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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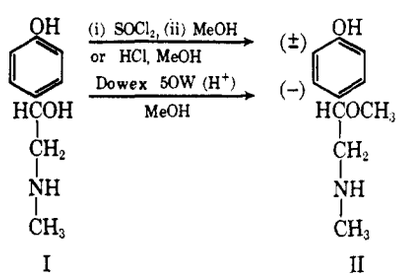
(−)-Synephrine (I) and several other phenolic amines are present in the leaves and fruit of citrus.[2-5] Recently, an unknown phenolic amine was detected during chromatography of "Dancy" tangerine leaf extracts. This compound has been isolated[6] and identified as (−)-4-(1-methoxy-2-methylamino ethyl 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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frared and mass spectra as well as chromatographic analyses.

Further work in our laboratory has shown that β-methoxysynephrine can be synthesized by dissolving (−)-synephrine in 2 *N* anhydrous HCl in methanol. This procedure, like the one using thionyl chloride, gives the racemic compound. A third method of synthesis resulted in the formation of optically active (−)-β-methoxysynephrine. (−)-Synephrine absorbed on a Dowex 50W (H^+) ion exchange resin in methanol was rapidly converted to (−)-β-methoxysynephrine.

Preliminary experiments indicate that (−)-octopamine is similarly converted to (−)-β-methoxyoctopamine. This method of synthesizing ethers of optically active phenolic amines on ion exchange resins may have application for syntheses of other classes of compounds. Furthermore, the possibility that (−)-methoxysynephrine from the tangerine extract could be an artifact formed on the ion exchange column during isolation cannot be overlooked. The ease with which this reaction occurs must be recognized as a possible source of artifacts in the isolation of compounds from biological materials.

Experimental Section

Racemic β-Methoxysynephrine Hydrochloride.—(−)-Synephrine (1 g) was added slowly to an excess of thionyl chloride (15 g) under nitrogen. Reaction was complete after a few minutes, and the chloro compound which precipitated was filtered and washed first with benzene and then with ether (yield 0.95 g). The chloro compound was refluxed in 10 ml of methanol in a water bath at 60° for 1 hr. The mixture was evaporated to a small volume on a flash evaporator at 30°. Acetone was added and crystals formed on cooling. After two recrystallizations from absolute ethanol and ether, the yield of the hydrochloride was 0.59 g, mp 175–176°.

Anal. Calcd for $C_{10}H_{15}NO_2 \cdot HCl$: C, 55.29; H, 7.37; N, 6.45; OCH_3, 14.29. Found: C, 54.63; H, 7.16; N, 6.72; OCH_3, 14.36.

The mass spectra of the hydrochloride showed major peaks at *m/e* 44, 77, 107, 121, 137, and 181. The compound did not react with potassium periodate which degrades synephrine to *p*-hydrozybenzaldehyde. β-methoxy-synephrine was converted to synephrine after standing overnight in 6 *N* aqueous HCl.

The free base was made by passing the hydrochloride salt in methanol through a Dowex 50 (NH_4^+) resin column and eluting with 2 *N* NH_4OH in methanol. When the eluate was taken to dryness, the free base was found to be very hygroscopic. The hydrochloride and oxalate salts were much more satisfactory for analysis than the free base.

Descending chromatography on No. 1 Whatman paper using tertiary amyl alcohol–methyl amine–water 80:10:10 (v/v) separated a prepared mixture of β-methoxysynephrine (R_f 0.80), synephrine, (R_f 0.53), and octopamine (R_f 0.33). The compounds were detected with diazotized *p*-nitroaniline. β-Methoxysynephrine gave a bluish-pink color that was slow to form, synephrine and octopamine gave pink spots, and *p*-methoxy compounds did not react. Ion exchange chromatography by methods previously described[5] also separated β-methoxysynephrine (eluted in 44 min), synephrine (42 min), and octopamine (39 min).

Racemic β-methoxysynephrine was also prepared as follows. (−)-Synephrine (1 g) was dissolved in 25 ml of 2 *N* anhydrous HCl in methanol and left overnight at 25°. Analysis by ion exchange chromatography showed 99% conversion of synephrine to β-methoxysynephrine.[5] The mixture was neutralized with ammonia and diluted with water to 100 ml. The remaining synephrine was degraded by treating the mixture overnight with potassium periodate (1 g). The mixture was then passed through a Dowex 50 (NH_4^+) resin column and washed with methanol. The ether was eluted with 2 *N* NH_4OH in methanol and taken to dryness in a flash evaporator at 30°. The residue was dissolved in methanol, neutralized with 2 *N* methanolic HCl, clarified with Darco 60 charcoal and then filtered. Absolute ethanol was added and the solvent evaporated. When ethyl ether was added to the concentrated solution, colorless crystals formed. After two crystallizations, the yield was 0.60 g of the hydrochloride salt. The infrared and mass spectra, and chromatographic analysis indicated that this compound was the same as that synthesized with thionyl chloride.

(−)-β-Methoxysynephrine.—(−)-Synephrine (1 g) dissolved in 100 ml of methanol was neutralized with 2 *N* anhydrous HCl in methanol. A Dowex 50 H^+ column 30 mm × 55 mm was prepared by passing methanol through the column to remove water. The synephrine methanol mixture was then passed through the column followed by a methanol wash. Synephrine remained on the column for about 2 hr. The column was then eluted with 2 *N* NH_4OH in methanol. The resin was stirred to help dissipate the heat. The eluate was taken to dryness on a flash evaporator at 30°. Analysis of the eluate indicated 99% conversion to the methyl ether.

The hydrochloride salt was formed and the remaining synephrine removed by the procedure reported above. After recrystallization twice from absolute ethanol and ethyl ether, the yield was 0.62 g of the hydrochloride salt. The infrared spectra and chromatographic analysis indicated the compound was similar to that synthesized from the thionyl chloride and HCl–methanol procedures. However, the compound prepared on the resin column had an optical rotation $[\alpha]^{25}D$ −11.2. It is not certain that this constitutes complete retention of optical activity since the rotation of the optically pure methyl ether is not known.

Registry No.—Racemic β-methoxysynephrine hydrochloride, 15096-17-0; (−)-β-methoxysynephrine, 15096-18-1.

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Reactions of Some Fluorine-Containing Vinyllithium Compounds with Triethylchlorosilane

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We have reported[1] the preparation of trifluoroisopropenyllithium and trifluoropropynyllithium and have studied their reactions with carbonyl compounds and triethylchlorosilane

In an accompanying paper,[2] we described the preparation of a series of fluorine-containing vinyllithium reagents and studied their reactions with carbonyl compounds. Several of these lithium reagents (CF_2=CFLi, CF_2=CClLi, and CFCl=CClLi) were obtained *via* proton-exchange reactions using butyllithium rather than by the more conventional halogen-exchange procedure; *e.g.*

$$CF_2{=}CClH + C_4H_9Li \xrightarrow[-78°]{\text{ether}} CF_2{=}CClLi + C_4H_{10}$$

$$CF_2{=}CClLi \xrightarrow{(CF_3)_2C{=}O} CF_2{=}CClC(OH)(CF_3)_2$$

56%

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