with the findings of Cushley, *et al.*,[5] that the C-2′ acetyl signal in acetylated furanosyl pyrimidine nucleosides is shifted to higher field than the C-3′ or C-5′ acetyl signals when the C-1′ and C-2′ substituents are *cis*. This diamagnetic shift was attributed to the anisotropic effect of the 5,6 double bond. Since the C-1′, C-2′ substituents in IV are also *cis*, one would expect the C-2′ methoxyl signal in IV to be significantly more shielded than the C-3′ methoxyl in IX. It appears likely therefore that the method[5] for establishing the anomeric configuration of acetylated pyrimidine nucleosides is equally applicable to their methylated counterparts. The H-2′ signal in IV, established by a field sweep decoupling experiment from H-1′ ($\nu = -134$ Hz), occurs 0.22 ppm to higher field than H-2′ in IX and 0.19 ppm to higher field than H-2′ in spongouridine in accord with the greater shielding effect of methoxyl *vs.* hydroxyl.

It is of interest to note that the anomeric signal (H-1′) in IV is found 0.23 ppm downfield from H-1′ in IX, and 0.18 ppm downfield from H-1′ in spongouridine apparently due to deshielding by the C-2′ methoxyl group.

The behavior of IV and IX in aqueous base was consistent with the structures assigned. IV was relatively stable in NaOH (0.1 *N*) and its ultraviolet absorption spectrum remained essentially unaltered after 1 hr at 25°. Compound IX, on the other hand, exhibited marked instability in NaOH (0.1 *N*) with the rapid loss of selective absorption in the ultraviolet region ($t_{1/2}$ = 22 min at 25°). The reactivity of IX is readily explained by the presence of a 2′ hydroxyl group in an "up" (arabino) position. The reactivity of such a structure is consistent with the findings recently reported[6] for the reaction of 1-(β-D-arabinofuranosyl)-5-fluoro-3-methyluracil (X, R_1 = CH_3, R_2 = F, R_3 and R_4 = H) in aqueous base. Treatment of this compound with NaOH (0.1 *N*) resulted in attack by the 2′-hydroxy anion on C-6 of the uracil moiety to form a 6,2′-anhydro bridge with concomitant cleavage of the N_3–C_4 bond to give the open-chain ureide structure XI (R_1 = CH_3, R_4 = H, R_2 = F). It is probable that the product formed upon treating IX with base had a similar ureide structure, namely, XI (R_1 and R_4 = CH_3, R_2 = H).

The addition of base to a solution of IX causes an immediate bathochromic shift of the maximum of 5 mμ (261 to 266 mμ). This shift is probably due to the localization of the π electrons of the 5,6-double bond caused by polarization due to the proximity of the *O*-2′ anion.

Experimental Section

Nmr spectra were recorded on a Varian A-60 spectrometer equipped with a spin decoupler (Varian, Model V-6058A). Melting points were determined by the capillary method and are corrected. Microanalyses were made by the Spang Microanalytical Laboratories, Ann Arbor, Mich.

1-(2-*O*-Methyl-β-D-arabinofuranosyl)-3-methyluracil (IV).—The preparation of 1-(3,5-di-*O*-trityl-β-D-arabinofuranosyl)uracil (II) from 1-(5-*O*-trityl-β-D-arabinofuranosyl)uracil (I) was carried out as previously described[3] except that II was separated from unreacted I on alumina (Bio-Rad, AG 7), using ethanol–ethyl acetate as the eluant. Compound II (0.40 g, 0.55 mmole) in dimethylformamide (10 ml) was stirred for 22 hr at 23–25° with methyl iodide (0.80 g, 5.6 mmoles) and silver oxide (0.35 g, 1.5 mmole). Compound III was obtained as a colorless solid (0.42 g). Without further purification III (0.20 g), dissolved in ether (10 ml), was treated with anhydrous ethereal HCl (20 ml, 50% saturated). Colorless crystals (0.07 g, 96%) were obtained, which upon recrystallization from ethanol gave needles, mp 198–200°, $[\alpha]^{25}D$ +127° (*c* 0.2, EtOH). The proton nmr spectrum determined in DMSO-d_6 consisted of H-6 (τ 2.28, doublet, $J_{5,6}$ = 8.0 Hz), H-1′ (τ 3.80, doublet, $J_{1',2'}$ = 5.1 Hz), H-5 (τ 4.26, doublet), OH (C-3′) (τ 4.44, doublet, $J_{OH,H\text{-}3'}$ ~4.5 Hz), OH(C-5′) (τ ~5.03, broad peak), H-2′, H-3′ (τ ~6.07, multiplet), H-4′, H-5′, H-5′ (τ ~6.34, narrow multiplet), –O–CH_3 (τ 6.73, singlet), –N–CH_3 (τ 6.82, singlet).

Anal. Calcd for $C_{11}H_{16}N_2O_6$: C, 48.52; H, 5.92; N, 10.29. Found: C, 48.68; H, 5.96; N, 10.31.

1-(3-*O*-Methyl-β-D-arabinofuranosyl)-3-methyluracil (IX).—The reaction of 2,2′-anhydro-1-β-D-arabinofuranosyluracil (VI, 0.23 g, 1.0 mmole) with methyl iodide (0.90 g, 6.3 mmoles) and silver oxide (0.46 g, 2.0 mmoles) in dimethylformamide (5 ml) for 69 hr with stirring gave, after crystallization from ethanol, 0.04 g (15%), of colorless prisms, mp 127–131°, $[\alpha]^{25}D$ +130° (*c*, 0.2, EtOH). The proton spectrum determined in DMSO-d_6 consisted of H-6 (τ 2.31, doublet, $J_{5,6}$ = 8.0 Hz), H-1′ (τ 4.03, doublet, $J_{1',2'}$ = 4.2 Hz), H-5 (τ 4.21, doublet), OH (C-2′) (τ 4.38, doublet, $J_{OH,H\text{-}2'}$ = 5.0 Hz), OH (C-5′) (τ 4.92, triplet, splitting of 5.2 Hz), H-2′ (τ ~5.80, multiplet), H-3′, H-4′, H-5′, H-5′ (τ ~6.30, multiplet), –O–CH_3 (τ 6.63, singlet), –N–CH_3 (τ 6.82 singlet).

Anal. Calcd for $C_{11}H_{16}N_2O_6$: C, 48.52; H, 5.92; N, 10.29. Found: C, 48.52; H, 5.85; N, 10.25.

Registry No.—IV, 15040-83-2; IX, 15040-84-3.

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Synthesis and Catalytic Hydrogenation of 3α,19-Dihydroxycholest-5-ene and Its Derivatives[1]

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Considerable progress has been made recently in the synthesis of 19-substituted steroids,[3-5] especially as intermediates for synthesis of 19-nor steroids. However, 19-substituted steroids having a 3α substituent have not yet been reported. The present Note reports a convenient synthesis of 3α,19-dihydroxycholest-5-ene and its derivatives, together with the catalytic hydrogenation of the above compounds.[6]

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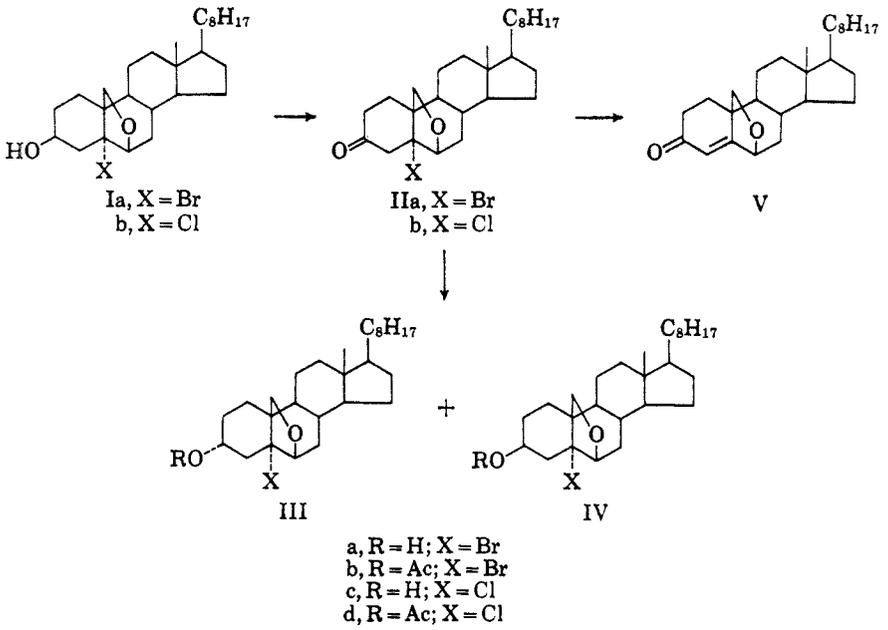
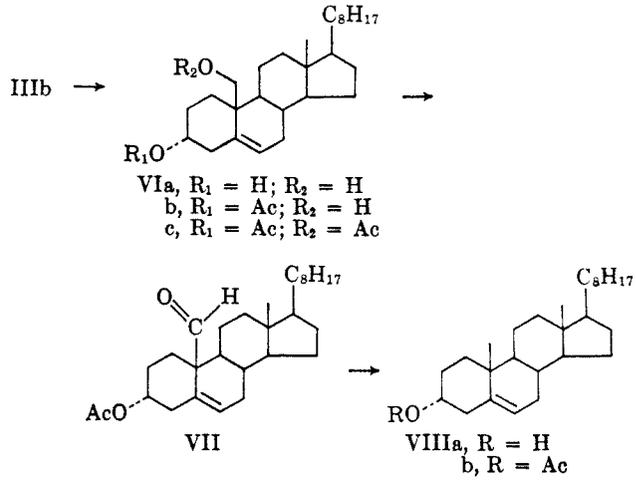
SCHEME I



Many attempts were made to synthesize 3α,19-dihydroxycholest-5-ene from 3β,19-dihydroxycholest-5-ene,[4] but these reactions did not afford satisfactory routes for the present purpose. When 3β-hydroxy-5-bromo-6β,19-epoxy-5α-cholestane (Ia) was oxidized with chromium trioxide at low temperature, 5-bromo-6β,19-epoxy-5α-cholestan-3-one (IIa) was obtained in good yield. II was reduced with sodium borohydride in methanol followed by acetylation to give 80% of 3α-acetoxy-5-bromo-6β,19-epoxy-5α-cholestane (IIIb) and 12% of the 3β isomer (IVb). They were separated by column chromatography. Similarly, 5α-chloro-3-one (IIb)[5] gave 75% of the 3α compound (IIId) and 10% of the 3 epimer (IVd). These results appear to show that the axial 5α bromine or chlorine atom in the ketones shields the α side from approach of reagent in reduction.[7-9] (See Scheme I.)

3α-Acetoxy-5-bromo-6β,19-epoxy-5α-cholestane (IIIb) was reduced with zinc in acetic acid to 3α-acetoxy-19-hydroxycholest-5-ene (VIb), which gave the 3α,19-diacetate (VIc) and 3α,19-diol (VIa) by acetylation and alkaline hydrolysis, respectively. The nmr spectrum of VIb showed a relatively sharp signal at 5.01 ppm of the equatorial 3β proton and the olefinic proton resonance was found at 5.67 ppm. The C-19 methylene protons gave a characteristic four-line AB pattern signal at 3.61 and 3.79 ppm; the geminal coupling constant is -10.5 cps. In the reduction of 3α-acetoxy-5α-chloro compound (IIId) by the same procedure, the 19-alcohol was not obtained, but the starting material was recovered unchanged. When the compound (VIb) was oxidized with chromium trioxide in acetone, 3α-acetoxy-19-oxocholest-5-ene (VII) was obtained in good yield and the aldehyde was converted to 3α-hydroxycholest-5-ene (VIIIa) by Wolff–Kishner reduction. This result provides the chemical evidence to support the structure of VIb. (See Scheme II.)

SCHEME II



The catalytic hydrogenation of 3α-acetoxy-19-hydroxycholest-5-ene with rhodium or platinum catalyst in acetic acid and in isopropanol was examined. The proportion of 5α- and 5β-dihydro compounds was determined by glpc. The results of the hydrogenation are shown in Table I, together with the results of the hydrogenation of 3α-hydroxycholest-5-ene (VIIIa) and its 3α-acetoxy derivatives (VIIIb) under the same condition.

The configuration at C-5 of the hydrogenated products of 3α,19-dihydroxycholest-5-ene was determined by comparison with a sample synthesized as below. 3β,19-Dihydroxy-5β-cholestane (XI)[6] was oxidized with chromium trioxide to 3,19-dioxo-5β-cholestane (XII), which was reduced with sodium borohydride to give 80% of 3α,19-dihydroxy-5β-cholestane (Xa) and 20% of the 3β isomer[6] by glpc. The former, separated by column chromatography, was identical with the main product of the catalytic hydrogenation of 3α,19-dihydroxycholest-5-ene. On the other hand, 3,19-dioxo-5α-cholestane (XIV) gave 8% of 3α,19-dihydroxy-5α-cholestane (IXa) and 92% of the 3β

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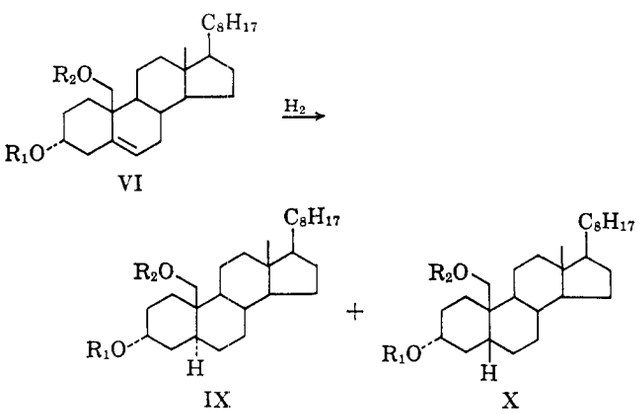
TABLE I

PROPORTION OF 5α- AND 5β-DIHYDRO COMPOUNDS FORMED IN CATALYTIC HYDROGENATION[a]

Compd	Substituent 3α	Substituent 19	Pt/AcOH 5α, %	Pt/AcOH 5β, %	Rh/AcOH 5α, %	Rh/AcOH 5β, %	Rh/i-PrOH 5α, %	Rh/i-PrOH 5β, %
VIIIa[b]	OH	H	37	63	38	62	54	46
VIIIb[b]	OAc	H	21	79	18	82	19	81
VIa	OH	OH	10	90	2	98	10	90
VIb	OAc	OH	3	97		>99		>99

[a] The products of hydrogenation were always accompanied by a small amount of the compounds produced by hydrogenolysis, but these were excluded in the calculation of the proportion of 5α and 5β compounds. [b] Shoppee, *et al.*, reported the results of an investigation dealing with the stereochemistry of the hydrogenation of VIIIa and VIIIb, and showed that the former gave *ca.* 50% of the 5β-dihydro compound, while the latter gave more than 90% of the 5β compound in methanol or ethyl acetate containing acid as a promoter: C. W. Shoppee and J. R. Lewis, *J. Chem. Soc.*, 1365 (1955). For comparison, we examined the hydrogenation of the two compounds under the same condition as in the case of 19-hydroxy compounds.

isomer XIII.[6] Owing to the minor yield of 3α,19-dihydroxy-5α-cholestane (IXa), it was identified by comparison of the retention time in glpc.



a, R_1 = H; R_2 = H
b, R_1 = Ac; R_2 = H

Apparently from the results shown in Table I, the 19-hydroxy group is more effective in product determination than is the 3α-hydroxy, as is expected from our previous data.[6]

Experimental Section[10]

3β-Hydroxy-5-bromo-6β,19-epoxy-5α-cholestane (Ia).—A solution of 1.25 g of 3β-acetoxy-5-bromo-6β,19-epoxy-5α-cholestane[4] in 120 ml of methanol and 12 ml of water was refluxed for 1 hr with 1.2 g of potassium carbonate, and methanol was removed *in vacuo*. The residue was worked up in the usual way and 1.2 g of the crude product was recrystallized from methanol: mp 145–146°; $[\alpha]^{27}D$ +8° (*c* 1.25, $CHCl_3$); ν_{max}^{KBr} 3500, 1497, 1105, 1065, 1030, 1005, 915, 906 cm^{-1}.

Anal. Calcd for $C_{27}H_{45}O_2Br$: C, 67.34; H, 9.42. Found: C, 67.32; H, 9.30.

3α-Acetoxy-5-bromo-6β,19-epoxy-5α-cholestane (IIIb).—A suspension of 200 mg of Ia in 40 ml of acetone was stirred with 0.15 ml of 8 *N* chromic–sulfuric acid solution at 0° for 30 min. After addition of ether and water, the organic layer was washed with water and dried over sodium sulfate. Concentration *in vacuo* below 30° gave 200 mg of the crude product (IIa) in crystalline form, ν_{max}^{KBr} 1735 cm^{-1} (>C=O). This ketone is very unstable in the atmosphere and was immediately reduced with sodium borohyride. The crude 3-one steroid (IIa, 200 mg) was suspended in 20 ml of methanol, and 200 mg of sodium borohydride was added. After stirring at room temperature for 30 min, the solution was acidified with acetic acid and concentrated *in vacuo*. The residue was taken up into ether and the ethereal solution was washed with dilute sodium bicarbonate aqueous solution and water. Evaporation of the solvent *in vacuo* gave 190 mg of the residue, which was treated with pyridine and acetic anhydride at room temperature overnight. Chromatography of 185 mg of the acetylated crude product on alumina (5.5 g), eluting with *n*-hexane–chloroform (50:3), gave 22 mg of 3β-acetoxy-5-bromo-6β,19-epoxy-5α-cholestane, which was identical with an authentic sample in a mixture melting point test and infrared comparison. Further elution with *n*-hexane–chloroform (10:1) gave 150 mg of IIIb, mp 139–142°. Recrystallization from methanol gave a pure sample: mp 143°; $[\alpha]^{27}D$ +37° (*c* 1.64 $CHCl_3$); ν_{max}^{KBr} 1742, 1500, 1265, 1240, 1025, 955 cm^{-1}.

Anal. Calcd for $C_{29}H_{47}O_3Br$: C, 66.52; H, 9.05. Found: C, 66.37; H, 9.00.

3α-Hydroxy-5-bromo-6β,19-epoxy-5α-cholestane (IIIa).—A mixture of 50 mg of IIIb and 50 mg of potassium carbonate in 7 ml of methanol and 0.7 ml of water was refluxed for 2 hr. After concentration *in vacuo*, the mixture was dissolved in ether and water, and the organic layer was washed with water. The crude product (45 mg) was recrystallized from methanol: mp 151–151.5°; $[\alpha]^{27}D$ +15° (*c* 0.65 $CHCl_3$); ν_{max}^{KBr} 3440, 1495, 1160, 1090, 1020, 945, 915 cm^{-1}.

Anal. Calcd for $C_{27}H_{45}O_2Br$: C, 67.34; H, 9.42. Found: C, 67.40; H, 9.53.

5-Chloro-6β,19-epoxy-5α-cholestan-3-one (IIb).—A solution of 1.2 g of 3β-hydroxy-5-chloro-6β,19-epoxy-5α-cholestane (Ib)[4] in 75 ml of acetone was treated with 1.2 ml of 8 *N* chromic–sulfuric acid solution at 0° for 30 min. After work-up in the usual way, 1.2 g of the crude product was obtained in crystalline form, mp 137–141°. Recrystallization from methanol gave a pure sample: mp 141.5°; $[\alpha]^{27}D$ +49° (*c* 2.05 $CHCl_3$); ν_{max}^{KBr} 1730, 1500, 1035, 900 cm^{-1}.

Anal. Calcd for $C_{27}H_{43}O_2Cl$: C, 74.53; H, 9.96. Found: C, 74.28; H, 9.84.

3α-Hydroxy-5-chloro-6β,19-epoxy-5α-cholestane (IIIc).—A suspension of 220 mg of IIb in 22 ml of methanol was stirred with 220 mg of sodium borohydride at room temperature for 30 min and treated in the usual way. Chromatography of 200 mg of the crude product on alumina, eluting with *n*-hexane–chloroform (4:1), gave 150 mg of the 3α-hydroxy compound (IIIc), mp 138–139°. Further elution with the same solvent gave 20 mg of 3β-hydroxy-5-chloro-6β,19-epoxy-5α-cholestane identical with an authentic sample. The 3α-hydroxy compound (IIIc) obtained by chromatography was recrystallized from methanol: mp 139°; $[\alpha]^{27}D$ +10° (*c* 1.00 $CHCl_3$); ν_{max}^{KBr} 3430, 1160, 1090, 1040, 1025, 1015, 952, 920 cm^{-1}.

Anal. Calcd for $C_{27}H_{45}O_2Cl$: C, 74.19; H, 10.38. Found: C, 74.03; H, 10.16.

3α-Acetoxy-5-chloro-6β,19-epoxy-5α-cholestane (IIId).—IIIc was treated with acetic anhydride and pyridine at room temperature overnight. Addition of water, extraction into ether, and crystallization from methanol gave the acetate (IIId): mp 142.5–143°; $[\alpha]^{27}D$ +40° (*c* 0.99 $CHCl_3$); ν_{max}^{KBr} 1745, 1260, 1230, 1095, 1025, 955 cm^{-1}.

Anal. Calcd for $C_{29}H_{47}O_3Cl$: C, 72.69; H, 9.89. Found: C, 72.56; H, 10.37.

3α-Acetoxy-19-hydroxycholest-5-ene (VIb).—To a solution of 170 mg of IIIb in 12.5 ml of acetic acid and 0.6 ml of water was added 1.9 g of zinc dust during 15 min at 45–50°; the mixture was maintained at 45–50° for 1.5 hr with vigorous stirring. After cooling, the excess zinc was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in ether and water, and the organic layer was washed with dilute sodium bicarbonate aqueous solution and with water, dried, and evaporated *in vacuo*. Chromatography of the residue on alumina, eluting with *n*-hexane–chloroform (5:1), gave 110 mg of VIb as an oily substance, which gave one spot on thin layer chromatography: $[\alpha]^{27}D$ −8° (*c* 1.22, $CHCl_3$); ν_{max}^{KBr} 3450, 1742, 1245, 1030 cm^{-1}.

Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 77.96; H, 11.06.

3α,19-Diacetoxycholest-5-ene (VIc).—The alcohol (VIb) was treated with acetic anhydride and pyridine at room temperature overnight. Addition of water and extraction into ether gave the acetate (VIc), which was recrystallized from methanol: mp 68.5°; $[\alpha]^{27}D$ −81° (*c* 0.87, $CHCl_3$); ν_{max}^{KBr} 1745, 1735 (s), 1240, 1235 (s) cm^{-1}.

(10) All melting points are uncorrected. Nmr spectra were measured in chloroform-*d* solution at 100 Mc and chemical shifts are given with reference to tetramethylsilane.

Anal. Calcd for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.26; H, 10.65.

3α,19-Dihydroxycholest-5-ene (VIa).—The 3α,19-dihydroxy compound (VIa) was obtained by hydrolysis of VIb with 5% potassium hydroxide in ethanol. Recrystallization of the crude product gave a pure sample: mp 156°; $[\alpha]^{27}D$ −75° (*c* 0.60, $CHCl_3$); ν_{max}^{KBr} 3420, 1040, 1025, 1005 cm^{-1}.

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.00; H, 11.78.

3α-Acetoxy-19-oxocholest-5-ene (VII).—A solution of 30 mg of VIb in 3 ml of acetone was stirred with 0.1 ml of 8 *N* chromic–sulfuric acid solution at 0° for 10 min. After addition of water and ether, the organic layer was washed with water and evaporated. The residue (30 mg) was crystallized by addition of a small amount of methanol. The product was recrystallized from methanol: mp 81°; $[\alpha]^{27}D$ −163° (*c* 1.05 $CHCl_3$); ν_{max}^{KBr} 1742, 1728 (s), 1262, 1250, 1240 (s).

Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.53; H, 10.60.

Reduction of 3α-Acetoxy-19-oxocholest-5-ene by Wolff–Kishner Method.—A mixture of 10 mg of the 19-oxo compound, 0.2 ml of hydrazine hydrate, and 0.2 ml of ethanol was heated in a sealed tube at 110° for 15 hr. After addition of *ca.* 40 mg of potassium hydroxide, the mixture was heated again in a sealed tube at 220° for 4 hr. After cooling, the mixture was dissolved in ether and the ethereal solution was washed with water, dried, and evaporated. Recrystallization of the crude product (7 mg, mp 136–138°) from methanol gave 5 mg of 3α-hydroxycholest-5-ene, mp 139°, identical with an authentic sample in a mixture melting point test (140–141°) and infrared comparison.

Catalytic Hydrogenation of 3α-Hydroxy-5-ene Derivatives.—The following example is illustrative.

A.—A solution of 10 mg of VIb in 1 ml of acetic acid was hydrogenated in the presence of 5 mg of prereduced rhodium oxide under atmospheric pressure at room temperature for 2 hr. After the catalyst was removed by decantation, ether and water were added. The ethereal solution was washed with dilute sodium bicarbonate aqueous solution and with water, dried, and evaporated. The residue was converted to the trimethylsilyl ethers of 3α,19-dihydroxycholestanes, which were analyzed by glpc.

B.—A solution of 10 mg of VIb in 2 ml of isopropanol was hydrogenated with 5 mg of prereduced rhodium hydroxide for 3 hr. After addition of ether, the catalyst was removed by filtration. Evaporation of the solvent *in vacuo* gave a product, which was analyzed by glpc, similarly as in the case of A.

The following compounds were hydrogenated by the same procedure: 3α-hydroxycholest-5-ene (VIIIa), 3α-acetoxycholest-5-ene (VIIIb), and 3α,19-dihydroxycholest-5-ene (VIa).

3α,19-Dihydroxy-5β-cholestane (Xa). A.—A solution of 200 mg of 3β,19-dihydroxy-5β-cholestane in 20 ml of acetone was treated with 0.5 ml of 8 *N* chromic–sulfuric acid solution at 0° for 15 min. After addition of ether and water, the ethereal solution was washed with water. Evaporation of the solvent gave 190 mg of the residue, which was purified by column chromatography on silica gel, eluting with *n*-hexane. An oily substance was obtained, which gave one spot on thin layer chromatography; ν_{max}^{KBr} 1725 cm^{-1} (broad). This aldehyde ketone (XII) was unstable to change to other substances even on standing at room temperature.

A suspension of 100 mg of XII in 10 ml of ethanol was treated with 100 mg of sodium borohydride for 1 hr. Addition of water and acetic acid, extraction into ether, and evaporation of the solvent gave 90 mg of the residue, which consisted of 80% of the 3α-hydroxy compound (Xa) and 20% of the 3β isomer (XI) by glpc analysis. Chromatography of the residue on alumina, eluting with *n*-hexane–chloroform (1:2), gave 55 mg of 3α,19-dihydroxy-5β-cholestane, which was recrystallized from ether: mp 172°; $[\alpha]^{27}D$ +33° (*c* 0.33 $CHCl_3$); ν_{max}^{KBr} 3360, 1070, 1040, 1030 (s) cm^{-1}.

Anal. Calcd for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96. Found: C, 80.41; H, 12.07.

B.—A solution of 30 mg of VIb in 6 ml of isopropanol was hydrogenated with 15 mg of prereduced rhodium hydroxide. Hydrolysis of the product with 5% potassium hydroxide in ethanol gave crude 3α,19-dihydroxy-5β-cholestane (Xa). Recrystallization of the crude product from ether gave a pure one (20 mg, mp 171°), which was identical with a sample prepared by the method described in A, by mixture melting point and infrared comparison.

3,19-Dioxo-5α-cholestane (XIV).—The 3,19-dioxo compound (XIV) was obtained from 3β,19-dihydroxy-5α-cholestane by the same procedure as in the case of XII. Recrystallization of the crude product from methanol afforded a pure sample: mp 153°; $[\alpha]^{27}D$ +25° (*c* 0.99 $CHCl_3$); ν_{max}^{KBr} 1750, 1730 (s) cm^{-1}.

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 81.00; H, 11.37.

Registry No.—Ia, 14908-10-2; IIb, 14908-11-3; IIIa, 14908-12-4; IIIb, 14908-13-5; IIIc, 14908-14-6; IIId, 15077-31-3; VIa, 14908-15-7; VIb, 15077-32-4; VIc, 14908-16-8; VII, 14908-17-9; Xa, 14908-18-0; XIV, 14908-19-1.

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Synthesis of (-)-β-Methoxysynephrine[1]

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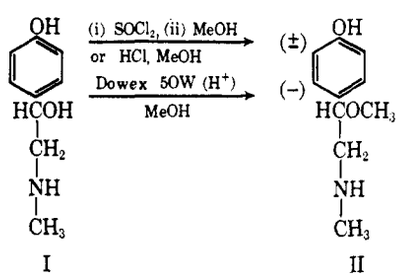
(−)-Synephrine (I) and several other phenolic amines are present in the leaves and fruit of citrus.[2-5] Recently, an unknown phenolic amine was detected during chromatography of "Dancy" tangerine leaf extracts. This compound has been isolated[6] and identified as (−)-4-(1-methoxy-2-methylamino ethyl phenol), ((−)-β-methoxysynephrine) (II), which is not believed to



have been previously reported. β-Methoxysynephrine is similar in structure to the methyl ether of adrenaline which produces stimulation of the central nervous system.[7] Mattok has synthesized β-methoxycatechol compounds using thionyl chloride and methanol[8] and following our correspondence (±)-β-methoxysynephrine was synthesized in his laboratory by a similar procedure. The β-methoxysynephrine thus formed was optically inactive, but otherwise identical with the compound isolated from tangerine leaf extracts as shown by in-

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