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Norsteroids. III. Preparation of B-Norcholestane Derivatives by an Ester Condensation of a 5,6-*seco*-Cholestane Keto Ester[1]

HAROLD R. NACE AND ERNEST CAPSTACK, JR.[2]

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Condensation of methyl 3-acetoxy-5,6-*seco*-cholestan-5-one-6-oate with sodium methoxide in methanol gave methyl B-norcholest-3-en-5-ol-6-carboxylate (61%). The use of sodium hydride in toluene gave the same compound in 43% yield, while sodium *t*-butoxide in *t*-butyl alcohol gave B-norcholesta-3,5-diene (30%) and B-norcholesta-3,5-diene-6-carboxylic acid (24%). Evidence that elimination of the 3-acetoxy group preceded condensation was obtained. The structures of the condensation products were proved by conversion to known B-norsteroids by unequivocal reactions.

Although a variety of methods has been employed for the preparation of ring-norsteroids, very little use has been made of the ester condensation of the esters of *seco* acids or *seco*-keto acids, which is somewhat surprising in view of the ready availability of these types of compounds. Rull and Ourisson[3] obtained 2,11,20-triketo-A-norpregnane by a Dieckmann condensation (followed by hydrolysis and decarboxylation) from the dimethyl ester of the corresponding 2,3-*seco* acid, but Jacobs and Takahashi were[4a] unable to cyclize the dimethyl ester of the 2,3-*seco* acid from cholestenone. However, Fuchs and Loewenthal[4b] successfully condensed the methyl esters from the saturated 2,3-*seco*- and 1,2-*seco*-compounds and obtained good yields of the 3-carboxy and 2-carboxy derivatives, respectively.

The ready availability of 3-acetoxy-5,6-*seco*-cholestan-5-one-6-oic acid (I, R^1 = Ac, R^2 = H) suggested its use for the synthesis of B-norsteroids by an ester condensation. Treatment of this compound with benzoyl chloride and pyridine had been shown previously[5] to lead to B-norsteroids, thus making available for comparison purposes B-norcholestanes of known structure.

When methyl 3-acetoxy-5,6-*seco*-cholestan-5-one-6-oate (I, R^1 = Ac, R^2 = CH_3) was heated with sodium methoxide in methanol for 144 hours, the major product was methyl B-norcholest-3-en-5-ol-6-carboxylate (III, R = CH_3) (61%), accompanied by trace amounts of what was presumably methyl B-norcholestane-3,5-diol-6-carboxylate (IV). Although III could not be obtained crystalline, its structure was established on the basis of its reactions, infrared spectrum, and conversion to known B-norsteroids, as described below. No evidence for the presence of isomers in the oily III could be obtained by careful and extensive chromatography on alumina. The use of sodium hydride in toluene as the condensation reagent gave (after forty-eight hours under reflux) a 43% yield of III, R = CH_3. The use of sodium *t*-butoxide in *t*-butyl alcohol gave (after forty minutes under reflux) a 30% yield of B-norcholesta-3,5-diene (VI), accompanied by 24% of oily B-norcholesta-3,5-diene-6-carboxylic acid (V, R = H). Apparently under the latter conditions condensation was followed by dehydration, ester hydrolysis, and in part, decarboxylation.

While various condensation products could be envisaged for the reaction, the most likely ones were considered to be those containing a five- or a seven-membered ring, as shown. The infrared spectrum of the product indicated the presence of an ester grouping, and therefore hydrolysis and decarboxylation were carried out for the initial proof of structure. The methyl ester III was very resistant to hydrolysis with sodium hydroxide in boiling aqueous methanol, but was saponified with sodium hydroxide in boiling aqueous *n*-amyl alcohol to give, after acidification, B-norcholest-3-en-5-ol-6-carboxylic acid (III, R = H) (46% yield). The acid was noncrystalline, but when it was heated to

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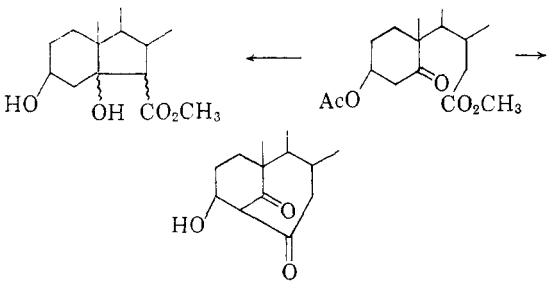
(1) For the previous paper in this series see N. Pappas and H. R. Nace, *J. Am. Chem. Soc.*, **81**, 4556 (1959).

(2) Abstracted from the Ph.D. thesis of Ernest Capstack, Jr., Brown University, 1959. Jesse Metcalf Fellow, 1956–1958.

(3) T. Rull and G. Ourisson, *Bull. soc. chim. France*, **1958**, 1578.

(4) (a) T. L. Jacobs and N. Takahashi, *J. Am. Chem. Soc.*, **80**, 4865 (1958); (b) B. Fuchs and H. J. E. Loewenthal, *Tetrahedron*, **11**, 199 (1960).

(5) (a) A. Windaus and C. Resau, *Ber.*, **48**, 851 (1915); (b) H. Lettre, *Z. physiol. Chem.*, **219**, 67 (1933); (c) F. Sorm, *Collection Czechoslov. Chem. Commun.*, **12**, 436 (1947); F. Sorm and H. Dykova, *Collection Czechoslov. Chem. Commun.*, **13**, 407 (1948); (d) W. G. Dauben and G. Fonken, *J. Am. Chem. Soc.*, **78**, 4736 (1956); (e) G. A. Boswell, W. G. Dauben, G. Ourisson, and T. Rull, *Bull. soc. chim. France*, **1958**, 1598; (f) K. Tanabe, R. Hayashi, and R. Takasaki, *Chem. & Pharm. Bull. (Tokyo)*, **9**, 12 (1961).



300° (16 mm.) dehydration and decarboxylation occurred to give the known B-norcholesta-3,5-diene[5] (VI) in 36% yield, and the condensation product was thus shown to be a B-norcholestane derivative. While some of the seven-membered bridged ring product may have been formed in the reaction, none could be isolated, and no evidence could be obtained for the presence of a β-diketone in the reaction mixture. In view of the fact that ester condensations are reversible it is also possible that bridged-seven-membered ring compounds are formed early in the reaction, and then undergo reversal and subsequent condensation to the thermodynamically more stable B-nor compounds.[6]

Treatment of the B-norester III with boron trifluoride etherate and acetic anhydride resulted in dehydration (this reaction is discussed further below) to give methyl B-norcholesta-3,5-diene-6-carboxylate (V, R = CH_3) (52% yield), which was identical with the diene prepared by pyrolysis (at 200° in the presence of alumina) of a sample of methyl B-norcholest-5-en-3β-ol-6-carboxylate (VII, R^1 = H, R^2 = CH_3). The same diene, V R = CH_3, was also obtained by heating methyl B-norcholest-5-en-3β-ol-6-carboxylate 3-benzenesulfonate (VII, R^1 = $C_6H_5SO_2$, R^2 = CH_3) in dimethyl sulfoxide[7] at 115°. In the latter reaction 20% of B-norcholesta-3,5-diene (VI) was also obtained. The methyl B-norcholest-5-en-3β-ol-6-carboxylate was obtained from the corresponding acid, VII, R^1 = R^2 = H, which was first prepared by Woodward and Clifford[8] by treatment of 3-acetoxy-5,7-dibromo-6-ketocholestane with pyridine.

The methyl B-norcholesta-3,5-diene-6-carboxylate was hydrolyzed with sodium hydroxide in aqueous *n*-amyl alcohol to the corresponding acid (V, R = H), which on pyrolysis at 300° also gave B-norcholesta-3,5-diene (42% yield). The B-nordiene ester, V, R = CH_3, took up slightly more than two equivalents of hydrogen with Adams' platinum catalyst to give what appeared to be, on the basis of its infrared spectrum, methyl B-norcholestane-6-carboxylate (VIII). This compound could not be obtained in crystalline form and was not investigated further. These additional reactions and interconversions with known B-norcholestanes supply further proof for the carbon skeleton proposed for the condensation product.

With the basic ring structure shown to be that of a B-norsteroid it remained to establish the position of the functional groups. The B-nor product expected from the condensation of methyl 3-acetoxy-5,6-*seco*-cholestan-5-one-6-oate (I, R = CH_3) was methyl 3β,5-dihydroxy-B-norcholestane-6-carboxylate (IV). However, the intensity of the O—H stretching band in the infrared spectrum of the condensation product was suggestive of the presence of only one hydroxyl group in the molecule. The substance could not be acetylated with pyridine–acetic anhydride or acetyl chloride, which indicated that only a tertiary hydroxyl group was present. When acetylation with acetic anhydride and boron trifluoride etherate was attempted, dehydration occurred to give methyl B-norcholesta-3,5-diene-6-carboxylate (V, R = CH_3) (discussed above), confirming the presence of a tertiary hydroxyl group at position 5, and further, suggesting the presence of a double bond at position 3. In addition, the condensation product III was obviously different from the known methyl B-norcholest-5-en-3β-ol-6-carboxylate (VII, R^1 = H, R^2 = CH_3) but both compounds gave the same dehydration product V.

The condensation product was hydrogenated in the presence of Adams' platinum catalyst to give methyl B-norcholestan-5-ol-6-carboxylate (IX, R = H). This compound also could not be acetylated with acetic anhydride–pyridine, but on treatment with acetic anhydride and boron trifluoride etherate it gave methyl 5-acetoxy-B-norcholestane-6-carboxylate (IX, R = CH_3CO). The fact that dehydration was not observed with the hydrogenated compound can be ascribed to the loss of the driving force supplied by the double bond at position 3, and lends credence to this assignment, rather than that of a double bond at position 2. The saturated hydroxy ester, IX, R = H, was dehydrated with thionyl chloride and pyridine to yield methyl B-norcholest-5-ene-6-carboxylate (X), as evidenced by the infrared and ultraviolet spectra and elemental analysis.

The structure of the condensation product was thus established beyond reasonable doubt as III. The loss of the 3β-acetoxyl (or hydroxyl) group was somewhat surprising since it was anticipated that if any dehydration occurred in the reaction it would involve the tertiary 5-hydroxyl group. The possibility was then examined that the 3-acetoxyl group was lost before the cyclization step to give an α,β-unsaturated ketone II, R = CH_3, which then underwent condensation.

Dauben and Fonken reported[5d] that treatment of the starting material I, R^1 = Ac, R^2 = H, with sodium bicarbonate in methanol gave 3-hydroxy-

(6) *Cf.* the paper by W. S. Johnson, J. J. Korst, R. A. Clemont, and J. Dutta, *J. Am. Chem. Soc.*, **82**, 614 (1960) for a discussion and examples of this phenomenon in analogous systems.

(7) H. R. Nace, *J. Am. Chem. Soc.*, **81**, 5428 (1959).

(8) R. B. Woodward and A. F. Clifford, *J. Am. Chem. Soc.*, **63**, 2727 (1941).

5,6-*seco*-cholestan-5-one-6-oic acid (I, R^1 = R^2 = H), characterized as the methyl ester, m.p. 92.5–94°. Repetition of their experiment in this laboratory invariably resulted in the formation of 5,6-*seco*-cholest-3-en-5-one-6-oic acid (II, R = H) (95% yield), which was also converted to the methyl ester II, R = CH_3. Neither compound could be obtained crystalline. A sample of the crystalline methyl ester I, R^1 = H, R^2 = CH_3, of Dauben and Fonken was prepared by treating the β-lactone [5d,e] XI with sodium bicarbonate in methanol, and when the noncrystalline ester II, R = CH_3, was seeded with this compound, crystallization did not occur. The infrared and ultraviolet spectra of the oily products clearly showed the presence of an α,β-unsaturated carbonyl group, and were distinctly different from those of the 3-hydroxy compounds of Dauben and Fonken. Attempted acetylation of the noncrystalline unsaturated ester II, R = CH_3, with acetic anhydride and pyridine failed to regenerate the starting material, methyl 3-acetoxy-5,6-*seco*-cholestan-5-one-6-oate (I, R^1 = Ac, R^2 = CH_3), thus furnishing further evidence that the 3-hydroxyl group had been lost. Presumably the driving force for this facile β-elimination is the presence of the 5-carbonyl group. The reasons for the discrepancy between the results of Dauben and Fonken and those reported here are unknown at present.

The methyl ester of the Δ^3-compound II, R = CH_3, was then condensed with sodium methoxide in methanol using the same conditions as described for the 3-acetoxy compound, and a 51% yield of methyl B-norcholest-3-en-5-ol-6-carboxylate (III, R = CH_3) was obtained. It thus appears very likely that in the reaction with the 3-acetoxy compound, β-elimination precedes condensation, although a very small fraction of the material apparently undergoes condensation before elimination can occur, as evidenced by the isolation of small amounts of the 3,5-dihydroxy compound IV. The factors which lead to the formation of the B-nor product, rather than the bridged ring diketone, discussed above for the 3-acetoxy compound, would apply equally well to the Δ^3-compound.

EXPERIMENTAL[9]

Methyl B-norcholest-3-en-5-ol-6-carboxylate (III, R = CH_3) *by condensation of methyl 3-acetoxy-5,6-seco-cholestan-5-one-6-oate* (I, R^1 = CH_3CO, R^2 = CH_3). (*a*) *With sodium methoxide in methanol.* To a solution of sodium methoxide in methanol (0.40 g., 0.017 g.-atom, of sodium in 100 ml. of methanol) was added a solution of 3.0 g. (6.1 mmoles) of methyl 3-acetoxy-5,6-*seco*-cholestan-5-one-6-oate[6] (I, R^1 = CH_3CO, R^2 = CH_3) in 50 ml. of methanol and the resulting solution was boiled under reflux for 6 days. (During the course of the reaction, a red solid deposited on the wall of the flask. It was collected by filtration to give 0.24 g., m.p. 210–230°, no residue on ignition, soluble in ether or acetone, insoluble in methanol or water. It was not characterized further.) The solution was then acidified with acetic acid, most of the solvent was evaporated, and ether was added to the residue. The ether solution was washed twice with water, dried over anhydrous sodium sulfate, and then the ether was evaporated to give 2.7 g. of a viscous yellow oily residue.

The oil was dissolved in 150 ml. of hexane and the solution was chromatographed on 49 g. of alumina. The various fractions eluted with 30% benzene-hexane to pure benzene appeared to be homogeneous on the basis of their infrared spectra. This was found to be the case in several experiments, and, in addition, any one of the fractions exhibited the same behavior when rechromatographed. The fractions were therefore combined and the oil, which resisted all attempts at crystallization, was used in subsequent experiments as methyl B-norcholest-3-en-5-ol-6-carboxylate (III, R = CH_3). The yield was 1.6 g. (61%); $\lambda_{max}^{CCl_4}$ 2.82, 5.72 (sh.), 5.80μ; $\lambda_{max}^{cyclohexane}$ 222mμ (end adsorption).

(*b*) *With sodium hydride in toluene.* A mixture of 1.0 g. (2.04 mmoles) of methyl 3-acetoxy-5,6-*seco*-cholestan-5-one-6-oate (I, R^1 = CH_3CO, R^2 = CH_3), 150 ml. of toluene and 0.1 g. (4.2 mmoles) of sodium hydride was boiled under reflux for 48 hr. The excess sodium hydride was destroyed by the addition of acetic acid, and the toluene solution was then washed twice with water and dried over anhydrous sodium sulfate. The toluene was evaporated and the viscous yellow oil (0.7 g.) which remained was chromatographed as above on 30 g. of alumina to give 0.38 g. (43%) of material which corresponded, in its infrared spectrum and behavior on chromatographic elution, to the oily methyl B-norcholest-3-en-5-ol-6-carboxylate (III, R = CH_3) described above.

Attempted acetylation of this material (III, R = CH_3) with acetic anhydride and pyridine or with acetyl chloride resulted in an 82% recovery of starting material.

(*c*) *With sodium t-butoxide in t-butyl alcohol.* To a solution of sodium *t*-butoxide in *t*-butyl alcohol (1.0 g., 0.044 g.-atom of sodium in 200 ml. of *t*-butyl alcohol) was added 5.0 g. (10.2 mmoles) of methyl 3-acetoxy-5,6-*seco*-cholestan-5-one-6-oate (I, R^1 = CH_3CO, R^2 = CH_3), and the solution was boiled under reflux for 40 min. The solution was then acidified with acetic acid, and most of the solvent was removed under reduced pressure. The residue was taken up in ether and water; the ether layer was extracted twice with dilute sodium hydroxide solution, and the ether layer was saved.

The basic extract was acidified with dilute hydrochloric acid and extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and the ether was evaporated to give 0.98 g. (24%) of an oily acid which could not be crystallized and presumably was impure B-norcholesta-3,5-diene-6-carboxylic acid (V, R = H).

The neutral ether solution was then dried over anhydrous sodium sulfate, the ether was evaporated, and the yellow oily residue (2.24 g.) was taken up in hexane and chromatographed on 60 g. of alumina. Hexane eluted 1.69 g. of a colorless oil which crystallized from acetone to yield 1.07 g. (30%) of B-norcholesta-3,5-diene (VI), m.p. 75.5–76.5°, no depression of melting point on admixture with an authentic sample prepared by the method of Sorm.[5c]

Methyl B-norcholest-3-en-5-ol-6-carboxylate (III, R = CH_3) *by condensation of methyl 5,6-seco-cholest-3-en-5-one-6-oate* (II, R = CH_3) *with sodium methoxide.* (*a*) *Preparation of* II, R = CH_3. A mixture of 3.0 g. (6.1 mmoles) of 3-acetoxy-5,6-*seco*-cholestan-5-one-6-oic acid (I, R^1 = CH_3CO, R^2 = H), 1.4 g. (17 mmoles) of sodium dicarbonate, and 100 ml. of methanol was stirred at room temperature for 40 hr., during which time the sodium dicarbonate gradually dissolved. The reaction mixture was acidified with acetic acid, most of

(9) All melting points are corrected. The analytical samples were crystallized to constant melting point. Micro analyses were performed by Dr. S. M. Nagy and associates, Microchemical Laboratory, Massachusetts Institute of Technology. Infrared spectra were determined with a Perkin-Elmer Infracord; ultraviolet spectra were determined with a Beckman DU spectrophotometer. Merck alumina (suitable for chromatographic absorption) was used for the chromatographic separations.

the solvent was evaporated, water was added, and the resulting mixture was extracted with ether. The extract was dried over anhydrous sodium sulfate, and the ether was evaporated to give 2.4 g. (95%) of 5,6-*seco*-cholest-3-en-5-one-6-oic acid (II, R = H) as an oil which could not be crystallized.

An ether solution of the acid was esterified with ethereal diazomethane to give 2.4 g. of an oil which was chromatographed on 49 g. of alumina. The fractions eluted with 35% benzene in hexane to 75% benzene in hexane were spectroscopically (infrared) identical and were combined to yield 1.5 g. (61%) of methyl 5,6-*seco*-cholest-3-en-5-one-6-oate (II, R = CH_3) as an oil which could not be crystallized, and had λ_{max}^{film} 5.95, 5.77 μ, $\lambda_{max}^{CH_3OH}$ 230 mμ (log ϵ 4.04).

(b) *Condensation of* II, R = CH_3. To a solution of sodium methoxide in methanol (0.20 g., 0.0087 g.-atom of sodium in 100 ml. of methanol) was added 1.5 g. (3.5 mmoles) of methyl 5,6-*seco*-cholest-3-en-5-one-6-oate, and the resulting solution was boiled under reflux for 6 days. The solution was then acidified with acetic acid, most of the solvent was evaporated, and the residue was extracted with ether. The extract was washed twice with water, dried over anhydrous sodium sulfate, and the ether was evaporated to give 1.4 g. of a viscous yellow oil which was taken up in hexane and chromatographed on 35 g. of alumina. Elution with 30% benzene in hexane to pure benzene gave 0.93 g. (51%) of methyl B-norcholest-3-en-5-ol-6-carboxylate (III, R = CH_3) identical with the material described above.

B-Norcholest-3-en-5-ol-6-carboxylic acid (III, R = H). A mixture of 0.96 g. (2.2 mmoles) of methyl B-norcholest-3-en-5-ol-6-carboxylate (III, R = CH_3), 0.30 g. (7.5 mmoles) of sodium hydroxide, 3 ml. of water, and 130 ml. of *n*-amyl alcohol was boiled under reflux for 24 hr. Most of the amyl alcohol was removed from the dark reaction mixture by steam distillation, and the residue was extracted with ether. Three phases formed after the extraction, an upper ether layer, an intermediate layer of insoluble oily sodium salt of the acid, and a lower aqueous layer containing some of the sodium salt. The two lower layers were combined, acidified with dilute hydrochloric acid, and extracted with ether. The extract was washed twice with water, dried over anhydrous sodium sulfate, and the ether was evaporated to give 0.42 g. (46%) of B-norcholest-3-en-5-ol-6-carboxylic acid (III, R = H) as a reddish brown oil which could not be crystallized, and had $\lambda_{max}^{CCl_4}$ 5.94 (broad) and 6.20 μ (broad).

Methyl B-norcholesta-3,5-diene-6-carboxylate (V, R = CH_3). (a) *From methyl B-norcholest-3-en-5-ol-6-carboxylate* (III, R = CH_3). A mixture of 1.6 g. (3.7 mmoles) of methyl B-norcholest-3-en-5-ol-6-carboxylate (III, R = CH_3), 5 drops of boron trifluoride etherate and 11 ml. of acetic anhydride was heated on a steam bath for 30 min., and then cooled in an ice bath. Water was added, followed by dilute sodium bicarbonate solution, and the resulting mixture was extracted with ether. The extract was washed twice with water, dried over anhydrous sodium sulfate, and the ether was evaporated to give a yellow oil which was taken up in hexane and chromatographed on alumina. Hexane eluted an oil which crystallized from ethanol. One recrystallization from ethanol gave 0.79 g. (52%) of methyl B-norcholesta-3,5-diene-6-carboxylate (V, R = CH_3), m.p. 85.0–85.5° $[\alpha]_D$ −98° (1% in chloroform) $\lambda_{max}^{CCl_4}$ 5.84 and 6.20 μ, $\lambda_{max}^{C_2H_5OH}$ 268 mμ (log ϵ 4.2).

Anal. Calcd. for $C_{28}H_{44}O_2$: C, 81.50; H, 10.75. Found: C, 81.44; H, 1 .79.

(b) *From methyl B-norcholest-5-en-3β-ol-6-carboxylate* (VII, R^1 = H, R^2 = CH_3). A mixture of 153 mg. (0.355 mmole) of methyl B-norcholest-5-en-3β-ol-6-carboxylate and 0.5 g. of alumina (previou ly activated by heating at 400° for 1 hr.) was placed in a small Hickman flask, and this was gradually heated to 200° in an oil bath. Distillation commenced at this temperature and was complete in 30 min. The distillate was taken up in ether, the ether was evaporated, and the residue was crystallized from ethanol to give 47 mg. (32%) of methyl B-norcholesta-3,5-diene-6-carboxylate (V, R = CH_3) m.p. 85–86°, not depressed when mixed with a sample of the same material described above.

(c) *From Methyl B-norcholest-5-en-3β-ol-6-carboxylate 3-benzenesulfonate* (VII, R^1 = $C_6H_5SO_2$, R^2 = CH_3). A mixture of 107 mg. (0.19 mmole) of methyl B-norcholest-5-en-3β-ol-6-carboxylate 3-benzenesulfonate, 0 30 g. of sodium carbonate, and 4 ml. of dimethyl sulfoxide was heated at 115° for 2 hr. The reaction mixture was then poured into salt water and extracted with ether, and the ether extract was washed several times with salt water, dried over anhydrous sodium sulfate, and the solvent was then evaporated. The residue was taken up in hexane and chromatographed on 2.5 g. of alumina. Hexane eluted 17 mg. of an oil which crystallized from acetone-water to give 13 mg. (20%) of B-norcholesta-3,5-diene (VI), m.p. 76–77°, no depression on admixture with an authentic sample.

Elution with 10% benzene in hexane gave 17 mg. of an oil which crystallized from ethanol to give 12 mg. (16%) of methyl B-norcholesta-3,5-diene-6-carboxylate (V, R = CH_3), m.p. 85–86°, no depression on admixture with an authentic sample.

Methyl B-norcholestane-6-carboxylate (VIII). To a mixture of 0.10 g. of platinum oxide and 40 ml. of glacial acetic acid, which had been prereduced with hydrogen, was added 120 mg. (0.29 mmole) of methyl B-norcholesta-3,5-diene-6-carboxylate (V, R = CH_3). Hydrogen uptake ceased after 2.2 molar equivalents had been taken up. After removal of the catalyst and solvent, the residue was taken up in ether; the ether extract was dried over anhydrous sodium sulfate and then evaporated to give 103 mg. (83%) of methyl B-norcholestane-6-carboxylate as a colorless oil which had $\lambda_{max}^{CCl_4}$ 5.74 μ.

B-Norcholesta-3,5-diene-6-carboxylic acid (V, R = H). A mixture of 0.24 g. (0.58 mmole) of methyl B-norcholesta-3,5-diene-6-carboxylate (V, R = CH_3), 0.10 g. of sodium hydroxide, 1 ml. of water, and 11 ml. of freshly distilled *n*-amyl alcohol was boiled under reflux for 24 hr. The amyl alcohol was removed by steam distillation and the residue, after extraction with ether to remove neutral material, was

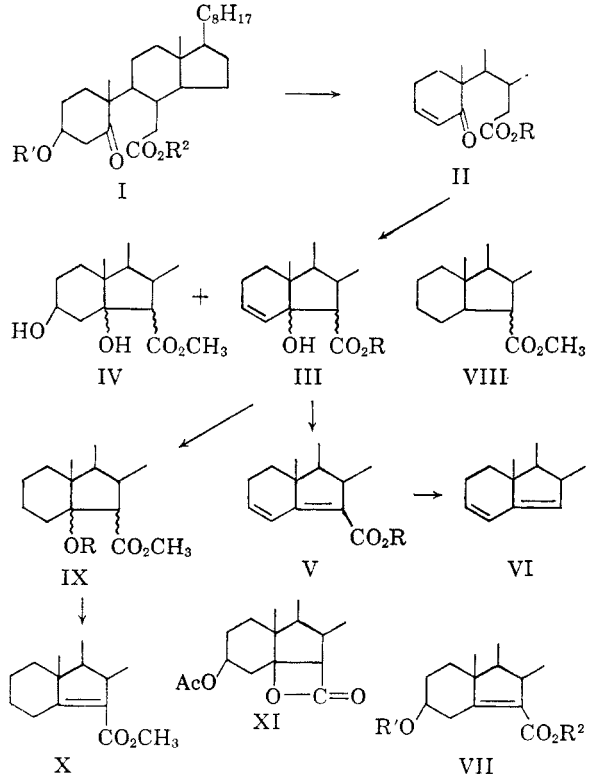


Fig. 1. The preparation of B-norcholestane derivatives.

acidified with dilute hydrochloric acid and extracted with ether. The ether extract was then dried over anhydrous sodium sulfate, and the ether was evaporated to give 0.16 g. (69%) of oily B-norcholesta-3,5-diene-6-carboxylic acid (V, R = H), $\lambda_{max}^{CCl_4}$ 5.94 and 6.25 μ.

B-Norcholesta-3,5-diene (VI). (*a*) *From B-norcholest-3-en-5-ol-6-carboxylic acid* (III, R = H). A sublimation apparatus containing 0.62 g. (1.5 mmoles) of B-norcholest-3-en-5-ol-6-carboxylic acid (III, R = H) was heated to 300° (16 mm.), whereupon a light yellow semisolid slowly formed on the condenser. This material was recrystallized three times from ethanol to yield 0.19 g. (36%) of B-norcholesta-3,5-diene (VI), m.p. 76.5–77°, no depression when admixed with an authentic sample.

(b) *From B-norcholesta-3,5-diene-6-carboxylic acid* (V, R = H). A sublimation apparatus containing 72 mg. (0.18 mmole) of B-norcholesta-3,5-diene-6-carboxylic acid was heated to 300° under a slow stream of nitrogen. The sublimate was taken up in hexane and chromatographed on 1.1 g. of alumina. Hexane eluted 30 mg. of material which was recrystallized from ethanol to give 27 mg. (42%) of B-norcholesta-3,5-diene, m.p. 76–77°, no depression when admixed with an authentic sample.

Methyl B-norcholest-5-en-3β-ol-6-carboxylate (VII, R^1 = H, R^2 = CH_3). A solution of 541 mg. (1.30 mmoles) of B-norcholest-5-en-3β-ol-6-carboxylic acid (VII, R^1 = H, R^2 = H) (prepared by the method of Woodward and Clifford[8]) in 15 ml. of ether was treated at ice-bath temperature with small portions of diazomethane in ether until the yellow color persisted. The solvent was distilled, and the residue crystallized from methanol-water to give 528 mg. (94%) of methyl B-norcholest-5-en-3β-ol-6-carboxylate (VII, R^1 = H, R^2 = CH_3). Recrystallization from hexane gave a m.p. of 153–154°.

Anal. Calcd. for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77. Found: C, 78.08; H, 10.86

Methyl 3β-acetoxy-B-norcholest-5-ene-6-carboxylate (VII, R^1 = CH_3CO, R^2 = CH_3). A solution of 160 mg. (0.350 mmole) of 3β-acetoxy-B-norcholest-5-ene-6-carboxylic acid (VII, R^1 = CH_3CO, R^2 = H) (prepared by the method of Woodward and Clifford[8]) in 10 ml. of ether was treated with small portions of diazomethane in ether until the yellow color persisted. The solvent was then evaporated, and the residue was crystallized from methanol to give 133 mg. (80%) of methyl 3-acetoxy-B-norcholest-5-ene-6-carboxylate (VII, R^1 = CH_3CO, R^2 = CH_3) m.p. 125–127°, $\lambda_{max}^{C_2H_5OH}$ 220 mμ (log ϵ3.6).

Anal. Calcd. for $C_{30}H_{48}O_4$: C, 76.22; H, 10.24. Found: C, 75.95; H, 10.23.

Methyl-B-norcholest-5-en-3β-ol-6-carboxylate 3-benzenesulfonate (VII, R^1 = $C_6H_5SO_2$, R^2 = CH_3). A solution of 150 mg. (0.350 mmole) of methyl B-norcholest-5-en-3β-ol-6-carboxylate (VII, R^1 = H, R^2 = CH_3) and 0.5 ml. of benzenesulfonyl chloride in 5.0 ml. of anhydrous pyridine was kept at room temperature for 20 hr., and then ice water was added. The resulting mixture was extracted with ether, the extract was washed once with dilute hydrochloric acid, twice with water, dried over anhydrous sodium sulfate, and the ether was evaporated. The residue was crystallized from methanol to give 157 mg. (79%) of methyl B-norcholest-5-en-3β-ol-6-carboxylate 3-benzenesulfonate (VII, R^1 = $C_6H_5SO_2$, R^2 = CH_3) m.p. 140–140.5°.

Anal. Calcd. for $C_{34}H_{50}O_5S$: C, 71.54; H, 8.83; S, 5.62. Found: C, 71.88; H, 9.05; S, 5.89.

Methyl B-norcho estan-5-ol-6-carboxylate (IX, R = H). A 1.19-g. (2.76 mmoles) sample of methyl B-norcholest-3-en-5-ol-6-carboxylate (III, R = CH_3) was freed from solvent by heating at 50° (0.2 mm.) for 10 hr. It was then shaken under hydrogen with Adams' platinum in acetic acid (0.3 g. of platinum oxide monohydrate was prereduced in 100 ml. of glacial acetic acid) at room temperature and atmospheric pressure. Hydrogen uptake ceased at 62% of the calculated amount, whereupon the catalyst was removed by filtration and most of the acetic acid was removed from the filtrate by distillation under reduced pressure. The residue was dissolved in ether, and the solution was washed once with dilute sodium hydroxide solution, twice with water, and then dried over anhydrous sodium sulfate. The ether was evaporated, and the residue was taken up in 100 ml. of hexane and chromatographed on 18 g. of alumina. Elution with 60% benzene in hexane gave, after crystallization from ethanol-water, 310 mg. (26%) of methyl B-norcholestan-5-ol-6-carboxyla e (IX) (R = H), m.p. 71–72°, $[\alpha]_D$+33° (1% in chloroform), $\lambda_{max}^{CCl_4}$ 2.81 and 5.81 μ.

Anal. Calcd. for $C_{28}H_{48}O_3$: C, 77.72; H, 11.18. Found: C, 77.57; H, 11.23.

Methyl 5-acetoxy-B-norcholestane-6-carboxylate (IX, R = CH_3CO). A mixture of 96 mg. (0.22 mmole) of methyl B-norcholestan-5-ol-6-carboxylate (IX, R = H), 5 drops of boron trifluoride etherate, and 5 ml. of acetic anhydride was heated on a steam bath for 2 hr. Ice water was then added, the mixture was extracted with ether, and the extract was washed once with dilute sodium hydroxide solution, twice with water, and dried over anhydrous sodium sulfate. The residue was taken up in hexane and chromatographed on 3 g. of alumina. The fractions eluted with hexane and 10% benzene in hexane were combined and crystallized from ethanol to give 51 mg. (49%) of methyl 5-acetoxy-B-norcholestane-6-carboxylate (IX, R = CH_3CO), m.p. 79.5–80.0°, $[\alpha]_D$ + 130° (1% in chloroform), $\lambda_{max}^{CCl_4}$ 5.74 μ.

Acetylation of methyl B-norcholestan-5-ol-6-carboxylate was attempted with acetic anhydride and pyridine. After the reaction had stood overnight at room temperature, it was poured onto ice. Extraction with ether gave an oil whose infrared spectrum was almost identical to that of the starting material. Chromatography of the oil resulted in recovery of crystalline starting material (53%) and no material corresponding to the 5-acetate could be isolated.

Methyl B-norcholest-5-ene-6-carboxylate (X). A solution of 230 mg. (0.53 mmole) of methyl B-norcholestan-5-ol-6-carboxylate (IX, R = H) in 5 ml. of anhydrous pyridine was cooled to 5°, 1 ml. of thionyl chloride was added, and the mixture was kept in an ice bath for 1 hr. Water was then added, and the resulting suspension was extracted with ether. The extract was washed once with dilute hydrochloric acid, twice with water, dried over anhydrous sodium sulfate, and the ether was evaporated. The residue was taken up in hexane and chromatographed on 10 g. of alumina. Elution with hexane gave 169 mg. of an oil which was crystallized from ethanol to give 109 mg. (50%) of methyl B-norcholest-5-ene-6-carboxylate (X), m.p. 78.5–79.5°, $\lambda_{max}^{CCl_4}$ 5.82 and 6.14 μ, $\lambda_{max}^{C_2H_5OH}$ 221 mμ (log ϵ 3.5).

Anal. Calcd. for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. Found: C, 81.13; H, 11.20.

Methyl B-norcholestane-3,5-diol-6-carboxylate (IV). When concentrated ethanol solutions of the oily methyl B-norcholest-3-en-5-ol-6-carboxylate (III, R = CH_3) were stored in the cold for a period of a week or more, small amounts of a crystalline solid deposited. In this manner approximately 100 mg. of the substance was collected during the course of a year. The substance appeared to be methyl B-norcholestane 3,5-diol-6-carboxylate (IV), m.p. 83–84°, $\lambda_{max}^{CCl_4}$ 2.84, 5.75 μ.

Anal. Calcd. for $C_{28}H_{48}O_4$: C, 74.95; H, 10.78. Found: C, 75.08; H, 10.97.

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