Anal. Calcd. for $C_{16}H_{15}NO_2$: N, 5.53. Found: N, 5.65.

A mixture of 1.00 g. of Ig and 25 ml. of 48% hydrobromic acid was refluxed gently (oil-bath temperature of 110°) under nitrogen for 12 hr. Water was added and the mixture extracted with ether and with chloroform. The organic solutions were extracted with 2% sodium hydroxide solution and dried over sodium sulfate. Evaporation of the solvents yielded a residue which on alumina chromatography and elution with ether gave 195 mg. of starting material. Elution with chloroform yielded 172 mg. of a solid, m.p. 160–165°, which on crystallization from ethyl acetate had a m.p. 180–187°. Sublimation (150°, 3 mm.) and recrystallization from ethyl acetate afforded 3,3-dimethyleneoxindole (IVa), m.p. 184–185°; spectra: ultraviolet (95% ethanol), λ_{max} 252 mμ (log ε 3.90), $\lambda_{shoulder}$ 280 mμ (log ε 3.17), λ_{min} 230 mμ (log ε 3.45); infrared (CCl_4) identical with that of an authentic sample.[10]

Anal. Calcd. for $C_{10}H_{11}NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.21; H, 6.02; N, 8.79.

Synthesis of 20-Isocholestane

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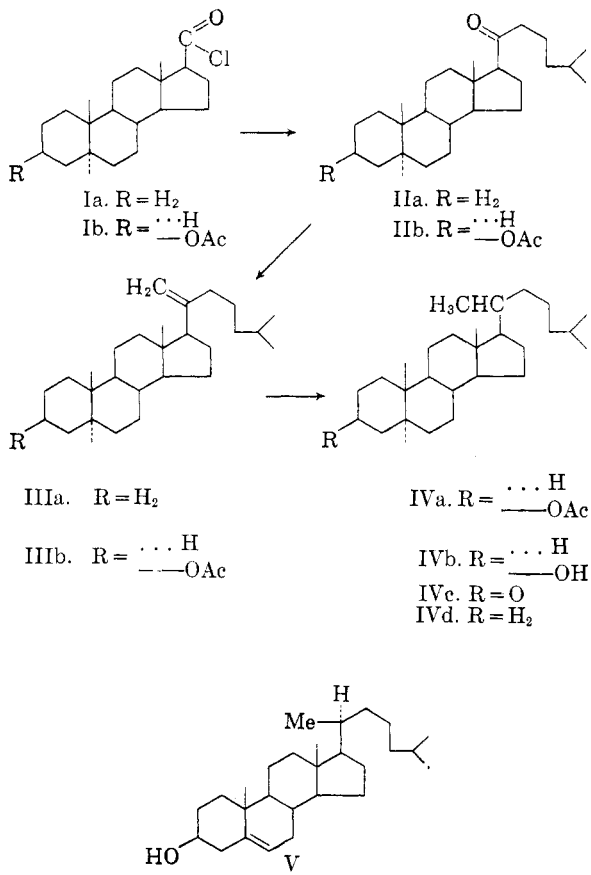
In the course of work directed toward the development of an improved synthetic route to substances with cholesterol side chain, Sondheimer and Mechoulam[1] isolated 20-isocholesterol (V) by selective hydrogenation of 20-dehydrocholesterol. Tsuda and co-workers[2] in Japan obtained 20-isocholesterol as a degradation product from sargasterol; further attempts to synthesize the former failed in their laboratory. Later Tsuda and Sakai[3] synthesized 20-iso-22-dehydrocholesterol from 3β-acetoxy-20α-methylpregn-5-ene-21-al.

In connection with a project under way in this laboratory on the synthesis of 20-isosteroids, we have had occasion to follow up Sondheimer and Mechoulam's[1] synthetic route to the cholesterol side chain for the preparation of 20-isocholestane. Commercially available 3β-hydroxyetioallocholanic acid was converted to etioallocholanic acid in good yield, and the acid chloride (Ia) of the latter was treated with diisohexylcadmium according to the method described by Kurath[4] to yield 21-nor-20-ketocholestane (IIa). This then was converted to the 20-dehydrocholestane (IIIa) in 50% yield through Wittig's reaction with triphenylphosphinemethylene. Hydrogenation of this compound in ethanol using palladium–calcium carbonate, gave a mixture of cholestanes which could not be resolved by column or gas–liquid chromatography.



Assuming that the 3β-hydroxy group would facilitate resolution of the epimers in a column of alumina, we then started the synthesis with 3β-acetoxyetioallocholanic acid chloride (Ib) to obtain the 21-nor-20-ketocholestan-3β-ol acetate (IIb). This compound, through the Wittig reaction as before, and after acetylation, gave the 20-dehydrocholestanylacetate (IIIb). Hydrogenation of IIIb in ethanol over palladium–calcium carbonate or in glacial acetic acid over platinum oxide, resulted in inseparable mixtures. The mixture of cholestanol acetates thus obtained was hydrolyzed and chromatographed on alumina grade II. Early benzene–ether fractions gave 20-isocholestanol (IVb, 20-iso), and further elution with ether gave cholestanol[5] (IVb, 20-*n*). Oxidation of the 20-isocholestanol to the keto compound (IVc), followed by conversion to the thioketal and reduction with Raney-nickel gave 20-isocholestane (IVd, 20-iso).

(1) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **80**, 3087(1958).

(2) K. Tsuda, R. Hayatsu, Y. Kishida, and S. Akagi, *ibid.*, **80**, 921 (1958).

(3) K. Tsuda and K. Sakai, *Chem. Pharm. Bull.* (Japan), **9**, 529 (1961).

(4) P. Kurath and M. Capezzuto, *J. Am. Chem. Soc.*, **78**, 3527 (1956).

(5) Sondheimer and Mechoulam had tried a complete hydrogenation on 20-dehydrocholesteryl acetate, but could isolate only *ca.* 25% cholestanyl acetate (IVb, 20-*n*), after direct crystallization and chromatography. Our experience with nonpolar acetates and hydrocarbons was similar, but when a double bond (as in cholesteryl acetate) or hydroxyl (as in cholestanol) were present in the molecule, resolution of the epimers on the column became easy.

Experimental[6]

21-Nor-20-ketocholestane (IIa).—Etioallocholanic acid (5 g.) was converted to the acid chloride by refluxing a benzene solution (30 ml.) with thionyl chloride (25 ml.) for 2 hr. and later evaporating the solvent. A benzene solution of the above (Ia) was run into a stirred solution of diisohexylcadmium, prepared from magnesium (1.88 g.), ether (100 ml.), isohexyl bromide (18.0 g.), and cadmium chloride (8.88 g.), as described by Kurath.[4] The ketone, after chromatography on alumina and recrystallization from acetone, melted at 58–59° (65%), $[\alpha]^{20}D$ +87.3 ± 2.0°.

Anal. Calcd. for $C_{26}H_{44}O$: C, 83.80; H, 11.90. Found: C, 83.92; H, 12.08.

Δ^{20}-Cholestene (20-Dehydrocholestane) (IIIa).—To a solution of butyllithium (80 ml. approx. 1 *N* in ether) in ether, (200 ml.) was added methytriphenylphosphonium bromide (9.5 g.) in lots under nitrogen atmosphere, with efficient stirring. After the addition (1.5 hr.), the orange-yellow solution was stirred for 6 hr. A solution of 21-nor-20-ketocholestane (IIa) (2.5 g.) in ether (100 ml.) was run slowly into the reaction vessel (1 hr.), and the mixture was stirred for an additional 4 hr. and allowed to stand overnight at room temperature. Ether was replaced by tetrahydrofuran, the mixture was refluxed and worked up as described by Sondheimer,[1] and the oily material was chromatographed on alumina. Elution with petroleum ether gave (IIIa) (1.8 g.) melting at 58–60°, $[\alpha]^{20}D$ +11.4 ± 2.0°.

Anal. Calcd. for $C_{27}H_{46}$: C, 87.49; H, 12.51. Found: C, 87.66; H, 12.57.

Hydrogenation of 20-Dehydrocholestane.—20-Dehydrocholestane (IIIa) (500 mg.) was dissolved in ethanol (100 ml.) and hydrogenated over 5% palladium–calcium carbonate (100 mg.) catalyst. When the absorption of hydrogen had stopped, the catalyst was filtered and evaporated. After repeated chromatography and crystallization from acetone, a product melting at 79–80° was obtained (70 mg.), which showed no depression on admixture with an authentic sample of cholestane. The mother liquors after evaporation gave an intractable mixture melting above 40°.

21-Nor-20-ketocholestan-3β-ol Acetate (IIb).—3β-Acetoxyetioallocholanic acid (4 g.) was converted to the acid chloride (benzene 30 ml. and thionyl chloride 25 ml.) and a benzene solution of the acid chloride (Ib) was run into diisohexylcadmium [prepared from magnesium (1.5 g.), isohexyl bromide (14.3 g.), and cadmium chloride (7.0 g.) as described before]. The ketone was acetylated in the usual way and crystallized from methanol, m.p. 88–89° (3.6 g.), $[\alpha]^{20}D$ +70.8 ± 3.0°.

Anal. Calcd. for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77. Found: C, 78.27; H, 10.84.

Δ^{20}-Cholesten-3β-ol Acetate (IIIb).—21-Nor-20-ketocholestan-3β-ol acetate (IIb) (900 mg.) was converted to the 20-dehydro compound (IIIb) by treatment with butyl lithium and methyltriphenylphosphonium bromide as above. The reaction product was acetylated (pyridine acetic anhydride at room temperature) and, after chromatography and crystallization from methanol, was obtained as platelets, m.p. 111–112°, $[\alpha]^{20}D$ +1.2 ± 1.2°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.35; H, 10.98.

Cholestan-3β-ol, 20-Iso, and 20-*N* (IVb, 20-iso and 20-*n*).—Δ^{20}-Cholesten-3β-ol acetate (380 mg.) was dissolved in ethanol (50 ml.) and hydrogenated over palladium–calcium carbonate (100 mg.) as before. Separated from the catalyst, the residue after evaporation was found to be a mixture, and all attempts to separate it into pure components failed.

A similar hydrogenation carried out in glacial acetic acid and platinum oxide gave identical results.

Cholestan-3β-ol acetate (IVa, 20-iso and 20-*n*) (520 mg.) was hydrolyzed in methanolic caustic potash (potassium hydroxide 2 g., water, 5 ml., and methanol, 80 ml.) at refluxing temperature for 4 hr. The hydrolyzed product (465 mg.) was chromatographed on alumina grade II. Elution with benzene–ether (3:7) and (1:9) gave a product (325 mg.) which after recrystallization from ethanol melted at 154–157°. After repeated recrystallizations from ethanol the melting point was sharp at 160–161°, $[\alpha]^{20}D$ 6.0 ± 1.0°.

Anal. Calcd. for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.58; H, 12.27.

The melting point was depressed on admixture with an authentic sample of cholestanol. Further elution of the column with ether gave a product, m.p. 135–137°, which, after several crystallizations, melted at 143–144° and was identical with cholestanol (mixed m.p. and infrared).

20-Iso-17-*n*-cholestane (IVd).—20-Isocholestan-3β-ol (158 mg.) was dissolved in acetone (60 ml.) and oxidized with 8 *N* chromic acid at 0°. The solution then was diluted and filtered. The precipitate was dried and chromatographed on fluorisil (100 mesh). Elution with benzene–petroleum ether (3:1) gave the ketone (IVc) (123 mg.). Infrared showed band at 1,718 cm.$^{-1}$. This then was converted to the thioketal in the usual manner (ethanedithiol and boron trifluoride). After chromatography and crystallization from acetone, the compound melted at 141–143°.

20-Isocholestan-3-one thioketal (75 mg.) dissolved in dioxane (15 ml.) was refluxed with Raney nickel (3 g.) for 5 hr. The reaction was cooled and filtered; the filtrate was evaporated and crystallized from acetone giving (IVd), m.p. 62–65° (54 mg.). A highly purified analytical sample melted at 67–69°, $[\alpha]^{20}D$ +7.6 ± 0.5°.

Anal. Calcd. for $C_{27}H_{48}$: C, 87.02; H, 12.98. Found: C, 87.10; H, 12.70.

(6) Melting points are uncorrected. Rotations were determined at 20° in chloroform solution. The chromatograms were made with Woelm aluminum oxide, neutral, activity grade I unless otherwise mentioned. Analyses and rotations were performed by the Analytical Services, NIAMD, under the direction of Mr. H. G. McCann.

Synthesis of 3-Trifluoromethyltyrosine[1]

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In a recent paper[2] we reported the synthesis of 2-trifluoromethyl-*dl*-tyrosine and 3-trifluoromethyl-4-methoxy-*dl*-phenylalanine. Attempts to prepare 3-trifluoromethyl-*dl*-tyrosine (I) were unsuccessful, however, because of the hydrolytic instability of the trifluoromethyl group *ortho* to the hydroxyl group.[3]

It has been previously shown[2,4,5] that the Meerwein arylation reaction provides a useful and often, a preferred, route to aromatic α-amino acids. For the synthesis of compound I, it was therefore desirable to prepare the previously unreported key intermediate, 2-trifluoromethyl-4-nitrophenol (II).

(1) Paper No. III in the series on fluorinated aromatic amio acids.
(2) R. Filler and H. Novar, *J. Org. Chem.*, **26**, 2707 (1961).
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(5) R. Filler, L. Gorelic, and B. Taqui Khan, *Proc. Chem. Soc.*, 117 (1962).