Synthesis of Bridged Steroids. I. Steroids having a Bridged Bicyclo[3.2.1]octane Ring System of the Phyllocadene Type

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Steroidal derivatives having a bicyclo[3.2.1]octane bridged ring of the phyllocadene type on the A ring such as compounds (IVa), (IVb), (XXIV) and (VIIa) were synthesized starting from 5α-cyanocholestan-3-one by three routes. The route consisting of conversion of the cyano group into an acetyl group, and subsequent cyclization was found to be most preferable for the synthesis.

A considerable number of bridged ring compounds having interesting biological properties have been found in the diterpene field. For instance, gibberellins are known as plant-growth regulating hormones, 2) and some diterpene alkaloids have been well noted because of their high toxic properties. 3) We have been interested in preparing steroids which contain such bridge systems as those found in the diterpene field, since it was hoped that such hybrid molecules might show some unique pharmacological activities, and since the work would

![Chemical structures](image)

Chart 1

1) Location: Fukuishima-kas, Osaka.
serve as a model experiment for syntheses of representative diterpenes and diterpene alkaloids. In this paper, we describe syntheses of some steroid bicyclo[3.2.1]octane systems of the phyllocadene (I) type.

As the starting compounds, 5α-cyano-3-keto steroids (II) were selected, since the materials were easily available by applying the new hydrocyanation methods, discovered recently in our laboratory, to the corresponding Δ4-3-keto steroids. At the outset of the work, two routes were designed starting from compounds (II). The first route consisted of initial attachment of the necessary two-carbon chain to the 3α-position utilizing the C3-keto function and cyclization of the resulting intermediates (III) or (V) (X represents a suitable leaving group such as tosyloxy) either by the Dieckmann condensation or substitution reaction giving IV or VI. The second route was to lengthen the angular cyano group to a two-carbon chain giving VII for instance which was then cyclized to VIII of the desired ring system by the Claisen condensation.

For attaching a two-carbon chain to the C3-position, the triethyl phosphonoacetate condensation, instead of the Reformatsky reaction, was applied to 5α-cyano-3-ketosteroids

![Chemical Structures]

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(IIa)\(^6\) and (IIb)\(^6a,6b,10\) in view of the fact that the latter reaction generally gives a mixture of double bond isomers and therefore makes work-up difficult. After treatment with sodium triethyl phosphonoacetate, compounds (IIa) and (IIb) gave the crystalline \(\alpha,\beta\)-unsaturated acid esters (IXa) and (IXb), but each of the products was found to be a mixture of two geometrical isomers as judged by the wide range of their melting points. Catalytic hydrogenation of IXa and IXb using platinum oxide afforded the \(3\alpha\)-carbethoxymethyl derivatives (IIIa) and (IIIb). The former was obtained as a sole product, and the latter was contaminated with a minor amount of X. The stereochemical assignment was based upon the favorable attack of hydrogen on the catalyst surface from the less-hindered \(\beta\)-side and also upon the later successful cyclization. The side chain of the minor product (X) was assigned a \(3\beta\) configuration. Compounds (IIIa) and (IIIb) were next subjected to the Dieckmann condensation. Whereas the 19-nor steroid (IIIa) was cyclized by the usual treatment; i.e., by refluxing the toluene solution in the presence of potassium tert-butoxide, to the desired crystalline enaminocetone ester (IVa) in 27\% yield, the corresponding normal steroid (IIIb) could not be cyclized under the same conditions. This marked contrast may be explained by the assumption that the probable transition state such as XI requires more energy in the case of the normal steroid compound (IIIb) because of the increased rigidity of the molecule as compared with the 19-nor steroid. In accordance with this interpretation compound (IIIb) could be cyclized to the oily enaminocetone ester (IVb) in a yield of about 45\% by changing the reaction medium from toluene to ether. It is quite reasonable that stabilization of the considerably polarized transition state (XI) in such a polar medium might overcome the difficulty of the formation arising from the high steric hindrance. The structural assignment of the products (IVa) and (IVb) was based on the absorption band at 293 m\(\mu\) in the ultraviolet\(^{11}\) as well as the bands at 3529, 3337, 1651, 1614, and 1532 cm\(^{-1}\) for IVa and at 3563, 3335, 1645, 1613, and 1527 cm\(^{-1}\) for IVb in the infrared. An attempt to convert the enaminocetone esters into the \(5\alpha\)-keto bridged compounds (XIIa) and (XIIb) was unsuccessful. Hydrolysis with base or acid or deamination with nitrous acid and subsequent decarboxylation gave an intractable mixture of various products. While our work along this line was interrupted, Kundu and Dutta\(^9\) reported a successful synthesis of the bridged compound (XV) starting from the 9-cyano-\textit{trans}--2--decalone (XIII) \textit{via} a similar intermediate (XIV). The cyclization step was carried out in almost the same manner as used by us. The difference between the two cases may be ascribed to the marked difference in rigidity of the molecules. Although a reagent can easily attack an angular functional group in the bicyclic series, this is not the case in the tetracyclic series. Such a trend of lowering reactivity of angular functional groups and also of increasing difficulty in introducing a carbon substituent into an angular position with increasing ring number of polycyclic systems is well observed in the literature.\(^10,12\)

Since application of the Dieckmann condensation to cyclization is unsatisfactory because of its reversible character, and conversion of the resulting enaminocetone esters into compounds of the bridged cyclopentanone system failed, we next examined another process (a\(_9\)) (in Chart 1) involving a favorable irreversible substitution reaction. 5\(\alpha\)-Hydroxymethylcholestan-3-one 3-ethylene ketal (XVIa)\(^{19}\) was converted into its acetate (XVIIc), which was then deketalized to the ketol acetate (XVIIc). Compound (XVIIc) was treated with sodium triethyl phosphonoacetate in 1,2-dimethoxyethane at 80\(^\circ\), and the resulting mixture was subjected to alumina chromatography. The desired \(\alpha,\beta\)-unsaturated ester (XVIII), 4,\(5\alpha\)-cyclopropano ketone (XIX), the hydrolysis product (XX) and the lactonic compound (XXI) were isolated in yields of 14,16.5, and 6\%, respectively, together with a 2\% yield of the starting

compound (XVIIc). Compound (XVIII) showed an absorption band at 226 m\(\mu\) (\(\epsilon=16500\)) indicating the assigned structure. The presence of a conjugated cyclopropane system in compound (XIX) is evident from the fact that the compound showed a band at 209 m\(\mu\) (\(\epsilon=6400\)) in the ultraviolet, a band at 3093 cm\(^{-1}\) corresponding to CH of cyclopropane in the infrared, and no signal of the olefinic proton in the NMR spectrum. The same compound was also obtained from compound (XVIIb) by treatment with aqueous acetic acid. This fact also supports the assigned structure (XIX). In contrast to 5\(\alpha\)-methylochrolstan-3-one,\(^{14}\) compound (XIX) showed a strong negative Cotton effect in the ORD curve.\(^{15}\) Compound (XX) is known\(^{19}\) and identified. Assignment of the lactonic structure to compound (XXI) was based only upon the elementary analysis and the bands at 3609 and 1762 cm\(^{-1}\) due to a hydroxyl and a \(\gamma\)-lactone group, respectively, in the infrared, and therefore tentative. Catalytic hydrogenation of compound (XVIII) and subsequent hydrolysis and esterification gave two epimeric products (XXII) and (XXIII) in yields of 10\% and 24\%, respectively. The 3\(\alpha\)-configuration was assigned to the carbethoxymethyl group of the minor product (XXII) from the later cyclization to a cyclopentane derivative. The reverse steric course in the hydrogenation of XVIII as compared with that of the corresponding 5\(\alpha\)-cyano derivative (IX) is surprising. However, this may be rationalized by assuming a directing effect of the acetoxy group arising from its absorption on the catalyst surface.\(^{16}\) When the compound (XXII), in which both functional groups are situated in a cis relation, was treated with \(\rho\)-toluenesulfonyl chloride in pyridine at room temperature, spontaneous cyclization took place to afford the desired bridged product (XXIV) in 65\% yield, whereas the epimeric compound (XXIII) normally gave the tosylate (XXV). Although the facile cyclization in this example realized our expectation that an irreversible reaction would be much more advantageous for construction of a bridged ring system at an angular position of a polycyclic system, the observed low yield in the condensation step of XVII→XVIII is intolerable.

We next investigated the second route (b) involving initial conversion of the angular cyano group into a two-carbon chain with an appropriate functional group. It has been known from evidence accumulated in this laboratory that a 5\(\alpha\)-cyano group in steroids, more generally a trans-oriented angular cyano group in a polycyclic system, resists the usual addition reaction

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with an alkylating agent, as predicted from its neopentyl type situation. For instance, the cyano ketal (XXIX)\(^{14}\) derived from the cyano ketone (IIb) by the usual ketalization shows complete reluctance to the Grignard reaction. However, in the course of our study, Haworth \textit{et al.}\(^{15}\) reported the successful formation of a bicyclo[3.2.1]octane bridged ring in the bicyclic series. In this work, performed along the same line as ours, methylaluminum was used to convert the \textit{trans}-oriented angular cyano group of the decalone derivative (XXVI) into an acetyl group giving the diketone (XXVII), which was then cyclized to the bridged compound (XXVIII). Although the work was quite instructive, it was not known whether the same reaction could be successfully applied to a tetracyclic analog. The process proved to be quite applicable. Thus, treatment of the cyano ketal (XXIX) with methyl lithium gave a crystalline product of mp 114—116°/123—130° which showed bands at 3238 and 1635 cm\(^{-1}\) ascribable to an imino group in the infrared and an additional sharp methyl signal at 8.07\(\tau\) in the NMR spectrum supporting the assigned structure of XXX. Hydrolysis of this compound with an aqueous mineral acid gave in 84\% over-all yield from XXIX the diketone (VII), which was then cyclized to the bridged ketol (VIII\(a\)) by treatment with aqueous alkali in a yield of 94\%. The structural assignment of this compound is based on the bands at 1731 cm\(^{-1}\) in the infrared spectra and the absence of an additional angular methyl signal in the NMR spectra of both the ketol (VIII\(a\)) and its acetate (VIII\(b\)) eliminating another possible structure (XXXI) or (XXXII). Moreover, the compounds (VIII\(a\)) and (VIII\(b\)) showed strong negative Cotton effects in the ORD curves in good accordance with the description of Henderson and Hodges\(^{18}\) that the phyllocladene nor-ketone (XXXIV) shows a positive Cotton effect, whereas the isomeric nor-ketone (XXXIII) a negative one.

\(^{18}\) R. Henderson, and R. Hodges, \textit{Tetr.}, 11, 228 (1960).
The work aimed at building up the bicyclo[3.2.1]octane bridged ring of the phyllocadene type on the steroidal A-ring was thus accomplished through three routes. As clear from the above discussions, the last route is most preferable from the viewpoint of fewer reaction steps, high selectivity and a better over-all yield.

**Experimental**

Ethyl 17β-Acetoxy-5α-cyanoestran-3-ylideneacetate (IXa) — To a suspension of NaH (350 mg) in 1,2-dimethoxyethane (50 ml) was added dropwise triethyl phosphonoacetate (3.25 g) with stirring and ice-cooling, and the mixture was stirred for 30 min at room temperature. To the resulting clear solution was added a solution of 5α-cyanoestran-17β-ol-3-one 17-acetate (IIa) (5.00 g) in 1,2-dimethoxyethane (160 ml) with stirring and ice-cooling, and the resulting mixture was stirred for 2 hr at room temperature, mixed with ice-water, and extracted with CHCl₃. The CHCl₃-layer was washed with H₂O, dried over Na₂SO₄, and evaporated. The residue was chromatographed on neutral Al₂O₃ (125 g). Fractions eluted with petroleum ether:benzene (2:1) — benzene were recrystallized from acetone to give IXa (1.544 g), mp 200—205°. An additional crop of IXa (3.03 g), mp 175—180°, was obtained from the mother liquor. The total yield is 76%. In another experiment, two geometrical isomers of IXa were separated by chromatography on neutral Al₂O₃ and recrystallization. Fractions eluted with petroleum ether:benzene (1:4) — benzene, on recrystallization from acetone, gave an isomer of mp 211—212.5°, [α]D⁰ +116.3 ± 3° (CHCl₃, ε = 1.031). Anal. Calcd. for C₂₃H₂₉O₅N: C, 72.60; H, 8.53; N, 3.39. Found: C, 72.56; H, 8.52; N, 3.42. UV λmax nm μ (e): 219 (17400). IR νmax cm⁻¹: 1540, 1718, 1662. Fractions eluted with petroleum ether—benzene (4:1) — (2:1), were recrystallized from acetone, giving, besides the above isomer, another isomer as big granular crystals, mp 198—202°, which were separated by picking up with a pinocette. The mixed melting point of both isomers was 178—185°. [α]D⁰ =—8.8 ± 2° (CHCl₃, ε = 1.030). Anal. Calcd. for C₂₃H₂₉O₅N: C, 72.60; H, 8.53; N, 3.39. Found: C, 72.33; H, 8.50; N, 3.16. UV λmax nm μ (e): 219 (17800). IR νmax cm⁻¹: 2235, 1718, 1658.

Ethyl 5α-Cyanoestran-3-ylideneacetate (IXb) — A reagent solution prepared by adding triethyl phosphonoacetate (7.87 g) to a suspension of NaH (843 mg) in 1,2-dimethoxyethane (60 ml) was mixed with a solution of 5α-cyanoestran-3-one (IIb) (11.124 g) in 1,2-dimethoxyethane (100 ml) in the same manner as described above. The reaction mixture was worked up in a similar manner as in the preparation of IXa, and the residue was recrystallized from CHCl₃-MeOH to give IXb (11.851 g, 86%), mp 129—132°. A pure sample melts at 133—134°. Anal. Calcd. for C₂₃H₂₉O₅N: C, 78.78; H, 10.67; N, 2.91. Found: C, 78.08; H, 10.70; N, 3.04. UV λmax nm μ (e): 221 (18100). IR νmax cm⁻¹: 2242, 1720, 1626.

Ethyl 17β-Acetoxy-5α-cyanoestran-3-ylacetate (IIIa) — Compound (IXa) (a mixture of the geometrical isomers) (4.712 g) dissolved in HClOAc (100 ml) was hydrogenated over platinum [from PtO₂·H₂O (650 mg)]. The catalyst was filtered, the filtrate concentrated to dryness in vacuo, and the residue chromatographed on neutral Al₂O₃ (125 g). Fractions eluted with petroleum ether:benzene (4:1) — CHCl₃ were recrystallized from MeOH to give IIIa (3.618 g, 77%), mp 140—141°. Further recrystallization did not raise the melting point. [α]D⁰ =—4.9 ± 2° (CHCl₃, ε = 1.007). Anal. Calcd. for C₂₃H₂₉O₅N: C, 72.25; H, 8.98; N, 3.37. Found: C, 72.13; H, 8.64; N, 3.51. IR νmax cm⁻¹: 2225, 1727.

Ethyl 5α-Cyanoestran-3-ylacetate (IIIb) and Ethyl 5α-Cyanoestran-3-β-acetate (X) — Compound (IXb) (11.117 g) dissolved in HClOAc (330 ml) was hydrogenated in the presence of PtO₂·H₂O (2.00 g), and the reaction mixture was worked up in the same manner as used for IIIa. The residue was recrystallized from MeOH to give IIIb (6.714 g), mp 105—106.5°. The residue of the mother liquor was chromatographed on neutral Al₂O₃ (125 g). Fractions eluted with petroleum ether:benzene (9:1—6:1) were recrystallized from CHCl₃-MeOH to give an additional crop of IIIb (1.015 g), mp 104.5—106°. The total yield is 7.729 g (69%). Fractions eluted with petroleum ether: benzene (2:1) were recrystallized from CHCl₃—MeOH to give X (0.586 g, 6%), mp 122—123°.


3a,5α-Etheno-5α-amino-3α-carbethoxyestrar-17β-ol (IVa) — To a refluxing solution of t-BuOK [prepared from K (2.0 g) and t-BuOH and sublimed] in abs. toluene (50 ml) was added dropwise a solution of IIla (600 mg) in abs. toluene (50 ml) over a period of 30 min, and the resulting mixture was refluxed for 2.5 hr. After cooling, it was worked up with HClOAc (7 ml) and mixed with ice. The mixture was extracted with CHCl₃ and CHCl₃—ether (1:3). The combined organic layers were washed with 2× K₂CO₃ and H₂O, dried, and evaporated to give a neutral residue (442 mg). The aqueous layer was acidified with 2× HCl and extracted with CHCl₃. The CHCl₃ layer was washed with H₂O, dried, and evaporated to give an acidic residue (94 mg, 18%). Recrystallization of the neutral residue from CHCl₃-MeOH gave IVa (145 mg, 27%), mp 220—242° (decomp.). A pure sample melts at 252—263° with decomposition. [α]D⁰ =—28.4 ± 5°.
(CHCI₃, c=0.335). Anal. Calcd. for C₈₆H₁₆₀N₄: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.50; H, 8.99; N, 3.78. UV λmax (μ: e): 293 (>6000). (The ε value was not determined correctly because the sample is sparingly soluble in CHCl₃. IR νCHCl₃ cm⁻¹: 3529, 3337, 1561, 1614, 1532.

3α,5α-Etheno-5α-aminoo-3a-carbethoxycholestan (IVb)—-Potassium (2.0 g) was dissolved in abs. t-BuOH (50 ml); the bulk of excess t-BuOH was evaporated in vacuo, and the last traces are removed by codistillation with abs. benzene (30 ml x 3). The residue, after being heated until t-BuOK began to sublime, was suspended in abs. ether (30 ml). The resulting suspension was heated to reflux, and a solution of HIb (1.0 g) in abs. ether (15 ml) was added dropwise with stirring under nitrogen over a period of 25 min, and the refluxing and stirring were continued for 1 hr. After cooling, the reaction mixture was poured into 2 N HCl (35 ml) ice and extracted with ether:CHCl₃ (3:1). The organic layer was washed with 2 N K₂CO₃ and H₂O, dried, and evaporated to give a neutral product (461 mg, 45%) as an oil, IR νCHCl₃ cm⁻¹: 3563, 3335, 1643, 1613, 1527. The aqueous layer was acidified with dil. HCl and extracted with CHCl₃-ether (3:1). The usual work-up an acidic product (544 mg, 55%), which was recrystallized from MeOH to give crystals of mp 195--196°. IR νCHCl₃ cm⁻¹: 2680 (broad), 2228, 1709.

3,3'-Ethyleneoxy-5α-hydroxy methylcholestan Tosylate (XVIb)—A solution of XViib (500 mg) in pyridine (10 ml) was mixed with tosyl chloride (1 g), and the mixture was kept standing for 2 days at room temperature. Ice was added thereto, and the resulting mixture was let stand for 1 hr at room temperature, poured into 4 N H₂PO₄ (50 ml) ice, and extracted with ether:CHCl₃ (3:1). The organic layer was washed with H₂O, 2 N Na₂CO₃ and H₂O, dried and evaporated. The residue was recrystallized from ether to give Xvib (583 mg, 88%), mp 106—107° (decomp.). [α]D²⁰ = -17.0 ± 2° (CHCl₃, c=0.996). Anal. Calcd. for C₈₆H₁₆₁O₆S: C, 72.27; H, 9.51; S, 5.21. Found: C, 72.34; H, 9.54; S, 5.30. IR νCHCl₃ cm⁻¹: 1602, 1372, 1188, 1178, 1090.

3,3'-Ethyleneoxy-5α-hydroxy methylcholestan Acetate (XVic)—-A mixture of Xvib (2146 g), pyridine (40 ml), and Ac₂O (20 ml) was let stand for 2 days at room temperature. The residue obtained from the usual work-up was recrystallized from acetone–MeOH to give Xvicer (2085 g, 89%), mp 106—107°. A pure sample was melted at 107—108°, [α]D²⁰ = +1.8 ± 2° (CHCl₃, c=1.022). Anal. Calcd. for C₈₆H₁₃O₈: C, 76.44; H, 10.83. Found: C, 76.29; H, 10.82. IR νCHCl₃ cm⁻¹: 1741, 1246, 1900.

5α-Hydroxy methylcholestan-3-one Acetate (XVic)—A solution of the residue from MeOH gave Xvic (1.694 g, 91%), mp 116—117°. A pure sample was melted at 117—118°, [α]D²⁰ = +30.7 ± 2° (CHCl₃, c=1.022). Anal. Calcd. for C₈₆H₁₅O₃: C, 78.55; H, 10.99. Found: C, 78.71; H, 11.04. IR νCHCl₃ cm⁻¹: 1745, 1712, 1233. ORD: [α]D²⁰ = -1700; [α]D²⁰ = +2340 (dioxane, c=0.509).

Reaction of Xvib with Triethyl Phosphonoacetate—To a stirred suspension of NaH (122 mg in 1,2-dimethoxyethane (10 ml) was added dropwise a solution of triethoxyphosphonoacetate (1.137 g) in 1,2-dimethoxyethane (2ml) with ice-cooling under nitrogen over a period of 10 min, and the mixture was kept under the same conditions until a clear solution was obtained. Thereto was added a solution of XVb (1.552 g) in 1,2-dimethoxyethane (18 ml); the mixture was heated at 80° for 2 hr. (XVic did not react at room temperature). The reaction mixture was poured into ice-water and extracted with CHCl₃-ether (1:4). The ether layer was washed with 2 N NaOH and H₂O, dried and evaporated. The residue was chromatographed on neutral Al₂O₃ (60 g). Fractions No. 5—9 eluted with petroleum ether–benzene (2:1) were recrystallized from ether–MeOH to give Xviiib (225 mg, 14%), mp 107.0—109.5. Anal. Calcd. for C₈₆H₁₄O₃: C, 77.22; H, 10.67. Found: C, 77.73; H, 10.84. UV λmax (μ: e): 226 (16500). IR νCHCl₃ cm⁻¹: 1745, 1715, 1642, 1240. Fractions No. 10—18 eluted with petroleum ether–benzene (2:1)—(8:1) were recrystallized from ether–MeOH to give XIX (213 mg, 16%), mp 134—135°. [α]D²⁰ = +11.5 ± 2° (CHCl₃, c=1.125). Anal. Calcd. for C₈₆H₁₄O₃: C, 84.35; H, 11.63. Found: C, 84.32; H, 11.59. UV λmax (μ: e): 290 (6400), 276 (39). UV λmax (μ: e): 195 (7700), 269 (128). IR νCHCl₃ cm⁻¹: 3093, 809, 855. ORD: [α]D²⁰ = +820, [α]D²⁰ = -4200, [α]D²⁰ = -3900, [α]D²⁰ = -4098, (dioxane, c=0.541). Δεmax = -5100, Δεmax = +10450, Δεmax = +10450, MeOH, c=0.400. NMR (in CDCl₃) no olefinic H. Fraction No. 20 (35 mg) eluted with benzene consists of XVic (confirmed by mixed mp and comparison of IR-spectra). Fractions No. 24—25 eluted with benzene–CHCl₃ (1:1) were recrystallized from CHCl₃–MeOH to give XX (98 mg, 6%), mp 251—255°, [α]D²⁰ = +31.1 ± 2° (CHCl₃, c=1.050). Anal. Calcd. for C₈₆H₁₄O₃: C, 78.96; H, 11.18 (for C₈₆H₁₄O₃: C, 78.55; H, 10.99). Found: C, 78.96; H, 11.02. IR νCHCl₃ cm⁻¹: 3609, 1762. NMR (in CDC₁₃): τ: ca. 5.6 (2H, quartet, –C₃H₂OH). Fraction No. 26—28 eluted with CHCl₃ were recrystallized from ether–MeOH to give XX (79 mg, 5%), mp 203—208°.

Deketalization of Xvib to XVIII and XIX—A mixture of Xvib (508 mg), tetrahydrofuran (25 ml), and 2 N H₂SO₄ (2.5 ml) was refluxed for 15 min. The mixture was concentrated in vacuo, poured into ice-water, and extracted with ether:CHCl₃ (4:1). The organic layer was washed with 2 N Na₂CO₃ and H₂O, dried and evaporated. Fractional crystallization of the residue (371 mg) from ether gave Xvib (51 mg, 11%), mp 116—117°, and XIX (70 mg, 21%), mp 132—134.5°. XVib, [α]D²⁰ = +5.8 ± 2° (CHCl₃, c=1.041). Anal. Calcd. for C₈₆H₁₄O₃: C, 73.64; H, 9.54; S, 5.62. Found: C, 73.65; H, 9.53; S, 5.64. IR νCHCl₃ cm⁻¹: 1714, 1601, 1377, 1191, 1179. ORD: [α]D²⁰ = -1620, [α]D²⁰ = +203 (dioxane, c=0.502). For physical constants
of XIX see above. In another experiment in which XVIb was heated in 86% HOAc at 100° for 45 min, only XIX was isolated.

Hydrogenation of XVIII followed by Hydrolysis and Esterification to XXII and XXIII—Compound XVIII (238 mg) dissolved in HOAc (15 ml) was hydrogenated in the presence of PtO-2H2O (53 mg) for 2 hr. The catalyst was filtered, the filtrate was evaporated, and a mixture of the residue (242 mg, no UV maximum), 2 N NaOH (10 ml), MeOH (20 ml), and tetrahydrofuran (20 ml) was refluxed for 2 hr. The mixture was concentrated in vacuo, acidified with 2 N HCl, and extracted with ether:CHCl3 (4:1). The residue (177 mg) obtained by the usual work-up of the extract was dissolved in ether-CHCl3 and methylated with ethereal diazomethane in the usual way. The residue (180 mg) containing the methyl esters (XXII) and (XXIII) was chromatographed on neutral Al2O3 (8 g). Fractions eluted with petroleum ether-benzene (1:2) were recrystallized from ether-MeOH to give XXII (22.2 mg, 10%), mp 182—185°. IR $\nu_{\text{max}}$ cm$^{-1}$: 3630, 3500, 1741. Fractions eluted with benzene:CHCl3 (2:1) were recrystallized from ether-MeOH to give XXII (50.5 mg, 24%), mp 157—158°. IR $\nu_{\text{max}}$ cm$^{-1}$: 3630, 3520, 1734.

3a,5a-Ethano-3a-carbethoxycholestan (XXIV)—A solution of XXII (22.2 mg) in pyridine (0.5 ml) was mixed with tosyl chloride (50 mg), and the resulting mixture was kept at room temperature for 16 hr. A small amount of ice was added thereto, and the mixture was stirred for 1 hr, poured into 2 N HCl-ice, and extracted with CHCl3-ether (1:3). The residue obtained by the usual work-up of the extract was recrystallized from ether to give XXIV (14.0 mg, 65%), mp 178—180°. A pure sample melts at 177—181°. Anal. Calcd. for C31H44O2: C, 81.52; H, 11.48. Found: C, 81.36; H, 11.36. UV: end absorption at 210—350 m$. IR $\nu_{\text{max}}$ cm$^{-1}$: 1749. Color reaction with tetrani-trimethane: negative.

Methyl 5a-Tosloxy methylcholestan-3a-ylaceate XXV—A solution of XXIII (50.5 mg) in pyridine (1 ml) was mixed with tosyl chloride (100 mg), and the mixture was kept at room temperature for 16 hr. The reaction mixture was worked up in a similar manner as used for XXIV, and the residue was recrystallized from ether to give XXV (55 mg, 83%), mp 134—137°. A pure sample melts at 135—136°. [a]$^0_{D}$ +0.8° (CHCl3, c=0.997). Anal. Calcd. for C31H44O2S: C, 72.57; H, 9.62; S, 5.16. Found: C, 72.30; H, 9.68; S, 5.13. UV $\lambda_{\text{max}}$ m$: 226 (11800), 256 (435), 262 (570), 268 (520), 273 (485). IR $\nu_{\text{max}}$ cm$^{-1}$: 1740, 1601, 1371, 1181, 1176.

3,3-Ethylene oxy-5a-acetimincholestan (XXX)—A solution of XXX (2000 g) dissolved in abs. ether (40 ml) was added 0.69 a ethereal CH2Li (31.6 ml) with ice-cooling. After being kept stand at room temperature for 4 hr, the mixture was poured into ice-water and extracted with ether to give XXX, mp 114—116° (130°) (double mp). [a]$^0_{D}$ + 35.4 $\pm$ 2° (CHCl3, c=1.004). Anal. Calcd. for C31H44O2N: C, 78.92; H, 11.32; N, 2.97. Found: C, 78.87; H, 11.34; N, 2.85. IR $\nu_{\text{max}}$ cm$^{-1}$: 3238 (weak), 1635, 1190. NMR (in CDCl3) $\tau$: 8.07 (3H, singlet, CH2-C=NH).

5a-Acyloxycholestan-3-one (VII)—A mixture of crude XXX (948 mg), tetrahydrofuran (100 ml), EtOH (100 ml), and 2 N HCl (50 ml) was refluxed for 27 hr. The mixture was concentrated in vacuo and extracted with ether:CHCl3 (3:1). The residue from the extract was recrystallized from ether-MeOH to give VII (645 mg), mp 159.5—161°. The residue of the mother liquor was dissolved in benzene and the solution was passed through neutral Al2O3 (10 g). The eluate was evaporated, and the residue was recrystallized from ether-MeOH to give an additional crop of VII (76 mg), mp 151—156°. The total yield is 84%. A pure sample melts at 165—166°. [a]$^0_{D}$ + 34.8 $\pm$ 2° (CHCl3, c=1.076). Anal. Calcd. for C31H44O2: C, 81.25; H, 11.29. Found: C, 81.66; H, 11.38. IR $\nu_{\text{max}}$ cm$^{-1}$: 1171. ORD: [a]$^0_{D}$ + 4100, [a]$^b_{b}$ + 3320, [a]$^c_{c}$ + 3840, (dioxane, c=0.339).

2a,5a-Ethanocholestan-3β-ol-5a-one (VIIIa) and Its Acetate (VIIIb)—A suspension of VII (499 mg) in EtOH (25 ml) and 2 N KOH (25 ml) was refluxed for 30 min, with stirring under nitrogen. When the reaction was complete, particles came to the surface of the reaction mixture. It was poured into an aqueous NaCl solution and extracted with ether:CHCl3 (3:1). The residue from the extract was recrystallized from CHCl3-MeOH to give VIIa (409 mg, 94%), mp 174.5—176.5°. This was again recrystallized from CHCl3-MeOH using active-charcoal to afford a pure sample, mp 176—177°. [a]$^b_{D}$ + 9.9 $\pm$ 2° (CHCl3, c=1.066). Anal. Calcd. for C31H44O2: C, 81.25; H, 11.29. Found: C, 80.98; H, 11.25. IR $\nu_{\text{max}}$ cm$^{-1}$: 3612, 3454, 1731. ORD: [a]$^0_{D}$ + 2810, [a]$^b_{D}$ - 1710, [a]$^c_{D}$ - 2720, (MeOH, c=0.394). A mixture of VIIa (4.900 g), pyridine (40 ml), and Ac2O (10 ml) was refluxed for 80 min. The mixture was concentrated to dryness in vacuo, the last traces of the solvent being removed by codistillation with toluene. The residue was recrystallized from CHCl3-MeOH to give VIIIb (4.821 g, 89%), mp 127—128°. A pure sample melts at 129—130°. [a]$^0_{D}$ - 18.6 $\pm$ 2° (CHCl3, c=0.987). Anal. Calcd. for C31H44O2: C, 78.10; H, 10.71. Found: C, 78.28; H, 10.65. IR $\nu_{\text{max}}$ cm$^{-1}$: 1740, 1230. ORD: [a]$^b_{D}$ + 3890, [a]$^b_{D}$ - 1690, [a]$^c_{D}$ - 1750, [a]$^c_{D}$ - 4150, (dioxane, c=0.361).

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