Anal. Calcd. for $C_{27}H_{27}NO_3S$: C, 72.77; H, 6.10; N, 3.14; S, 7.19. Found: C, 72.85; H, 6.28; N, 3.12; S, 7.10.

3α-Phenyl-3β-nortropanyl Phenyl Ketone (XVI).—8-Tosyl-3α-phenyl-3β-nortropanyl phenyl ketone (4.5 g.) was suspended in a mixture of 50 ml. of propionic acid, 16 ml. of 48% hydrobromic acid and 1.34 g. of phenol and refluxed for 1 hour. The cooled solution was filtered from the insoluble, unreacted starting compound (1.1 g.) and concentrated to a small volume under reduced pressure. The residue was diluted with 50 ml. of water, filtered, and the filtrate extracted with ethyl ether. The aqueous layer was treated with 10% sodium hydroxide and the separated white crystalline product was collected and crystallized from ethanol yielding 1.57 g. (70.8%) of 3α-phenyl-3β-nortropanyl phenyl ketone, m.p. 206–208° (reported 208–212°). The infrared spectrum in bromoform solution of XVI showed no carbonyl band near 6μ and a hydroxyl band at 2.84 μ. The infrared spectrum in methanol solution of XVI hydrochloride showed no carbonyl band near 6μ.[5]

Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.44; H, 7.27; N, 4.80. Found: C, 82.24; H, 7.40; N, 4.76.

The hydrochloride of XVI, after crystallization from ethanol–ethyl ether, melted at 280–282° (reported 297°).

Anal. Calcd. for $C_{20}H_{22}ClNO$: N, 4.27; Cl, 10.81. Found: N, 4.23; Cl, 11.00.

The oxime XVIII was prepared according the described[4] procedure. The hydrochloride after crystallization from water melted at 273–275° (reported 286°).

Anal. Calcd. for $C_{20}H_{23}ClN_2O$: N, 8.17; Cl, 10.34. Found: N, 7.90; Cl, 10.15.

3α-Phenyl-3β-tropanyl Phenyl Ketone (XVII).—3α-Phenyl-3β-nortropanyl phenyl ketone (1.45 g.) was dissolved in 3 ml. of 98% formic acid, then 2 ml. of 38% formaldehyde was added and the mixture was allowed to reflux for 7 hours. After cooling, 2 ml. of concentrated hydrochloric acid was added and the whole was concentrated under reduced pressure. On cooling, the oily residue was treated with 20% sodium hydroxide. The separated white product was collected by filtration, washed with water and dried yielding 1.10 g. (73) of XVII, m.p. 123–125°. A sample, after crystallization from hexane, melted at 125–126° (reported 121–122.5°).

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.57; H, 7.59; N, 4.58. Found: C, 82.51; H, 7.74; N, 4.60.

The hydrochloride of XVII, prepared by addition of alcoholic hydrogen chloride to an ethyl ether solution of the base, melted at 249–251° (after crystallization from absolute ethanol (reported 257–257.5°).

Anal. Calcd. for $C_{21}H_{24}ClNO$: N, 4.09; Cl, 10.37. Found: N, 4.24; Cl, 10.50.

The infrared spectrum of XVII in methanol solution showed a broad absorption with two peaks at 6.02 and 6.10 μ; in methylene chloride a band at 6.04 μ. The infrared spectrum of XVII hydrochloride in methanol solution showed a weak band at 6.00 μ.[5]

The oxime XIX hydrochloride was prepared according the described procedure[5]; m.p. 320–321° (reported 327°).

Anal. Calcd. for $C_{21}H_{25}ClN_2O$: N, 7.85; Cl, 9.94. Found: N, 7.75; Cl, 10.05.

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Synthesis of A-Norcholesterol

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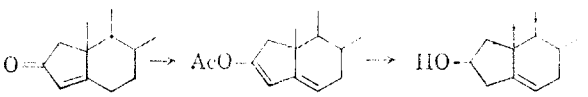
A-Norcholesterol (III) was prepared by a four-step procedure from A-norcoprostane-2,6-dione (IV). Attempts to prepare the sterol from A-norcholestenone (I) were unsuccessful.

The role of cholesterol in cardio-vascular diseases has attracted much interest in recent years, and the possible utilization of related steroids as dietary replacement factors has been investigated.[2] As it might be expected that any structural change in the immediate vicinity of the important C-3 hydroxyl function could affect the biological activity of a sterol, the preparation of A-norcholesterol (III) has been investigated.

With the recent availability of A-norcholestenone (I)[3,4] the standard method[5] used so successfully for the preparation of cholesterol from cholestenone was studied in the A-nor series. This method involves the conversion of a ring A enone (I) to the 2,5-dienol acetate (II) followed by reduction with sodium borohydride. Jacobs and Takahashi[3] have reported that preliminary attempts to prepare the dienol acetate II were unsuccessful. The preparation of II from A-norcholestenone (I) proved to be difficult in that under the usual reaction conditions employing isopropenyl acetate no reaction occurred.



I II III

Even when the forcing conditions used to prepare the enol acetate of A-norcholestane-2-one[4] were employed, II did not react with isopropenyl acetate.

It was found that when compound I was allowed to react for 24 hours with acetic anhydride containing a small amount of *p*-toluenesulfonic acid, there was obtained an oily product whose spectral features showed it to be the desired $\Delta^{2,5}$-A-norcholestadiene-3-ol acetate (II) contaminated with starting enone I. The dienol acetate could never be obtained pure and crystalline. Reduction of crude II with sodium borohydride in ethanol yielded an oily product which was treated with acid to dehydrate any allylic $\Delta^{3(5)}$-A-norcholestene-3-ol formed in the reaction. Chromatography of the resulting product gave only $\Delta^{2,5}$-A-norcholestadiene (IX), indicating the presence of only allylic alcohols in the reduction mixture. One reason for the failure of this method of preparation of β,γ-unsaturated alcohols from α,β-unsaturated ketones apparently could stem from the relatively slow rate of reduction of a cyclopentanone as compared to a cyclohexanone.[6]

(1) National Science Foundation Predoctoral Fellow, 1957–1958.

(2) For reviews, see *Ann. Rev. Biochem.*, **26**, 315 (1957); *Vitamins and Hormones*, **16**, 141 (1958); **17**, 233 (1959).

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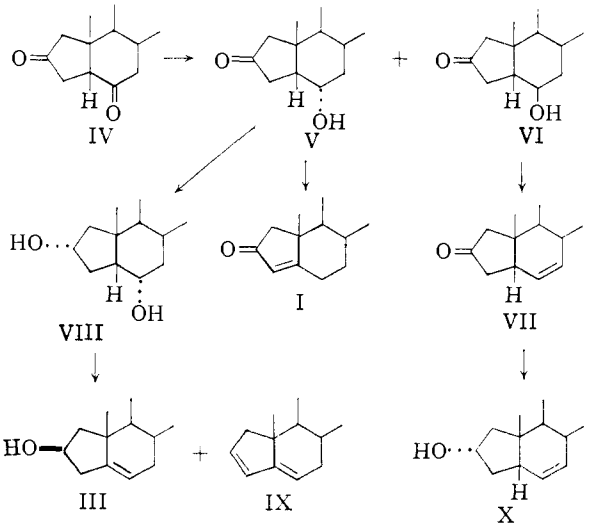
In the treatment of a dienol acetate with alcoholic sodium borohydride, the first step of the reaction is the hydrolysis of the ester to produce a β,γ-unsaturated ketone.[7] If the reduction of the ketone is slower than the migration of the double bond into conjugation, the α,β-unsaturated alcohol will result. Such an unfavorable competitive rate situation must prevail in the present case. Since the reduction of a dienol acetate with lithium aluminum hydride does not involve a prior hydrolysis of the ester, the method should be particularly applicable to the present case.[8] In one run, however, it was found that no digitonin-precipitable material remained after the usual acid treatment to remove allylic alcohols and the process was not studied further.

The successful preparation, albeit in low yield, of A-norcholesterol (III) was achieved by starting with A-norcoprostane-2,5-dione, A/B *cis* ring fusion being assigned by analogy with other hydrindanones.[9,10] Taking advantage of the greater reactivity toward sodium borohydride of a six-ring ketone as compared to a five-ring ketone,[6] the dione V was selectively reduced to give a 1:1.2 mixture of the epimeric 6-ols V and VI. The isomer VI was assigned a 6β-axial configuration since it moved more rapidly on alumina than epimer V. In line with



this assignment, it was found that when VI was allowed to react with phosphorus oxychloride in pyridine, a non-conjugated unsaturated ketone was formed in 80% yield and such a high yield in this type of elimination reaction is characteristic of an axial alcohol.[11] The enone showed no tendency to rearrange into a conjugated ketone and thus the double bond was placed into the 6,7-position, as in VII. Hydrogenation of VII yielded the known A-norcoprostane-2-one[12] and from this result it follows that the starting dione V was A/B *cis*, as assigned previously.[10] All these findings require that the C-6 hydroxyl function in VI be axial and be *cis* to the C-5 ring juncture hydrogen atom, that is 6β. When the epimeric olone V was treated with phosphorus oxychloride in pyridine, $\Delta^{3(5)}$-A-norcholestene-2-one (I) was obtained and only in 30% yield, a result expected from the 6α-equatorial isomer. The formation of 54% β–46% α in the borohydride reduction of the A-nor compound when compared with the apparent exclusive formation of the 6β-isomer from 3β-chlorocoprostane-6-one[13] shows the large effect a small change in a molecule can have on the steric course of a borohydride reduction.

Reduction of olone V with sodium borohydride yielded A-norcoprostane-2α,6α-diol (VIII). The 2α-configuration assignment was made by analogy with the finding of a predominant amount of the 3α-isomer in the borohydride reduction of coprostane-3-one.[7] The diol VIII was converted to a ditosylate which was then allowed to react with potassium acetate in dimethylformamide.[14] From this reaction there was obtained a mixture of A-norcholestadiene (IX) and the acetate of A-norcholesterol (III). The C-2 β-configuration was assigned to III since the compound formed a precipitate with digitonin and since displacement of the C-2 tosylate should proceed with inversion.

Experimental[15]

6α-Hydroxy-A-norcoprostane-2-one (V) and 6β-Hydroxy-A-norcoprostane-2-one (VI).—To a well-stirred solution of 2.21 g. (5.73 mmoles) of A-norcoprostane-2,6-dione (IV)[9,10] in 400 ml. of 95% ethanol cooled to 0°, there was added, dropwise, a solution of 85 mg. (2.24 mmoles, 9.0 meq.) of sodium borohydride in 10 ml. of ethanol (prepared at 0°). The reaction was stirred for 1 hour at 0° and then diluted with a large excess of cold water. After cautious acidification with 10% hydrochloric acid, the solution was extracted three times with ether. The ethereal extracts were washed with 5% sodium bicarbonate solution, water and finally with saturated sodium chloride solution. The solution was dried over magnesium sulfate and the solvent removed under reduced pressure to yield 2.19 g. (99%) of a crude mixture of epimeric hydroxyketones; $\lambda_{max}^{CS_2}$ 2.80, 2.90 and 5.77 μ. The colorless sirup was placed on a column of 75 g. of Woelm neutral alumina (Act. III) with petroleum ether. Elution with petroleum ether–benzene (1:1) afforded 272 mg. (12.4 %) of starting dione IV. Elution with benzene gave 1.014 g. (46%) of crystalline 6β-hydroxy-A-norcoprostanone-2-one (VI), m.p. 115–118°. After two recrystallizations from petroleum ether an analytical sample was obtained in the form of white blades, m.p. 119–121°, $[\alpha]^{25}D$ −22° (*c* 1.17); $\lambda_{max}^{CS_2}$ 2.80, 2.92 and 5.77 μ.

Anal. Calcd. for $C_{26}H_{44}O_2$ (388.61): C, 80.35; H, 11.41. Found: C, 80.52; H, 11.52.

The acetate was prepared by warming a sample of hydroxyketone with acetic anhydride on the steam-bath for 1 hour. The acetic anhydride was removed by distillation at reduced pressure and the residue dried under high vacuum. The product was recrystallized three times from methanol to give white needles, m.p. 108–109°, $[\alpha]^{30}D$ −37° (*c* 2.63); $\lambda_{max}^{CS_2}$ 5.78, 8.10 μ.

Anal. Calcd. for $C_{28}H_{46}O_3$ (430.65): C, 78.09; H, 10.77. Found: C, 77.80, H, 10.73.

Further elution with benzene–ether (9:1) gave 0.867 g. (39%) of 6α-hydroxy-A-norcoprostane-2-one (V) as long

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(15) Unless otherwise noted, all melting points were obtained using a calibrated Köfler melting point block. All rotations were taken in chloroform using a 1-dm. tube. All analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California.

silky needles. Recrystallization from acetone–petroleum ether gave material which crystallized in such a manner as to look like cotton, m.p. 130–133°. An additional recrystallization yielded an analytical sample, m.p. 135–136°, mixed m.p. with 6β-epimer 107–124°, $[\alpha]^{25}D$ −60° (*c* 0.97); $\lambda_{max}^{CS_2}$ 2.80, 2.95 and 5.77 μ.

Anal. Calcd. for $C_{26}H_{44}O_2$ (388.61): C, 80.35; H, 11.41. Found: C, 80.45; H, 11.62.

The acetate was prepared as described above. Recrystallization from methanol after passing through a column of alumina gave colorless needles. Two additional recrystallizations gave an analytical sample, m.p. 104–105°, $[\alpha]^{25}D$ −53° (*c* 1.20); $\lambda_{max}^{CS_2}$ 5.77, 8.04 μ.

Anal. Calcd. for $C_{28}H_{46}O_3$ (430.40): C, 78.09; H, 10.77. Found: C, 77.79; H, 10.76.

Δ⁶-A-Norcoprostene-2-one (VII).—A solution of 726 mg. (1.86 mmoles) of 6β-hydroxy-A-norcoprostane-2-one (VI) in 17 ml. of dry pyridine was cooled to ice temperature and treated, dropwise, with 4.5 ml. of phosphorus oxychloride. The mixture was allowed to stand at room temperature for 24 hours and the resulting red-brown mixture decomposed by the cautious addition of water. The solution was extracted with ether, the ethereal solution washed with 10% hydrochloric acid, water and saturated salt solution and dried. The solvent was evaporated and the crystalline residue (590 mg., 83.3%, m.p. 78–80°) was recrystallized from ether–methanol; m.p. 84–85°, $[\alpha]^{25}D$ −77° (*c* 1.53), $\lambda_{max}^{CS_2}$ 5.77 and 14.1 μ. The compound was stable to reflux in acid or base.

Anal. Calcd. for $C_{26}H_{42}O$ (370.60): C, 84.26; H, 11.42. Found: C, 84.01; H, 11.27.

Δ⁶-A-Norcoprostene-2α-ol (X).—A solution with 0.097 g. (0.26 mmole) of Δ⁶-A-norcoprostene-2-one (VII) in 20 ml. of 95% ethanol was treated with 0.20 g. of sodium borohydride in 20 ml. of 95% ethanol at room temperature. The reaction mixture was allowed to stir for 2 hours. At the end of this period, the reaction was decomposed with dilute hydrochloric acid and extracted with ether. The ether extracts were washed successively with water, dilute sodium bicarbonate solution and saturated salt solution, dried and the solvent evaporated. The oily residue was dissolved in ethanol containing a few drops of water and crystallization induced by scratching. The product was obtained as short, colorless needles, yield 0.056 g. (58%), m.p. 55–57°. Recrystallization from aqueous ethanol afforded material with m.p. 60–61°; $\lambda_{max}^{CS_2}$ 2.80, 3.00, 3.30 and 13.65 μ. In some runs it was necessary to chromatograph to obtain crystalline product.

Anal. Calcd. for $C_{26}H_{44}O \cdot {}^1/_2H_2O$ (381.63): C, 81.75; H, 11.89. Found: C, 81.11; H, 11.67.

A-Norcoprostane-2-one.—A solution of 103 mg. (0.28 mmole) of Δ⁶-A-norcoprostene-2-one (VII) in 35 ml. of ethanol and 20 mg. of 5% palladium-on-charcoal catalyst was shaken in a hydrogen atmosphere until hydrogen absorption ceased. The catalyst was removed and the solvent evaporated. The residual A-norcoprostane-2-one (100 mg., 98%) was recrystallized twice from ether–methanol, yield 61 mg. (59%), m.p. 107–109°, mixed m.p. with authentic sample 107–109°, $[\alpha]^{25}D$ −43°.

Δ³⁽⁵⁾-A-Norcholestene-2-one (I) from V.—A solution of 445 mg. (1.14 mmoles) of 6α-hydroxy-A-norcoprostane-2-one (V) in 12 ml. of dry pyridine was cooled to ice temperature and treated, dropwise, with 3.0 ml. of phosphorus oxychloride. The red solution was allowed to remain at room temperature for 24 hours and then processed in the usual manner. The residual material (182 mg., 42.8%, λ_{max}^{EtOH} 235 mμ (ε 10,000), $\lambda_{max}^{CS_2}$ 5.86 and 6.17 μ) was purified by chromatography on neutral Woelm alumina (Act. III). Elution with petroleum ether–benzene (1:1) gave crystalline material and recrystallization of the solid from ether–methanol gave Δ³⁽⁵⁾-A-norcholestene-2-one, m.p. 85–87°, yield 100 mg. (23.7%), $[\alpha]^{25}D$ −14° λ_{max}^{EtOH} 235 mμ (ε 15,500). As reported earlier,[4] the material is dimorphic with m.p. 87–88° and 96–97°.

A-Norcoprostane-2α,6α-diol (VIII).—To a stirred solution of 0.1 g. (0.257 mmole) of 6α-hydroxy-A-norcoprostane-2-one (VI) in 20 ml. of 95% ethanol, there was added 100 mg. of sodium borohydride in 30 ml. of 95% ethanol. The reaction mixture was allowed to stir overnight at room temperature and then decomposed by the addition of dilute hydrochloric acid. Water was added and the mixture was extracted with ether and the ethereal extracts washed with water, saturated salt solution and dried. The solvent was evaporated and the white crystalline residue (m.p. 165–170°, yield 95 mg. (94.5%)) was recrystallized twice from petroleum ether–ether; m.p. 177–178°, $[\alpha]^{25}D$ +15° (*c* 0.86, chf.).

Anal. Calcd. for $C_{26}H_{46}O_2$ (390.63): C, 79.94; H, 11.87. Found: C, 79.76; H, 11.75.

A-Norcholesterol (III).—A solution of 0.40 g. (1.02 mmoles) of A-norcoprostane-2α,6α-diol (VIII) and 0.90 g. (4.7 mmoles) of *p*-toluenesulfonyl chloride in 15 ml. of dry pyridine was allowed to stand at room temperature overnight. The reaction mixture was processed in the usual manner and there was obtained 0.36 g. of a clear oil which could not be obtained crystalline. The infrared spectrum indicated the material was a ditosylate.

A solution of the above oily ditosylate in 20 ml. of dimethylformamide was added to a solution of 7.3 g. of potassium acetate in 4 ml. of water and 20 ml. of dimethylformamide. The resulting solution was heated at 105° for 5 hours, poured into cold dilute hydrochloric acid and the mixture extracted with ether. The ethereal extracts were washed with water, saturated salt solution and dried. The solvent was evaporated and the infrared spectrum of the residual oil (0.21 g.) possessed bands at 5.78 and 8.1 μ, indicative of an acetoxyl group. The crude material was chromatographed on neutral Woelm alumina (Act. III) and from the petroleum ether eluates there was obtained 32 mg. of the diene hydrocarbon X. Elution with petroleum ether–benzene gave 120 mg. of an oily acetate which could not be obtained crystalline. The oily material was saponified with 25 ml. of 5% methanolic potassium hydroxide and the reaction product isolated in the standard manner. The 110 mg. of colorless oil, which slowly solidified when triturated with methanol, was dissolved in 20 ml. of 95% ethanol and to this solution there was added a solution of 550 mg. of digitonin in 27 ml. of 70% ethanol. After standing overnight in the refrigerator, the white digitonide was filtered, yield 220 mg. The solid was dissolved in 5 ml. of dry pyridine and the pyridine solution diluted with 75 ml. of ether. The precipitated digitonin was filtered and the filtrate was washed with dilute hydrochloric acid, water and saturated sodium chloride solution. The dried solution was evaporated and the crystalline residue recrystallized from methanol; yield 55 mg. (14.5% based on starting diol), m.p. 102–105°. Two additional recrystallizations from methanol gave an analytical sample, m.p. 105–108°, $[\alpha]^{20}D$ −27° (*c* 0.49).

Anal. Calcd. for $C_{26}H_{44}O \cdot {}^1/_2H_2O$ (381.61): C, 81.75; H, 11.88. Found: C, 81.32; H, 11.67.

Attempted Formation of Δ²,⁵-A-Norcholestadiene-3-ol Acetate (II).—A solution of 0.2 g. (0.54 mmole) of A-norcholestenone (I), 0.2 g. of *p*-toluenesulfonic acid and 20 ml. of acetic anhydride was heated under reflux for 12 hours and then 12 ml. of acetic anhydride allowed to distil. An additional 20 ml. of acetic anhydride was added to the reaction and the heating continued for an additional 12 hours. The solvent was removed by distillation and the residue added to an aqueous solution of sodium bicarbonate. The mixture was extracted with ether and the ethereal extracts washed with sodium bicarbonate and water. The dried solution was concentrated to yield 0.21 g. of a brown sirup, $\lambda_{max}^{Heptane}$ 227 mμ (ε 6,000) and 255 mμ (ε 4,000). The infrared spectrum showed strong bands at 5.70, 5.86 and 8.4 μ, attributable to the acetate and the cyclopentenone carbonyl groups. Also, there was a strong band at 6.06 μ.

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