, 8·00, 8·05 (2-acetate methyl and aromatic methyl), 8·84 (singlet, C-19 methyl). (Found: C, 75·57; H, 8·89. $C_{28}H_{40}O_4$ requires: C, 76·32; H, 9·15%.) Compound XI was obtained in the usual manner starting with X.

C-*Nor*-D-*homo-5β-cholane*-3α,12ξ,13ξ-*triolic acid methyl ester* (XII). Compound IV (2·08 g) was dissolved in 5 ml abs. ether and 1 ml pyridine, to which 2·0 g OSO_4 was added at room temp and allowed to stand for 8 days. H_2S gas was vigorously bubbled into the reaction mixture suspended in MeOH, filtered and the H_2S gas treatment repeated 4 times to the filtered solution. The solution was once more filtered through double filter paper, concentrated, and extracted with ether. The extract was washed with dil HCl, water, dried (Na_2SO_4) and solvent removed. The resulting oily compound (1·78 g) was chromatographed on alumina (72 g). Eluates of $CHCl_3$–MeOH (97:3) contained the main fraction and after removal of solvent deposited crystalline V. (1·2 g). Attempted recrystallization gave oil. $\nu_{max}^{CHCl_3}$ 3500, 1730, 1220 cm^{-1}. (Found: C, 70·98; H, 9·82. $C_{25}H_{42}O_5$ requires: C, 71·05; H, 10·02%.)

C-*Nor*-D-*homo-5β-cholane*-3α,12ξ,13ξ-*triolic acid* 3-*benzoate methyl ester* (XIII). Compound XII (500 mg) was dissolved in pyridine (5·5 ml) to which 0·17 ml benzoyl chloride was added, and held at 30° overnight. The reaction mixture was treated in the usual way, and the crude XIII (572 mg) chromatographed on silicic acid. The still crude benzoate (437 mg) was rechromatographed over alumina (17·5 g). Elution with hexane–ether (4:1) gave pure XIII. ν_{max}^{Nujol}3500, 1735, 1715, 1603, 1580, 1270 cm^{-1}. (Found: C, 72·91; H, 8·75. $C_{32}H_{46}O_6$ requires: C, 72·97; H, 8·80%.)

C-*Nor*-D-*homo-5β-cholane*-3α,12ξ,13ξ-*triolic acid* (XIV). Compound XIII (152 mg) was refluxed in 5 ml 5% methanolic KOH for 5 hr. After addition of water to the reaction mixture, white needles appeared, which on repeated recrystallization from MeOH gave crystalline XIV, (62 mg), m.p. 208–217°, $[\alpha]_{589}^{19}$ +63·0° (*c*, 0·337, pyridine), ν_{max}^{Nujol} 3300, 2650, 1715, 1040 cm^{-1}, NMR τ (in pyridine); 6·23 (C-3 proton), 8·52 (C-18 methyl), 8·87 (doublet, C-21 methyl, J = 7 c/s). 9·03 (C-19 methyl). (Found: C, 70·64; H, 9·82; $C_{24}H_{40}O_5$ requires: C, 70·55; H, 9·87%.)

C-*Nor*-D-*homo*-12,13-*seco-5β-cholane*-3α-*ol*,12,13 *dionic acid* (XV). Compound XIV (34·1 mg) was dissolved in AcOH (40 ml), to which 3 ml of N/25 $Pb(OAc)_4$ acetic acid soln (*f* = 1·12) was added. After 8·5 hr 0·956 mole of $Pb(OAc)_4$ was consumed. Ethylene glycol and water was added to the oxidation solution and kept for 1 hr at room temp in the dark, the solution was then concentrated under red. press. and extracted with ether. Evaporation of the solvent gave 28 mg of residue. The colourless oil was dried at 100° for 2 hr *in vacuo*. NMR τ (in $CDCl_3$) 6·28 (multiplet, C-3 proton), 7·80 (singlet, C-18 methyl, methyl ketone) 9·05 (singlet, C-19 methyl), 9·04 (doublet, C-21 methyl, J = 9 c/s). Diketocarboxylic acid (XV, 5 mg) was dissolved in MeOH (0·13 ml), in which an equivalent of K_2CO_3 in water + MeOH soln was added, heated, evaporated off and dried *in vacuo*. The IR absorption was measured with Nujol.

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