was filtered, and 0.15 g. of a white, non-fluorescent solid was collected. The solid was washed thoroughly with chloroform. This material did not melt, but slowly darkened between 300° and 450°. The infrared spectrum of this hexabromide of XI showed the presence of *trans*-hydrogens on a double bond.[11] *Anal.* Calcd. for $C_{32}H_{28}Br_6$: C, 43.08; H, 3.16. Found: C, 43.54; H, 3.17.

A similar reaction run 12 hours at reflux temperature yielded a similar material which did not melt but darkened as before. In this case the infrared absorption spectrum showed only slight absorption in the region characteristic of *trans*-hydrogens on a double bond.[11]

Anal. Calcd. for $C_{32}H_{26}Br_8$: C, 36.62; H, 2.51. Found: C, 34.64; H, 3.17.

Base-catalyzed Elimination Reaction on Hexabromide of XI.—A solution of 0.25 g. of the hexabromide and 6 g. of sodium methoxide in 20 ml. of diethylene glycol was heated at 260° for one hour. The resulting mixture was cooled, and 20 ml. of water was added. The insoluble residue was collected, and extracted 4 hours in a Soxhlet apparatus. The extract was evaporated to 5 ml., and the solid obtained from the cooled solution yielded 0.008 g. of a green-yellow solid. This solid decomposed at 276–278°. The analytical sample was purified by sublimation at 10^{-5} mm. and 250°.

Anal. Calcd. for $C_{32}H_{24}$: C, 94.08; H, 5.92. Found: C, 93.77; H, 5.66.

LOS ANGELES, CALIF.

[CONTRIBUTION FROM THE INSTITUTE OF APPLIED MICROBIOLOGY, UNIVERSITY OF TOKYO]

Steroid Studies. X.[1] Studies on the Configuration of 22-Hydroxycholesterol from *Narthecium ossifragum* Huds

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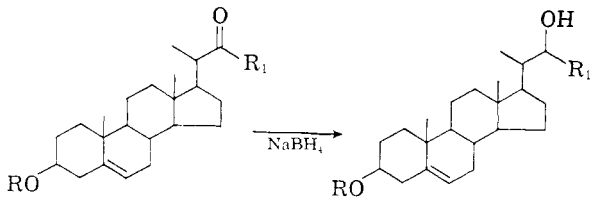
Epimeric pairs of 22-hydroxycholesterol at C-22 were prepared and the absolute configuration of each group at C-22 was determined by the Prelog method. It was thereby established that the natural 22-hydroxycholesterol has the 22α-hydroxy configuration in agreement with Klyne's conclusion. Some observations were made on the conformation of these compounds.

Stabursvik[3] extracted a new sterol, together with a carotenoid pigment, from *Narthecium ossifragum* Huds (Liliaceae) in 1953 and determined it to be 22-hydroxycholesterol. Klyne and Stokes[4] have deduced from the application of Cram's rule in the reduction[5] of 22-keto-cholestanyl acetate that Stabursvik's sterol is 22-α-hydroxycholesterol. In the present paper, we furnish additional support for Klyne's conclusion. Hayatsu[6] observed the formation of both epimeric alcohols by reduction of 22-ketocholesteryl acetate and isolated the two diastereomers as benzoates. One of these was found to agree with the benzoate of the natural sterol obtained by Stabursvik.

The carbonyl group in 22-ketocholesteryl acetate[7] has a great steric hindrance and does not react with carbonyl reagents. It is also resistant to the Meerwein–Ponndorf reduction and its reduction with sodium borohydride requires over 20 hours.[6]



I, R = CH_3CO, R_1 = iso-C_5H_{11}
III, R = CH_3, R_1 = iso-C_5H_{11}
V, R = CH_3CO, R_1 = C_6H_5
VII, R = CH_3, R_1 = C_6H_5

IIa, IIb, R = H, R_1 = iso-C_5H_{11}
IVa, IVb, R = CH_3, R_1 = iso-C_5H_{11}
VIa, VIb, R = H, R_1 = C_6H_5
VIIIa, VIIIb, R = CH_3, R_1 = C_6H_5

In addition to the two diastereomers IIa and IIb reported earlier[6] as these dibenzoates, we have now carried out the reduction of several other 22-ketocholesterol derivatives and have fully characterized the original pair: isomer A (IIa), m.p. 186°, α_D −39; diacetate, m.p. 103.5°, α_D −37.1°; dibenzoate, m.p. 256°, α_D −9.6°. Isomer B (IIb), m.p. 182°, α_D −52°; diacetate, m.p. 146°, α_D −51.5°; dibenzoate, m.p. 172°, α_D −19.6°. The yield[4,5] of isomer B (60–65%) is always better than that of A (35–40%). The molecular rotation (M_D) of IIa and IIb, cholesterol and the corresponding 3β-methoxy derivatives (IVa, IVb and 3β-methoxy-Δ^5-cholestene) are shown in Table I.

In order to determine the absolute configuration of asymmetry at C-22 in IIa and IIb, Prelog's asymmetric synthesis[8] was employed.

It is obvious that the size of the three residual groups in IIa and IIb, other than the 22-hydroxy, increases in the order of H, $-C(22)H_2-$ and $-C(23)CH_3.H-$,[8] and the asymmetric synthesis is expected to progress smoothly. In accordance with Prelog's theory, the absolute configuration of the carbon atom at 22 can be determined from the optical rotation of the optically active atrolactic acid thereby obtained.

The O-methyl ether of IIa and IIb were therefore prepared. 3β-Methoxy-bisnor-5-cholenic acid was converted to 22-ketocholesteryl methyl ether[9] (III), which was reduced with sodium borohydride to the 22-hydroxy compounds IVa, m.p. 109–111°,

(1) Part IX, *Chem. Pharm. Bull.* (*Tokyo*), in press.

(2) Takamine Laboratory, Sankyo Co., Ltd., Shinagawa, Tokyo, Japan.

(3) A. Stabursvik, *Acta Chem. Scand.*, **7**, 1220 (1953).

(4) W. Klyne and W. M. Stokes, *J. Chem. Soc.*, 1979 (1954); private communication of Dr. A. Stabursvik (Norges Tekniske Högskole, Norway).

(5) L. F. Fieser and Wei-Yuan Huang, THIS JOURNAL, **75**, 5356 (1953).

(6) R. Hayatsu, *Pharm. Bull.* (*Tokyo*), **5**, 452 (1957).

(7) W. Cole and P. L. Julian, THIS JOURNAL, **67**, 1369 (1945).

(8) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953); V. Prelog and H. L. Meier, *ibid.*, **36**, 320 (1953); W. G. Dauben, D. F. Dickel, O. Jeger and V. Prelog, *ibid.*, **36**, 325 (1953); V. Prelog and G. Tsatsas, *ibid.*, **36**, 1178 (1953).

(9) A. Romeo and R. Williotti, *Ann. Chim.* (*Rome*), **47**, 618 (1957).

TABLE I

Compound	M_D			M_D	
3,22-Diol	22-CH_2[a]	22-OH(IIa)	22-OH(IIb)	IIa-22CH_2	IIb-22CH_2
3,22-Diol	−151	−157	−209	−6	−58
	22-CH_2[b]	22-OH(IVa)	22-OH(IVb)	IVa-22CH_2	IVb-22CH_2
3β-Methoxy,22-ol	−170	−182	−241	−12	−71
			Average	− 9	−64

[a] Cholesterol. [b] 3β-Methoxy-Δ5-cholestene.

α_D −45.3°; and IVb, m.p. 78–80°, α_D −60.1°. Since IVa and IVb form the respective diacetate of IIa and IIb with acetic anhydride and *p*-toluenesulfonic acid, IVa and IVb are identical with the 3-methoxy compounds of IIa and IIb, respectively.

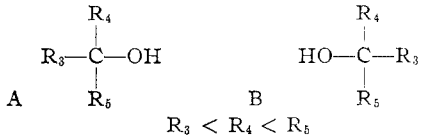
Reaction of 1.2 moles of methylmagnesium iodide with the phenylglyoxylic esters of IVa and IVb results in the formation of the atrolactic acid esters.

TABLE II

Alcohol	Yield, %	Atrolactic acid α_D[a]	P, %[b]
IVa	70	+ 7.0°	18.0
IVb	52	−12.6	33.5
VIIIa	45	+ 2.9	7.7
VIIIb	48	− 3.8	10.0
4,4-Dimethylcholesterol[c]	62	+ 9.4	25.0

[a] Measured in a chloroform solution. [b] Percentage values of active atrolactic acid present in excess, calculated from α_D values obtained experimentally, based on the optical rotation, α_D ± 37.7° in EtOH, of pure active atrolactic acid (optical yield). [c] Prepared by the method of Woodward.[10] Since the absolute configuration of its C-3 has already been determined through the work of Reichstein, *et al.*,[11] it was used as a criterion in the present series of Prelog's asymmetric synthesis (see Experimental).

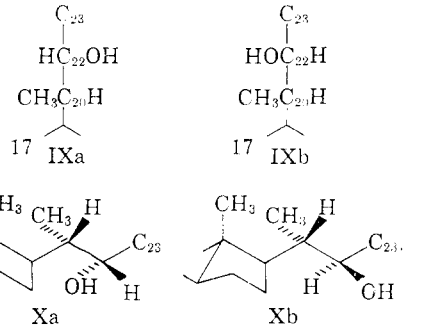
Alkali hydrolysis of these esters afforded dextrorotatory atrolactic acid from IVa and levorotatory acid from IVb, and the values of the optical rotations were fairly great. It therefore follows that the absolute configuration of IVa and IVb should be represented by the formulas A and B.



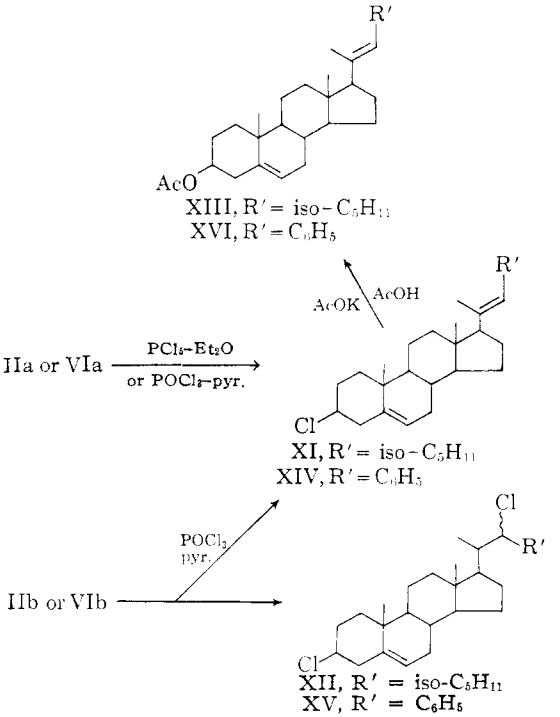
The foregoing results make it clear that the configurations of C-22 in IIa and IIb are 22α-OH and 22β-OH, respectively, and these results agree with Klyne's conclusion.[4]

On the other hand, the configuration of C_{20} in C-20-normal sterol has already been determined by Cornforth and others,[12] and by Jeger and others,[13] so that the partial absolute configurations of the positions 17 to 23 can be represented by formula IXa for IIa and IXb for IIb.[4]

By the action of phosphoryl chloride and pyridine,[5] IIa and IIb were dehydrated to 3β-chloro-Δ5,20(22)-cholestadiene (XI). Since XI can be converted to progesterone through Δ5,20(22)-cholestadienyl acetate (XIII), the correctness of its structure is beyond doubt.



By treatment of IIa or IIb with phosphorus pentachloride in ether, IIa is formed XI by dehydration, while IIb first formed the 3,22-dichloride XII which on treatment with pyridine finally was converted to XI; IIa and IIb should readily take the conformations of Xa and Xb. The dehydration of IIa can be explained by the facile *trans* elimination of Xa formula; on the contrary, IIb undergoes facile *cis* elimination, so that the heating of 3,22-dibenzoates of IIa and IIb at 150° under a reduced pressure liberates benzoic acid from IIb alone.



The optical rotations of the diasteromers (VIa, m.p. 203–205°, α_D +0.40°; and VIb, m.p. 241–243°, α_D −27.7°) formed on reduction of 3β-

(10) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelley, *J. Chem. Soc.*, 1131 (1957).

(11) K. Brenneisen, G. Tamm and T. Reichstein, *Helv. Chim. Acta*, **39**, 1233 (1956).

(12) J. W. Cornforth, I. Youhotsky and G. Popjak, *Nature*, **173**, 576 (1954).

(13) B. Riniker, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **37**, 546 (1954).

acetoxy - 22 - keto - 22 - phenyl - bisnor - 5 - cholene (V) with sodium borohydride, appear to indicate that VIb takes the same configuration at C-22 as that of IIb and the behavior of VIb against phosphorus pentachloride and ether agrees with the above assumption. While VIa forms 3β-chloro-22-phenyl-bisnor-Δ5,20(22)-choladiene (XIV) by this reaction, VIb forms the 3,22-dichloride XV, indicating that VIa is more easily dehydrated than VIb. The conversion of XV to XVI through XIV was also carried out.

The infrared spectral data also indicate that VIa and IIa have the same configuration at C-22, and VIb and IIb, approximately the same C-22 configuration. As shown in Fig. 1, the 3β-OH band at 1050–1060 cm.$^{-1}$ is of the same intensity but that of 22-OH band at 1020–1030 cm.$^{-1}$ is stronger in VIa and IIa than that in VIb and IIb. The absorption at 984–989 cm.$^{-1}$ in VIb and IIb is very strong.

The O-methyl ethers of VIa and VIb, *i.e.*, VIIIa and VIIIb, were prepared from 3β-methoxy-22-keto-22-phenyl-bisnor-5-cholene (VII) and converted to the acetates of VIa and VIb by acetolysis to confirm their structures. Prelog's asymmetric synthesis of VIIIa and VIIIb resulted in the formation of dextrorotatory and levorotatory atrolactic acid, respectively, though the values observed were small and were not as large as those in IVa and IVb. The order of the size of C-20 groupings and C-23 phenyl group could not be determined, so the configuration of these compounds cannot be determined solely by this asymmetric synthesis. Fortunately, optical rotation, infrared spectra and chemical evidence enable us to assign structures VIa and VIb, respectively, to IXa and IXb, and we can therefore deduce that the C-20 groupings has larger steric hindrance than the C-23 phenyl group, though the difference must be small.

Experimental[14]

Sodium Borohydride Reduction of 22-Keto-cholesteryl Acetate (I).—To a solution of 10 g. of I in 80 ml. of dioxane, 6 g. of sodium borohydride in 60 ml. of alcohol was added and the mixture was allowed to stand for 36 hours at room temperature. After the reaction ended, 40 ml. of 10% acetic acid solution was added to the cooled reaction mixture which was extracted with ether and the ethereal solution was washed with water and dried. The solvent was distilled off under a reduced pressure, the residual product was dissolved in 200 ml. of petroleum ether–benzene (PEB) (1:1) and passed through a column containing alumina (30 × 2 cm.). The column was eluted with the same solvent. The first fraction afforded a colorless solid which crystallized from methanol as needles, m.p. 141–142° (22-keto-cholesterol), yield 0.8 g.

The middle fractions gave a colorless solid which crystallized from methanol as colorless needles (IIa), m.p. 184–185°, α_D −39.0° (*c* 1.4), yield, 2.3 g.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.30; H, 11.79.

The diacetate and dibenzoate were obtained from IIa in the usual way; diacetate, m.p. 102–103.5° (from alcohol), α_D −37.1° (*c* 1.7). *Anal.* Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.44; H, 10.62. Dibenzoate, m.p. 254–256° (from ethyl acetate–alcohol), α_D −9.6° (*c*, 1.2). *Anal.* Calcd. for $C_{41}H_{54}O_4$: C, 80.61; H, 8.91. Found: C, 80.77; H, 8.96.

Compound IIa and its diacetate and dibenzoate were identical with natural steryl acetate and benzoate (from *Narthecium*) in physical data and infrared absorption spectra.

(14) Optical rotations were measured in chloroform.

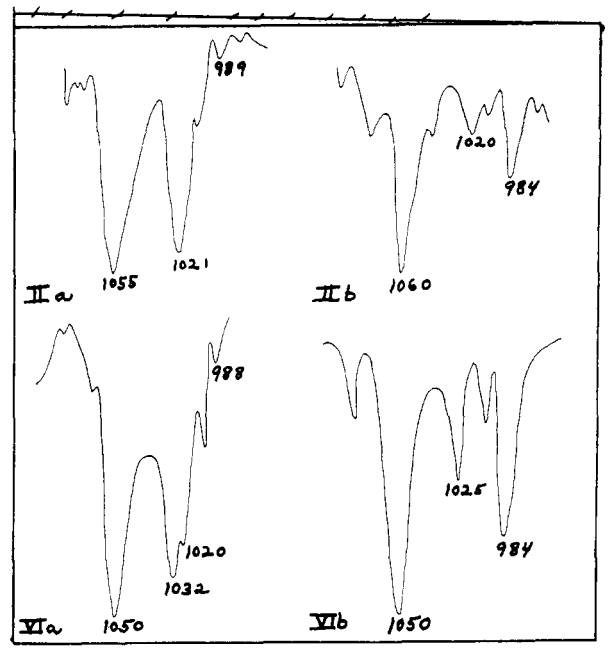


Fig. 1.

Further, they were identified by a mixed melting point determinations with corresponding natural sterol and its esters.

The latter fractions gave a colorless solid which crystallized from methanol as a colorless needles (IIb), m.p. 181–182°, α_D −52.0° (*c* 1.4), yield 3.5 g.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.22; H, 11.40.

Diacetate, m.p. 145–156° (from alcohol), α_D −51.5° (*c* 2.3). *Anal.* Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.71; H, 10.50. Dibenzoate, m.p. 169–172° (from ethyl acetate–alcohol), α_D −19.6° (*c* 1.5). *Anal.* Calcd. for $C_{41}H_{54}O_4$: C, 80.61; H, 8.91. Found: C, 80.37; H, 9.12.

Reduction of 3β-Methoxy-22-keto-Δ^5-cholestene (III).—Six grams of III was reduced with 3.5 g. of sodium borohydride in 40 ml. of alcohol for 30 hours at room temperature. The resulting product was purified by chromatography as described in reduction of I; IVa was obtained from the former fractions and crystallized from methanol to colorless needles, m.p. 109–111°, α_D −45.3° (*c* 1.6), yield 1.2 g.

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.33; H, 11.90.

The later fractions afforded a colorless oil, which was crystallized from methanol as colorless needles of IVb m.p. 78–80°, α_D −60.1° (*c* 1.2), yield 1.8 g.

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.37; H, 11.75.

Sodium Borohydride Reduction of 22-Phenyl Ketone V.—To a solution of 6 g. of the phenyl ketone V dissolved in 30 ml. of pyridine, 4 g. of sodium borohydride in 30 ml. of alcohol was added with stirring at room temperature. After 24 hours stirring, 10% acetic acid solution was added under ice cooling and the mixture was poured into water. The colorless oil that soon solidified on standing was collected by filtration, washed with water, dried, and crystallized from methanol (three times) as colorless needles of VIb, m.p. 242–243°, α_D −27.7° (*c* 1.3), yield 2.4 g.

Anal. Calcd. for $C_{28}H_{32}O_2$: C, 82.71; H, 9.42. Found: C, 83.00; H, 9.56.

Evaporation of the mother liquor (methanol) afforded an additional crop of crystals, which upon repeated recrystallization from benzene–methanol (5:1) yielded 1.3 g. of long needles (VIa), m.p. 203–205°, α_D + 0.4° (*c* 3.6).

Anal. Calcd. for $C_{28}H_{38}O_2$: C, 82.71; H, 9.42. Found: C, 82.88; H, 9.50.

The mother liquor (ethyl acetate–alcohol) gave an oily product which was purified through alumina column with

benzene. Recrystallization of the product from methanol gave colorless needles, m.p. 195–196° alone or mixed with 3β-hydroxy-22-phenyl-Δ^5-bisnorcholen-22-one, yield 1.0 g.

3β-Methoxy-22-phenyl Δ^5-bisnorcholene (VII).—A Grignard solution, prepared from 2.5 g. of magnesium, 16 g. of bromobenzene and 120 ml. of ether, was cooled in an ice-bath and treated with 14 g. of powdered anhyd. cadmium chloride. After stirring for one hour the mixture was refluxed for 2 hours, and the diphenylcadmium solution was treated with a benzene solution of the 3β-methoxy-Δ^5-bisnorcholenic acid chloride (10 g.). The mixture was refluxed for 3 hours with acid stirring and allowed to stand at room temperature for 10 hours. Usual treatment gave the ketone which recrystallized from chloroform–methanol (1:3) to colorless long needles, m.p. 176–177.5° (VII), yield 7 g., λ_{max}^{alc} 242.5 mμ (ε 11500).

Anal. Calcd. for $C_{29}H_{38}O_2$: C, 83.21; H, 9.15. Found: C, 83.40; H, 9.33.

Reduction of VII with Sodium Borohydride.—Five grams of VII was reduced with 3 g. of sodium borohydride in pyridine–alcohol (1:1, 40 ml.) for 30 hours at room temperature. The resulting products were purified by fractional crystallization as described under reduction of V; VIIIa, m.p. 140–141°, yield 1.1 g.

Anal. Calcd. for $C_{29}H_{40}O_2$ (VIIIa): C, 82.81; H, 9.59. Found: C, 83.10; H, 9.78. Calcd. for $C_{29}H_{40}O_2$ (VIIIb): C, 82.81; H, 9.59. Found: C, 83.66; H, 9.80; m.p. 163–165°, yield 1.5 g.

$\Delta^{5,20(22)}$-Cholestadienyl Chloride (XI).—To a solution of 1 g. of IIa dissolved in 15 ml. of ether–benzene (1:1), 500 mg. of phosphorus pentachloride was added and the mixture was allowed to stand for 10 hours at room temperature. The reaction mixture was poured into dil. alkali, extracted with ether, and the organic layer was washed with water, and dried. After evaporation of the solvent, an oily product was obtained which crystallized from acetone to colorless needles, m.p. 120–121°, yield 520 mg. The above product was also obtained by the chlorination of IIa or IIb with phosphonyl chloride in pyridine.

Anal. Calcd. for $C_{27}H_{43}Cl$: C, 80.47; H, 10.68; Cl, 8.82. Found: C, 80.12; H, 11.02; Cl, 9.21.

22-Chlorocholesteryl Chloride (XII).—A mixture of 1 g. of IIb and 500 mg. of phosphorus pentachloride in 15 ml. of ether–benzene (1:1) was allowed to stand for 10 hours at room temperature. The reaction mixture was poured into dil. alkali and the separated organic layer was washed with water, dried, and distilled under reduced pressure. The residue crystallized from acetone to colorless needles, m.p. 104–106°, yield 630 mg.

Anal. Calcd. for $C_{27}H_{44}Cl_2$: C, 73.80; H, 10.02; Cl, 16.17. Found: C, 73.40; H, 10.10; Cl, 16.43.

Chlorination of VIa and VIb.—The chlorination of VIa or VIb with phosphorus pentachloride–ether–benzene, as described above gave XIV from VIb and XV from VIa; XIV, m.p. 146–147°, yield 420 mg. (from 1 g.).

Anal. Calcd. for $C_{28}H_{35}Cl$ (XIV): C, 82.65; H, 8.61; Cl, 8.73. Found: C, 82.22; H, 8.88; Cl, 9.00. Calcd. for $C_{28}H_{36}Cl_2$ (XV): C, 75.84; H, 8.12; Cl, 16.02. Found: C, 75.66; H, 8.43; Cl, 15.74; m.p. 134–137°, yield 440 mg. (from 1 g.). Compound XIV was also obtained from XV by treatment with pyridine (100°, 3 hours).

$\Delta^{5,20(22)}$-Cholestadienyl Acetate (XIII).—A mixture of 1 g. of XI, 1 g. of potassium acetate and 30 ml. of glacial acetic acid was heated at 110° for 4 hours. The reaction mixture was poured into water and extracted with ether. The ethereal extract was washed with 10% sodium carbonate solution and water, dried and ether evaporated. The residue was crystallized from alcohol and three recrystallizations from the same solvent gave XIII as colorless needles, m.p. 124–126°, yield 610 mg.

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.39; H, 11.03.

Compound XVI was also obtained from XIV by the same procedure, m.p. 157.7–158.5°,[15] yield 530 mg. (from 1 g. of XIV).

Anal. Calcd. for $C_{30}H_{40}O_2$: C, 83.28; H, 9.32. Found: C, 83.60; H, 9.01.

(15) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1764 1949).

Progesterone from XIII.—A mixture of 1 g. of $\Delta^{5,20(22)}$-cholestadienol, which was obtained from the dienyl acetate by saponification, 10 ml. of freshly distilled cyclohexanone and 40 ml. of dry toluene was distilled until water was azeotropically removed. A solution of 1 g. of aluminum isopropoxide in 15 ml. of dry toluene was added, the mixture was refluxed for one hour and then cooled. About 10 ml. of saturated aqueous solution of Rochelle salt was added and the volatile solvent was removed by steam distillation. The oily residue was crystallized from methanol into $\Delta^{4,20(22)}$-cholestadien-3-one as colorless needles of m.p. 101–102°, yield 720 mg.

Anal. Calcd. for $C_{27}H_{42}O$: C, 84.75; H, 11.07. Found: C, 84.60; H, 11.22.

The above dienone (500 mg.) was treated with 2% ozone in chloroform–pyridine (30 ml.) for 10 minutes at −10°. To this mixture, 1.5 g. of zinc dust and 20 ml. of glacial acetic acid were added with stirring, which was continued for 1.5 hours at 10–15°, zinc was removed, and the solvent was concentrated under diminished pressure to remove chloroform. The acetic acid solution was poured into water and extracted with ether, ethereal extract was washed with 10% potassium carbonate and water. Removal of the solvent gave a colorless oil which was crystallized from methanol. Repeated recrystallization from methanol afforded 270 mg. of progesterone, m.p. 128–129.5°, which was identified by mixed melting point determination.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 81.21; H, 9.62. Found: C, 80.47; H, 9.88.

Pyrolysis of the Dibenzoates of IIa and IIb.—Hundred mg. of IIa dibenzoate was heated at −70° (oil-bath temperature) under a reduced pressure (0.05 mm.) for 1 hour, but benzoic acid was not obtained. Treatment of 100 mg. of IIb dibenzoate under the same conditions afforded colorless crystals and this was identified as benzoic acid (m.p. 121–122°).

Conversion of IVa into IIa.—To a solution of 1 g. of IVa in 40 ml. of acetic anhydride, 500 mg. of *p*-toluenesulfonic acid was added and the mixture was heated in an oil-bath of 100° for 3 hours. After the reaction ended, the mixture was poured into ice-water and extracted with ether. The ethereal solution was washed with 10% potassium carbonate solution and water, dried, and evaporated under reduced pressure. The resulting product was crystallized from alcohol to colorless needles, m.p. 101–102.5°, alone or mixed with diacetate of IIa from the reaction of I; yield 570 mg. The treatment of IVb by the same procedure, as above, gave IIb.

Conversion of VIIIa into VIa.—To a solution of 700 mg. of VIIIa in 40 ml. of acetic anhydride, 400 mg. of *p*-toluenesulfonic acid was added and the mixture was heated in an oil-bath of 100° for 5 hours. After the reaction ended, the mixture was poured into ice-water and extracted with ether. The ethereal solution was washed with dilute alkali and water, dried and evaporated under reduced pressure. The resulting crude diacetate was saponified with alcoholic 5% potassium carbonate solution under refluxing for 2 hours. The reaction mixture was poured into water and filtered. The resulting crude solid, crystallized from benzene–methanol (5:1), yielded 240 mg. of long needles, m.p. 202–204.5°, alone or mixed with VIa. The treatment of VIIIb by the same procedure as above gave VIb.

Phenylglyoxylic Acid Ester.—To a solution of 3 g. of 4,4-dimethylcholesterol in 25 ml. of pyridine–benzene (1:2), 1.5 g. of phenylglyoxyl chloride was added and the mixture was allowed to stand for 10 hours. The reaction mixture was poured into water, extracted with ether, the ethereal solution was washed with 10% alkali and water, dried, and distilled under reduced pressure. The resulting product was crystallized from ethyl acetate–methanol to colorless plates, m.p. 172–174°, yield 2.4 g.

A Grignard solution, prepared from 0.4 g. of magnesium, 2.8 g. of ethyl iodide and 40 ml. of ether, was cooled in an ice-bath and treated with 2 g. of 4,4-dimethylcholesteryl phenylglyoxylate in 30 ml. of ether for 3 hours with stirring at room temperature; then it was refluxed for 1 hour, and cold 10% hydrochloric acid solution was added dropwise. The organic layer was washed with water, dried, and distilled under a reduced pressure. The resulting oily product was saponified with 50 ml. of 5% alcoholic potassium hydroxide under refluxing for 5 hours in a nitrogen atmosphere; then the reaction mixture was processed under reduced pres-

sure to remove most of the solvent. The resulting product was extracted with ether (5 times) and benzene (7 times) and the aqueous layer was acidified with 10% hydrochloric acid (*p*H 5), was extracted with ether and benzene 3 times each. The organic solvent was distilled off under a reduced pressure and atrolactic acid was obtained as the residue; yield 0.27 g. (62%), α_D + 9.4° (*c* 12.6%).

Phenylglyoxylates of IVa (oil), IVb (m.p. 68–71°), VIIIa (m.p. 149–151°) and VIIIb (m.p. 182–185°), prepared as described above, were converted to atrolactic acid by the same procedure as 4,4-dimethylcholesteryl phenylglyoxylate and the results are summarized in Table II.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SYNTEX, S.A.]

Steroids. CXXVIII.[1] Synthesis of Halogenated Steroid Hormones: 6α-Fluoro-17α-acetoxyprogesterone and Some Unsaturated Analogs. A New Class of Highly Active Oral Progestational Hormones[2]

BY A. BOWERS, LAURA CUÉLLAR IBÁÑEZ AND H. J. RINGOLD

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A synthesis of 6α-fluoro-17α-acetoxyprogesterone (V) from Δ⁵-pregnen-3β,17α-diol-20-one 3-formate 17-acetate (Ia) is described. Oxidation of V by a modified chloranil procedure led to the Δ⁶-dehydro analog VII. Selenium dioxide oxidation of V and VII afforded the corresponding Δ¹-dehydro compounds VI and VIII, respectively. Compounds V, VI, VII and VIII exhibited extremely high oral progestational activities.

The utility of oral progestational hormones such as 19-nor-17α-ethinyltestosterone[3] (Norlutin) and its Δ⁵⁽¹⁰⁾-isomer (Enovid)[4] in various gynecologic and obstetric dysfunctions and their possible mass application as oral contraceptive agents has stimulated considerable efforts to find cheaper and more effective compounds. In particular, it was desirable to find compounds which still retained the C-10 methyl group since the C-19 nor compounds are all derived from the relatively expensive ring A-aromatic compounds by a Birch reduction[5] process.

Spectacular success in this direction was achieved recently when it was reported independently from three laboratories that the oral progestational activity of 17α-acetoxyprogesterone[6,7] was remarkably increased by the introduction of a 6α-methyl group.[8–10] This activity was further enhanced by the introduction of an additional double bond at C-1[10] or C-6.[10]

It has been shown recently that the addition of a 6α-fluoro substituent[2,11–16] to a series of steroid hormones favorably influenced biological activity and it was clearly desirable therefore to prepare the 6α-fluoro analogs of 17α-acetoxyprogesterone and its Δ¹ and Δ⁶-dehydro analogs.[17]

A convenient starting material was Δ⁵-pregnen-3β,17α-diol-20-one 3-formate 17-acetate[6b] (Ia) which readily underwent preferential partial hydrolysis with methanolic potassium hydroxide to afford the 3β-alcohol Ib.[18] Peracid oxidation of Ib at 0° and direct crystallization of the product gave the 5α,-6α-epoxide II in good yield. This product then underwent diaxial cleavage of the epoxide ring upon treatment with boron trifluoride etherate[1,11,13–16,19] to afford the 6β-fluoro-5α-hydroxyfluorohydrin (III). Oxidation of III with 8 *N* chromic acid[20] led smoothly to the 3-ketone IV. In accord with previous experience[11,13–16] treatment of IV with anhydrous hydrogen chloride in acetic acid for four hours at 15–20° led to elimination of the 5α-hydroxyl group and concomitant inversion of the fluorine atom at C-6 to afford 6α-fluoro-17α-acetoxyprogesterone (V), λ_{max}^{EtOH} 236 mμ, ε 16,500. The stereochemistry of the fluorine atom followed from its stability to further treatment with acid[21] and the intensity of its maximum absorption at 236 mμ. 6β-Fluoro-Δ⁴-3-ketones have maximum ε values from 10,000 to 13,000.[22]

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(21) These conditions are known to epimerize 6β-fluoro-Δ⁴-3-ketones to their 6α-epimers; *cf.* refs. 11, 15 and 16.

(22) For a full discussion of the differences in ultraviolet light absorption properties and rotatory dispersion curves between 6α- and 6β-Δ⁴-3-ketone, *cf.* ref. 15.