five hours. A vigorous evolution of hydrogen chloride took place in the initial stage of the reaction. The reaction mixture was cooled, the toluene and phosphorus oxychloride were removed under reduced pressure, ice was added, and the mixture was left overnight in an ice-chest. The semi-solid product was dissolved in benzene, and the benzene solution was washed with dilute sodium hydroxide solution and water. After drying over anhydrous sodium sulfate the solvent was removed. The residue (3.4 g.) crystallized when dissolved in a small amount of glacial acetic acid and was allowed to stand. Several recrystallizations from ligroin gave 1.8 g. (43%) of 1,1,2-tri-*p*-anisyl-2-chloroethylene (IV), m.p. 113–114°, reported[13] m.p. 113–114°.

α,α-Di-*p*-anisylacetophenone.[7]—A mixture of 4.0 g. (0.037 mole) of anisole, 15 ml. of glacial acetic acid and 8 g. (4.4 ml.) of concentrated sulfuric acid was treated with a solution of 2.1 g. (0.014 mole) of phenylglyoxal monohydrate[16] in 20 ml. of glacial acetic acid under the same conditions as above and the product was worked up as usual. The residual semi-solid material was crystallized from glacial acetic acid, and 3.4 g. (74%) of α,α-di-*p*-anisylacetophenone, m.p. 91–92°, was obtained.

Anal. Calcd. for $C_{22}H_{20}O_3$: C, 79.49; H, 6.06. Found: C, 79.79; H, 6.29.

1,2,2-Tri-*p*-anisylethanol (V).—A solution of 5.3 g. (0.015 mole) of crystalline *p*-methoxy-α,α-di-*p*-anisylacetophenone (I) in 80 ml. of absolute ethyl alcohol was heated to the reflux point, when 7 g. (0.30 mole) of sodium, cut in small pieces, was added, all at once, through the top of the condenser[17] (80 cm. long, internal diameter 2.8 cm.). A vigorous reaction occurred, but it subsided rapidly and the heating was continued to reflux until the pieces of sodium disappeared. The hot reaction mixture was poured into crushed ice and the precipitated solid was extracted with benzene. The extract was washed with water until neutral, dried with anhydrous sodium sulfate and evaporated. The residue crystallized on standing overnight and a single recrystallization from ethanol gave 2.4 g. (45%) of 1,2,2-tri-*p*-anisylethanol (V), m.p. 107–108°.

Anal. Calcd. for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.63; H, 6.57.

(16) This compound was prepared by hydrolysis of N,N-dimethylaminophenyl-α-benzoylnitrone which was prepared from phenacylpyridinium bromide, with 5 *N* sulfuric acid (*cf.* ref. 6).

(17) S. Bernstein and E. S. Wallis, THIS JOURNAL, **62**, 2871 (1940).

1,1,2-Tri-*p*-anisylethylene (VI).—A mixture of 1.7 g. (0.0047 mole) of 1,2,2-tri-*p*-anisylethanol (V) and 2 g. of *p*-toluenesulfonic acid in 80 ml. of dry toluene was heated to reflux for two hours. The reaction mixture was washed with water, dilute sodium hydroxide solution and water, and dried over anhydrous sodium sulfate. Removal of the solvent, followed by standing with ethanol, gave 1.3 g. (81%) of tri-*p*-anisylethylene (VI) which, after several recrystallizations from glacial acetic acid, melted at 97–98°. The recorded[13] m.p. is 100–101°.

1,1,2-Tri-*p*-anisylethylene (VI) by Grignard Reaction.—To a Grignard reagent, prepared from 37 g. (0.20 mole) of *p*-bromoanisole and 4.8 g. (0.20 mole) of magnesium in 85 ml. of dry ether, a solution of 9.5 g. (0.051 mole) of α-chloro-*p*-methoxyacetophenone in 100 ml. of benzene was added dropwise with ice-cooling and stirring. After boiling under reflux for two hours, a solution of 50 g. of ammonium chloride in 150 ml. of water was added and the precipitates were filtered off. The organic layer was separated and the aqueous layer and the precipitates were extracted with ether. The ether and benzene solutions were combined, washed with water and dried over anhydrous calcium chloride. After removing the solvent, the residue was treated with 2 g. of *p*-toluenesulfonic acid in 100 ml. of dry toluene and heated to reflux for two hours under exactly the same conditions as above. The residue was subjected to steam distillation in order to remove excess anisole. Two recrystallizations from glacial acetic acid gave 16 g. (90%) *p*-anisylethylene (VI), m.p. 97–98.5°,[13] which showed no depression when admixed with the product prepared from 1,2,2-tri-*p*-anisylethanol (V).

1,1,2-Tri-*p*-anisylethanol (VII) could be isolated, although with some difficulties, from the product of the above-mentioned Grignard reaction. The carbinol formed colorless prisms melting at 129° after several recrystallizations from ethyl alcohol. The recorded m.p.[13] is 130–131°.

NOTE ADDED IN PROOF.—Sumrell and Goheen[18] have reported that they could not obtain *p*-methoxy-α,α-di-*p*-anisylacetophenone (I) in crystalline form and were unable to prepare 1,1,2-tri-*p*-anisyl-2-chloroethylene (IV) or 1,1,2-tri-*p*-anisylethanol (V), from I with phosphorus pentachloride or sodium-ethanol, respectively. As yet the reason for this discrepancy has not been determined.

(18) G. Sumrell and G. E. Goheen, *ibid.*, **77**, 3805 (1955).

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[CONTRIBUTION FROM THE PHARMACEUTICAL INSTITUTE, MEDICAL FACULTY, UNIVERSITY OF KYUSHU]

Cholesterol and Related Compounds. IV. Synthesis of 11-Ketocholestan-3β-ol

BY KYOSUKE TSUDA AND RYOICHI HAYATSU[1]

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Chromic acid oxidation of 7-keto-$\Delta^{5,8(9)}$-cholestadien-3β-ol benzoate (III) yielded 7,11-diketo-$\Delta^{5,8(9)}$-cholestadien-3β-ol benzoate (IV) which, on reduction with acetic acid and zinc, formed 7,11-diketocholesteryl benzoate (VII). Catalytic reduction of VII yielded 7,11-diketocholestan-3β-ol benzoate (VIII) which was converted to 11-ketocholestanol (IX) by the Wolff-Kishner reaction.

Considerable research has been done on the introduction of a keto group into the 11-position of steroids with an unsubstituted C ring.[2–11] Our

(1) Takamine Research Laboratory, Sankyo Co., Ltd., Tokyo, Japan.

(2) L. F. Fieser, J. E. Herz and W.-Y. Huang, THIS JOURNAL, **73**, 2397 (1951); L. F. Fieser, J. C. Babcock, J. E. Herz, W.-Y. Huang and W. P. Schneider, *ibid.*, **73**, 4053 (1951).

(3) E. M. Chamberlin, W. V. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, *ibid.*, **73**, 2396 (1951).

(4) G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 3546 (1951); C. Djerassi, O. Mancera, G. Stork and G. Rosenkranz, *ibid.*, **73**, 4496 (1951).

(5) R. C. Anderson, R. Budziarek, G. T. Newbold, R. Stevenson and F. S. Spring, *Chemistry & Industry*, 1035 (1951).

(6) H. Heusser, K. Eichenberger, P. Kurath, H. R. Dallenbach and O. Jeger, *Helv. Chim. Acta*, **34**, 2106 (1951); H. Heusser, K. Heusler, K. Eichenberger, C. G. Honegger and O. Jeger, *ibid.*, **35**, 295 (1952); H. Heusser, R. Anliker, K. Eichenberger and O. Jeger, *ibid.*, **35**, 936 (1952).

(7) (a) L. F. Fieser, W.-Y. Huang and J. C. Babcock, THIS JOURNAL, **75**, 116 (1953); (b) L. F. Fieser and J. E. Herz, *ibid.*, **75**, 121 (1953); (c) L. F. Fieser, W. P. Schneider and W.-Y. Huang, *ibid.*, **75**, 124 (1953).

(8) G. Rosenkranz, M. Velasco, C. Djerassi and F. Sondheimer, *ibid.*, **75**, 4430 (1953).

(9) G. D. Laubach, E. C. Schreiber, E. J. Angenello, E. N. Lightfoot and K. J. Brunings, *ibid.*, **75**, 1514 (1953).

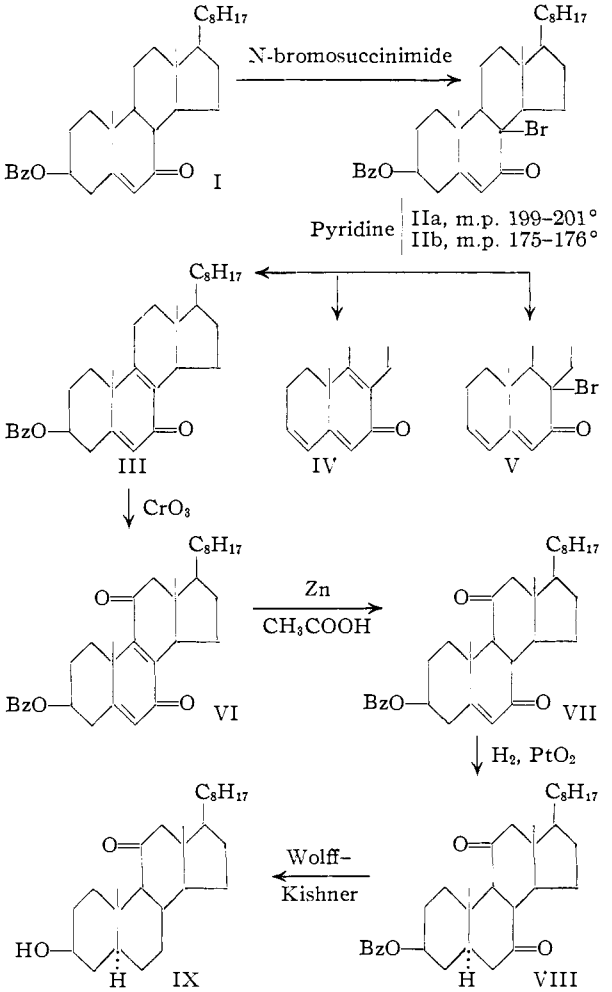
(10) P. Bladon, H. B. Henbest, E. R. H. Jones, G. W. Wood, D. C. Eaton and A. A. Wagland, *J. Chem. Soc.*, 2916 (1953); P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovell, G. W. Wood, G. F. Wood, J. Elks, R. M. Evans, D. E. Hathway, J. F. Oughton and G. H. Thomas, *ibid.*, 2921 (1953); J. Elks, R. M. Evans, C. H. Robinson, G. H. Thomas and L. J. Wyman, *ibid.*, 2933 (1953); D. C. Burk, J. H. Turnbull and W. Wildon, *ibid.*, 3237 (1953); (a) J. Ekls, R. M. Evans, A. G. Long and G. H. Thomas, *ibid.*, 451 (1954); (b) J. Elks, R. M. Evans, J. F. Oughton and G. H. Thomas, *ibid.*, 463 (1954).

(11) J. Lemin and C. Djerassi, THIS JOURNAL, **76**, 5672 (1954).

method for the preparation of 11-ketosteroids, which consists in the oxidation of 7-keto-$\Delta^{5,8(9)}$-steroids, is similar to that used by Ruzicka, *et al.*,[12] for the preparation of 11-ketosteroids from lanosterol and dihydrolanosterol.

The starting material, 7-keto-$\Delta^{5,8(9)}$-cholestadien-3β-ol benzoate (III), was prepared by the treatment of 7-ketocholesteryl benzoate (I) with N-bromosuccinimide to give the 8-bromo compounds IIa and IIb which were dehydrobrominated to III, as described for the preparation of 7-keto-$\Delta^{5,8(9)}$-cholestadien-3β-ol acetate.[13,14] Unlike the acetate, compound I yielded two 8-bromo derivatives IIa and IIb both of which, when heated with pyridine, gave III as the main product and 7-keto-$\Delta^{3,5,8(9)}$-cholestatriene (IV) and 8-bromo-7-keto-$\Delta^{3,5}$-cholestadiene (V) as by-products; thus IIa and IIb are stereoisomeric at the 8-position.

On heating with ethanolic potassium acetate, IIa and IIb do not undergo dehydrobromination, but lose the benzoxyl group in the 3-position to form V.



Since saponification of III followed by acetylation yielded 7-keto-$\Delta^{5,8(9)}$-cholestadien-3β-ol acetate[13,14] which was reconverted to III by saponification and subsequent benzoylation, there is no doubt concerning the structure assigned to III.

Oxidation of III with chromium trioxide afforded 7,11-diketo-$\Delta^{5,8(9)}$-cholestadien-3β-ol benzoate (VI) which was reduced to 7,11-diketo-Δ^{5}-cholesten-3β-ol benzoate (VII). The catalytic hydrogenation of VII with platinum oxide yielded 7,11-diketocholestan-3β-ol benzoate (VIII) which was identical with a sample prepared by the method of Fieser, *et al.*,[7a] from $\Delta^{7,9(11)}$-cholestadien-3β-ol benzoate, through 7,11-diketo-$\Delta^{8(9)}$-cholesten-3β-ol benzoate. VIII was converted to 11-ketocholestan-3β-ol (IX) by the Wolff–Kishner reduction, as described by Fieser.[7a]

Experimental[15]

8-Bromo-7-keto-Δ^{5}-cholesten-3β-ol Benzoate (IIa and b).—To a solution of 6.5 g. of 7-ketocholesteryl benzoate (I) in 40 ml. of carbon tetrachloride was added 3.2 g. of N-bromosuccinimide and 20 mg. of benzoyl peroxide. The mixture was refluxed for 40 minutes under the irradiation of a 275-watt infrared lamp from a distance of 40 cm.

After filtration, the filtrate was distilled under reduced pressure below 40°. The residual reddish oil crystallized on standing. Recrystallization from acetone yielded silky crystals of IIa, m.p. 199–201° dec., yield 2 g., $[\alpha]^{12}D$ −84.0 ± 3° (*c* 1.19) $\lambda_{max}^{Et_2O}$ 232 mμ (ε 10,200).

Anal. Calcd. for $C_{34}H_{47}O_3Br$: C, 69.98; H, 8.06. Found: C, 70.08; H, 7.79.

Evaporation of the mother liquor afforded an additional crop of crystals, m.p. 181° dec., which upon repeated recrystallization from acetone yielded 750 mg. of IIb, m.p. 175–176° dec., $[\alpha]^{12}D$ −52.8 ± 3°, $\lambda_{max}^{Et_2O}$ 232 mμ (ε 9,800).

Anal. Calcd. for $C_{34}H_{47}O_3Br$: C, 69.98; H, 8.06. Found: C, 70.22; H, 7.66.

Dehydrobromination of II.—A mixture of 5 g. of IIa and 30 ml. of anhydrous pyridine was refluxed for 10 hours and then poured into cold dilute hydrochloric acid. This mixture was extracted with ether; the ether layer was washed with 10% hydrochloric acid and water, dried with sodium sulfate, and the solvent was distilled. The ultraviolet absorption spectrum of the crude yellow product (2.6 g.) showed: λ_{max}^{EtOH} 239 and 281 mμ (optical density, 1.217 and 0.842 at 0.0025%).

Two grams of the crude product in 200 ml. of PEB (1:1) was chromatographed (50 g. of alumina in 2 × 24 cm., activity II/III) and the effluent was fractionated into 40-ml. portions. Fractions 1–3 yielded a colorless oil which crystallized from ethanol as needles of 7-keto-$\Delta^{3,5,8(9)}$-cholestatriene (IV), yield 180 mg., m.p. 119–120°, λ_{max}^{EtOH} 280.5 mμ (ε 25,180).

8-Bromo-7-keto-$\Delta^{3,5}$-cholestadiene (V)[14] was obtained from fractions 6–7; yield 220 mg., m.p. 117–118°, λ_{max}^{EtOH} 279.5 mμ (ε 17.350).

Further development of the column with PEB (1:3) afforded an oil which crystallized from acetone to give 7-keto-$\Delta^{5,8(9)}$-cholestadien-3β-ol benzoate (III); yield 1.05 g., m.p. 163–164°, $[\alpha]^{21}D$ −30.6 ± 3°, λ_{max}^{EtOH} 239 mμ (ε 21,200), ν_{max} 1725, 1679 and 1640 cm.$^{-1}$.

Anal. Calcd. for $C_{34}H_{48}O_3$: C, 80.95; H, 9.52. Found: C, 81.21; H, 9.22.

The same results were obtained by the treatment of IIb with pyridine.

Saponification of III.—A mixture of 150 mg. of III and 5% ethanolic potassium hydroxide was refluxed for 30 minutes. The saponified product was an oil which was allowed to stand overnight with 5 ml. of pyridine and 2.5 ml. of acetic anhydride. This mixture was then poured into ice-water and the oily acetate extracted with ether.

(12) L. Ruzicka, Ed. Rey and A. C. Muhr, *Helv. Chim. Acta*, **27**, 472 (1944).

(13) K. Tsuda, Ko Arima and R. Hayatsu, THIS JOURNAL, **76**, 2933 (1954).

(14) K. Tsuda and R. Hayatsu, *ibid.*, **77**, 665 (1955).

(15) Optical rotations were measured in chloroform and infrared absorption spectra in Nujol, unless otherwise noted. Acid-treated alumina columns were used for the chromatographic separations. A mixture of petroleum ether (b.p. 40–60°) and benzene, PEB, was used as the solvent and developer; exceptions are indicated in the text.

After the extract had been washed with water and dried, the ether was removed under reduced pressure. The residue, dissolved in 60 ml. of PEB (1:1), was passed through an alumina column (20 g. in 1 × 16 cm.; activity III) which was developed with PEB (1:3). The crystals from the eluate were recrystallized from ethanol; m.p. 153.5–155°, λ_{max}^{EtOH} 239.5 mμ (ε 26,400). This substance, which was identified as 7-keto-$\Delta^{5,8(9)}$-cholestadien-3β-ol acetate, yielded III upon saponification followed by benzoylation.

8-Bromo-7-keto-$\Delta^{9,5}$-cholestadiene (V).—A mixture of 500 mg. of IIa and 1 g. of potassium acetate, suspended in 50 ml. of anhydrous ethanol, was refluxed for 10 hours. After most of the solvent had been removed under reduced pressure below 40° the residue was poured into water. Several recrystallizations from ethanol gave colorless needles (m.p. 117–118°, yield 320 mg.) which were identified as V.

7,11-Diketo-$\Delta^{5,8(9)}$-cholestadien-3β-ol Benzoate (VI).—To 4 g. of III dissolved in a mixture of 25 ml. of chloroform and 240 ml. of glacial acetic acid, was added 3 g. of chromium trioxide over a period of 2 hours at 60–65°; the mixture was stirred during the additions and for 3 hours thereafter. Chromium trioxide was decomposed with ethanol, the solvent distilled under reduced pressure below 40°, and the residue poured into water. This mixture was extracted with ether; the ether layer was washed with sodium carbonate solution and water, dried (sodium sulfate) and the ether evaporated. The crude crystals (3.2 g.), dissolved in 100 ml. of PEB (1:1), were passed through an alumina column (80 g. in 2.5 × 32 cm.; activity II/III) which was developed with the solvent; the effluent was fractionated in 40-ml. portions.

Unidentified colorless needles were obtained from fractions 2–5 upon repeated recrystallization from acetone; yield 390 mg., m.p. 122–124°, λ_{max}^{EtOH} 258 mμ (ε 9,250).

Anal. Found: C, 69.85; H, 8.31.

This substance forms a pink crystalline 2,4-dinitrophenylhydrazone; m.p. 145° dec.; λ_{max}^{EtOH} 254, 258 and 374 mμ (ε 13,620, 13,600 and 16,000).

Anal. Found: N, 9.86.

The column was then developed with PEB (1:3). The crystals from fractions 6–8 (yield 320 mg., m.p. 163.5–164.5°) were identified as III by a mixed melting point determination.

Development with PEB (1:4) and recrystallization of the residue from fractions 9–10 yielded 450 mg. of unidentified colorless plates, m.p. 195–197°, which showed no ultraviolet absorption bands above 230 mμ.

Anal. Calcd. for $C_{34}H_{44}O_5$: C, 76.69; H, 8.27. Found: C, 77.12; H, 8.53.

Development with benzene yielded 40 mg. of the same crystals from fractions 11–12.

Development with benzene–ether mixture (1:2) and three recrystallizations of a pale yellow oil (fractions 15–16) from hot ethanol yielded 870 mg. of pale yellow needles, m.p. 143–146°, which were identified as 7,11-diketo-$\Delta^{5,8(9)}$-cholestadien-3β-ol benzoate (IV), $[\alpha]^{18}D$ +92 ± 2°, λ_{max}^{EtOH} 270 mμ (ε 10,700); ν_{max} 1728, 1681 and 1640 cm.$^{-1}$.

Anal. Calcd. for $C_{34}H_{44}O_4$: C, 79.07; H, 8.52. Found: C, 79.24; H, 8.83.

7,11-Diketo-Δ^{5}-cholesten-3β-ol Benzoate (VII).[16]—To a solution of 500 mg. of VI in 80 ml. of glacial acetic acid, under reflux and stirring, was added 5 g. of zinc dust over a period of 2 hours; the mixture was stirred for an additional 1.5 hours, cooled and filtered. The filtrate was slowly poured into 10% sodium carbonate solution and extracted with ether. After the ether layer had been washed with water and dried over sodium sulfate, the solvent was distilled under reduced pressure. The residual pale yellow oil crystallized from acetone–ethanol and was recrystallized from the same solvent. A solution of the crude crystals (420 mg. in 50 ml. of PEB 1:1) was passed through a column of alumina (18 g. in 1 × 15 cm.; activity III) and the effluent fractionated in 30-ml. portions. Fractions 7–8 yielded colorless needles which were identified as VII, yield 340 mg., m.p. 232–235°, $[\alpha]^{17}D$ −32.5 ± 3°, λ_{max}^{EtOH} 234.5 mμ (ε 8,900).

Anal. Calcd. for $C_{34}H_{46}O_4$: C, 78.72; H, 8.94. Found: C, 78.66; H, 9.20.

7,11-Diketocholestan-3β-ol Benzoate (VIII).—A solution of 200 mg. of VII in 40 ml. of ethyl acetate was shaken with 100 mg. of platinum oxide under hydrogen; 1.2 moles of hydrogen was absorbed in 2 hours. After three recrystallizations from acetone, colorless plates were obtained (m.p. 198–201.5°, yield 120 mg.) which gave no depression of m.p. on mixture with VIII prepared by the method of Fieser.[7b]

11-Ketocholestan-3β-ol (IX).—A mixture of 100 mg. of VIII, 300 mg. of potassium hydroxide, 0.3 ml. of hydrazine hydrate and 15 ml. of triethylene glycol was heated at 180–190° for 5 hours. After cooling, the dark brown mixture was poured into dilute hydrochloric acid and extracted with ether. The ether layer was washed with 10% hydrochloric acid and water, dried over sodium sulfate and the ether was evaporated under reduced pressure. The oily residue was dissolved in benzene and passed through an alumina column (12 g. in 1.1 × 12 cm.; activity III/IV) which was developed with benzene–ether (1:1). The effluent yielded 20 mg. of colorless needles which were identified as IX,[7b] m.p. 148.5–151.5°, $[\alpha]^{19}D$ +46.5° (dioxane, *c* 1.20).

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.82; H, 11.93.

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(16) For comparison with 7,11-diketo-$\Delta^{5,8(9),22}$-ergostatrien-3β-ol acetate, see ref. 10a.