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

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Steroidal derivatives having a bicyclo[3.2.1]octane bridged ring of the phyllocladene type on the A ring such as compounds (IVa), (IVb), (XXIV) and (VIIIa) 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

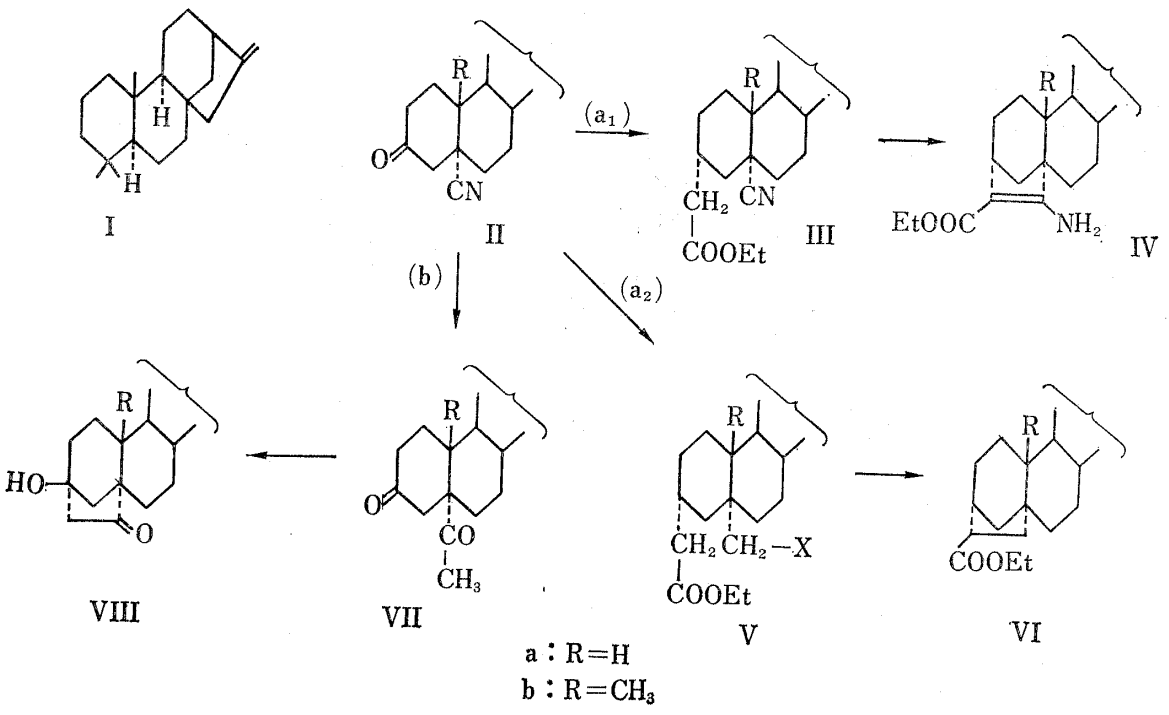

Chart 1

1) Location: *Fukushima-ku, Osaka.*

2) *a*) T. Yabuta, Y. Sumiki, K. Aso, and T. Hayashi, *J. Agr. Chem. Soc. Japan*, **17**, 1001 (1941); *b*) H. Linser, *Angew. Chem.*, **78**, 895 (1966); *c*) P.W. Brain, J.F. Grove, and J. MacMillan, "Progress in the Chemistry of Organic Natural Products," Vol. XVIII, Springer-Verlag, Vienna, **1960**, 350.

3) *a*) K. Wiesner and Z. Valenta, "Progress in the Chemistry of Organic Natural Products," Vol. XVI, **1958**, 26; *b*) E.S. Stern, "The Alkaloids, Chemistry and Physiology," Vol. VII, R.H. Manske and H.L. Holmes, Ed., Academic Press Inc., New York, N.Y., **1960**, 473; *c*) S.W. Pelletier, *Tetrahedron*, **14**, 76 (1961).

serve as a model experiment for syntheses[4,5] of representative diterpenes and diterpene alkaloids. In this paper, we describe syntheses of some steroid bicyclo[3.2.1]octane systems of the phyllocladene (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,[6] discovered recently in our laboratory, to the corresponding Δ^4-3-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 C_3-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 reaciton 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 C_3-position, the triethyl phosphonoacetate condensation,[7] instead of the Reformatsky reaction,[8,9] was applied to 5α-cyano-3-ketosteroids

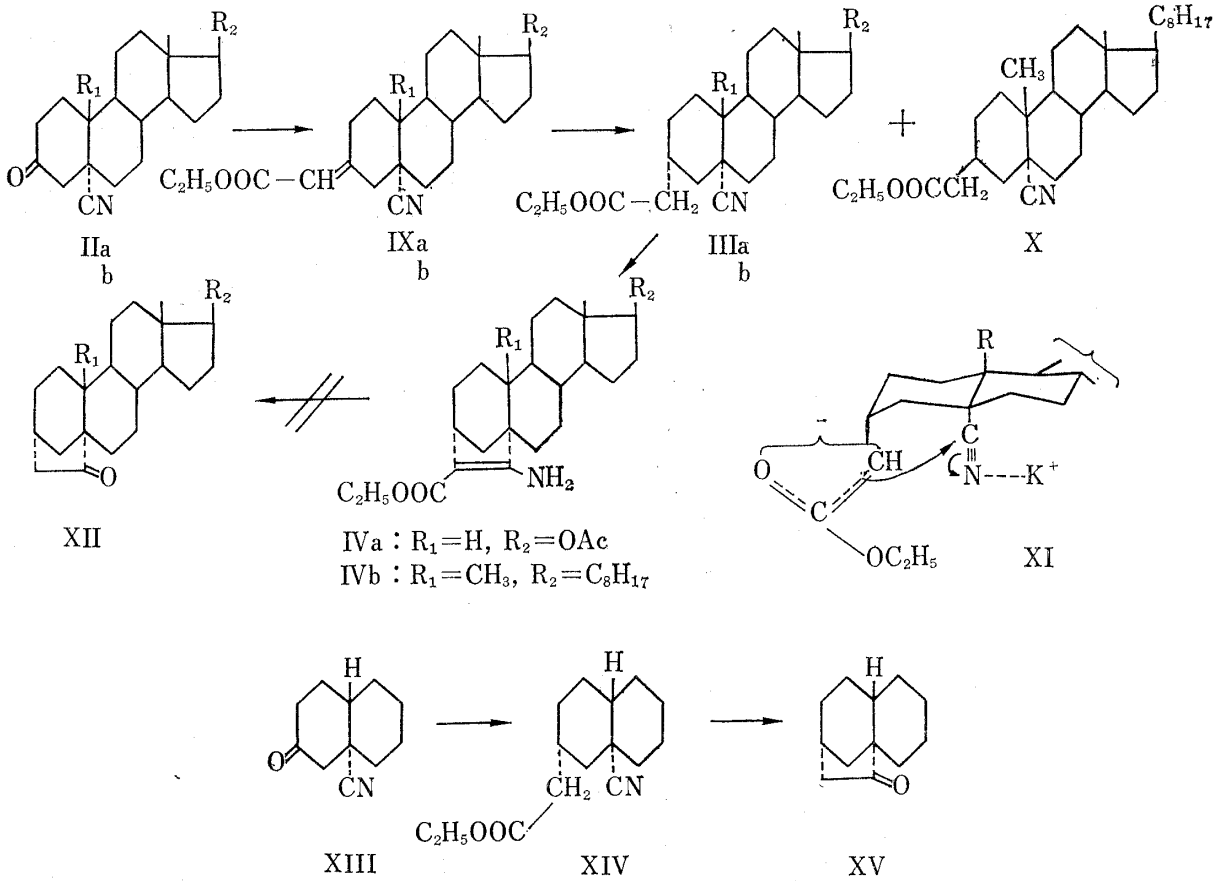

Chart 2

4) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Am. Chem. Soc.*, **85**, 2342 (1963); W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *ibid.*, **89**, 1483 (1967).
5) W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *J. Am. Chem. Soc.*, **86**, 929 (1964); W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *ibid.*, **89**, 1499 (1967).
6) *a*) W. Nagata, M. Yoshioka, and S. Hirai, *Tetrahedron Letters*, **1962**, 461; *b*) W. Nagata and M. Yoshioka, Proceedings of the 2nd International Congress on Hormonal Steroids, Milan, Italy, May 1966, Excerpta Medica Foundation, Amsterdam, 1966, p. 327; *c*) J. Fishman and M. Torigoe, *Steroids*, **5**, 599 (1965).
7) W.S. Wadsworth, Jr. and W.D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).
8) *cf.* R.B. Turner and P.E. Shaw, *Tetrahedron Letters*, No. 18, 24 (1960); R.B. Turner, K.H. Ganshirt, P.E. Shaw, and J.D. Turner, *J. Am. Chem. Soc.*, **88**, 1776 (1966).
9) N.G. Kundu and P.C. Dutta, *J. Chem. Soc.*, **1962**, 533.

(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 therfore makes work-up difficult. After treatment with sodium triethyl phosphonoacetate, compounds (IIa) and (IIb) gave the crystalline α,β-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 platinium oxide afforded the 3α-carbethoxymethyl derivatives (IIIa) and (IIIb). The former was obtained as a sole product, and the latter was contaminated wtih a minor amount of X. The stereochemical assignment was based upon the favorable attack of hydrogen on the catalyst surface from the less-hindered β-side and also upon the later successful cyclization. The side chain of the minor product (X) was assigned a 3β 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 enamino 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 enamino 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 mμ 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 enamino esters into the 5α-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-*trans*-2-decalone (XIII) *via* a similar intermediate (XIV). The cyclization step was carried out in almost the same manner as used by us. The difference between 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 enamino esters into compounds of the bridged cyclopentanone system failed, we next examined another process (a_2) (in Chart 1) involving a favorable irreversible substitution reaction. 5α-Hydroxymethylcholestan-3-one 3-ethylene ketal (XVIa)[13] was converted into its acetate (XVIc), which was then deketalized to the ketol acetate (XVIIc). Compound (XVIIc) was treated with sodium triethyl phosphonoacetate in 1,2-dimethoxyethane at 80°, and the resulting mixture was subjected to alumina chromatography. The desired α,β-unsaturated ester (XVIII), 4,5α-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

10) W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *J. Org. Chem.*, **26**, 2413 (1961).
11) *cf.* V. Prelog and S. Szpilfogel. *Helv. Chim. Acta*, **28**, 1684, (1954).
12) W. Nagata, I. Kikkawa, and M. Fujimoto, *Chem. Pharm. Bull.* (Tokyo), **11**, 226 (1963); W. Nagata and I. Kikkawa, *ibid.*, **11**, 289 (1963).
13) S. Hirai, *Chem. Pharm. Bull.* (Tokyo), **9**, 854 (1961).

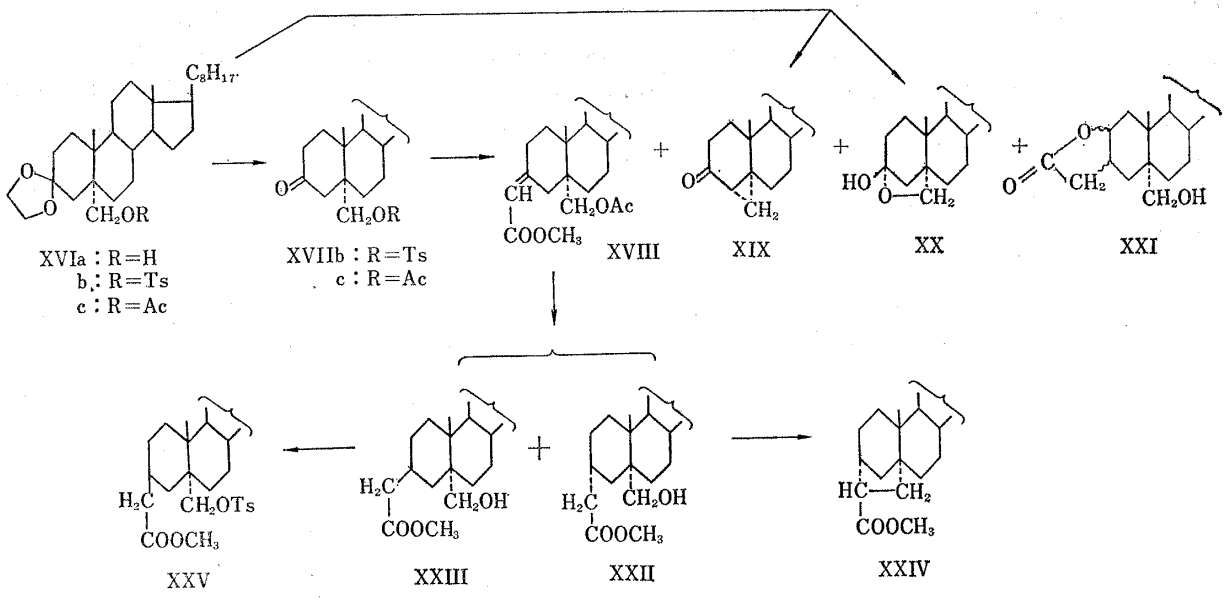

Chart 3

compound (XVIIc). Compound (XVIII) showed an absorption band at 226 mμ (ε=16500) supporting the assigend structure. The presence of a conjugated cyclopropane system in compound (XIX) is evident from the fact that the compound showed a band at 209 mμ (ε=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 (XVIb) by treatment with aqueous acetic acid. This fact also supports the assigned structure (XIX). In contrast to 5α-methylcholestan-3-one,[14] compound (XIX) showed a strong negative Cotton effect in the ORD curve.[15] Compound (XX) is known[13] 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 γ-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 3α-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 5α-cyano derivative (IX) is surprising. However, this may be rationalized by assuming a directing effect of the acetoxyl 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 *p*-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) normaly 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 5α-cyano group in steroids, more generally a *trans*-oriented angular cyano group in a polycyclic system, resists the usual addition reaction

14) W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *Liebigs Ann. Chem.*, **641**, 196 (1961).
15) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6377 (1956).
16) *a*) T.J. Howard, *Chem. Ind.* (London), **1963**, 1899; *b*) S. Nishimura and K. Mori, *Bull. Chem. Soc. Japan*, **36**, 318 (1963).

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 *et al.*[17] 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, methyllithium was used to convert the *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 wherther the same reaction could be successfully applied to a tetracyclic analog. The process proved to be

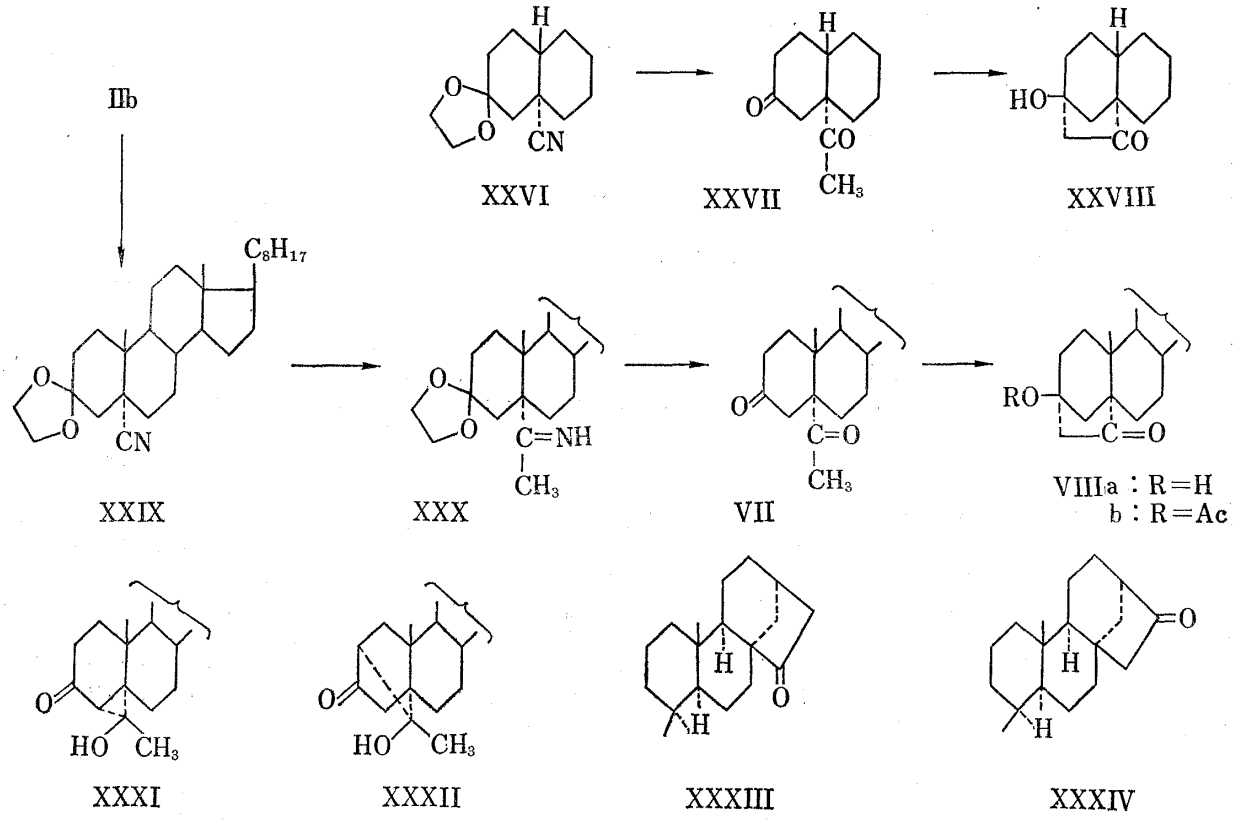

Chart 4

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 8.07τ 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 (VIIIa) 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 (VIIIa) and its acetate (VIIIb) eliminating another possible structure (XXXI) or (XXXII). Moreover, the compounds (VIIIa) and (VIIIb) 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 negitive one.

17) R.D. Haworth, B.G. Hutley, R.G. Leach, and G. Rodgers, *J. Chem. Soc.*, **1962**, 2720.
18) R. Henderson, and R. Hodges, *Tetrahedron*, **11**, 226 (1960).

The work aimed at building up the bicyclo[3.2.1]octane bridged ring of the phyllocladene 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 $CHCl_3$. The $CHCl_3$-layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on neutral Al_2O_3 (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 Al_2O_3 and recrystallization. Fractions eluted with petroleum ether:benzene (4:1)-benzene, on recrystallization from acetone, gave an isomer of mp 211—212.5°, $[\alpha]_D^{24}$ +116.3±3° ($CHCl_3$, c=1.031). *Anal.* Calcd. for $C_{25}H_{35}O_4N$: C, 72.60; H 8.53; N, 3.39. Found: C, 72.56; H, 8.52; N, 3.42. UV λ_{max}^{EtOH} mμ (ε): 219 (17400). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2236, 1718, 1662. Fractions eluted with petroleum ether-benzene (4:1)—(2:1), were recrystallized from acetone, to give, besides the above isomer, another isomer as big granular crystlas, mp 198—202°, which were separated by picking up with a pincette. The mixed melting point of both isomers was 178—185°. $[\alpha]_D^{24}$ −8.8±2° ($CHCl_3$, c=1.030). *Anal.* Calcd. for $C_{25}H_{35}O_4N$: C, 72.60; H, 8.53; N, 3.39. Found: C, 72.33; H, 8.50; N, 3.16. UV λ_{max}^{EtOH} mμ (ε): 219 (17800). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2235, 1718, 1658.

Ethyl 5α-Cyanocholestan-3-ylideneacetate (IXb)——A reagent solution prepared by adding triethyl phosphonoacetate (7.874 g) to a suspension of NaH (843 mg) in 1,2-dimethoxyethane (60 ml) was mixed with a solution of 5α-cyanocholestan-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 CH_2Cl_2-MeOH to give IXb (11.851 g, 86%), mp 129—132°. A pure sample melts at 133—134°. *Anal.* Calcd. for $C_{32}H_{51}O_2N$: C, 79.78; H, 10.67; N, 2.91. Found: C, 80.08; H, 10.70; N, 3.04. UV λ_{max}^{EtOH} mμ (ε): 221 (18100). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2242, 1720, 1626.

Ethyl 17β-Acetoxy-5α-cyanoestran-3α-ylacetate (IIIa)——Compound (IXa) (a mixture of the geometrical isomers) (4.712 g) dissolved in HOAc (100 ml) was hydrogenated over platinum [from $Pt_2O \cdot 2H_2O$ (650 mg)]. The catalyst was filtered, the filtrate concentrated to dryness *in vacuo*, and the residue chromatographed on neutral Al_2O_3 (125 g). Fractions eluted with petroleum ether:benzene (4:1)-$CHCl_3$ were recrystallized from MeOH to give IIIa (3.618 g, 77%), mp 140—141°. Further recrystallization did not raise the melting point. $[\alpha]_D^{22.5}$ +4.9±2° ($CHCl_3$, c=1.007). *Anal.* Calcd. for $C_{25}H_{37}O_4N$: C, 72.25; H, 8.98; N, 3.37. Found: C, 72.13; H, 8.64; N, 3.51. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2225, 1727.

Ethyl 5α-Cyanocholestan-3α-ylacetate (IIIb) and Ethyl 5α-Cyanocholestan-3β-ylacetate (X)——Compound (IXb) (11.117 g) dissolved in HOAc (330 ml) was hydrogenated in the presence of $Pt_2O \cdot 2H_2O$ (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 Al_2O_3 (125 g). Fractions eluted with petroleum ether:benzene (9:1—6:1) were recrystallized from CH_2Cl_2-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 CH_2Cl_2-MeOH to give X (0.586 g, 6%), mp 122—123°.

IIIb (pure sample, mp 108—109°), $[\alpha]_D^{27}$ +6.4±2° ($CHCl_3$, c=1.018). *Anal.* Calcd. for $C_{32}H_{53}O_2N$: C, 79.45; H, 11.04; N, 2.90. Found: C, 79.43; H, 11.07; N, 2.82. X (pure sample, mp 121—122°), $[\alpha]_D^{27}$ +12.1±2° ($CHCl_3$, c=1.006). *Anal.* Calcd. for $C_{32}H_{53}O_2N$: C, 79.45; H, 11.04; N, 2.90. Found: C, 79.93; H, 11.15; N, 3.06.

3α,5α-Etheno-5a-amino-3a-carbethoxyestran-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 IIIa (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 acidified with HOAc (7 ml) and mixed with ice. The mixture was extracted with $CHCl_3$ and $CHCl_3$-ether (1:3). The combined organic layers were washed with 2 N K_2CO_3 and H_2O, dried, and evaporated to give a neutral residue (442 mg). The aqueous layer was acidified with 2 N HCl and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried, and evaporated to give an acidic residue (94 mg, 18%). Recrystallization of the neutral residue from CH_2Cl_2-MeOH gave IVa (145 mg, 27%), mp 229—242° (decomp.). A pure sample melts at 252—263° with decomposition. $[\alpha]_D^{24.5}$ −28.4±5°

($CHCl_3$, c=0.335). *Anal.* Calcd. for $C_{23}H_{35}O_3N$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.50; H, 8.99; N, 3.78. UV λ_{max}^{EtOH} mμ (ε): 293 (>6000). (The ε value was not determined correctly because the sample is sparingly soluble in EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3529, 3337, 1651, 1614, 1532.

3α,5α-Etheno-5a-amino-3a-carbethoxycholestane (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×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 IIIb (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:CH_2Cl_2 (3:1). The organic layer was washed with 2 N K_2CO_3 and H_2O, dried, and evaporated to give a neutral product (461 mg, 45%) as an oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3563, 3335, 1643, 1613, 1527. The aqueous layer was acidified with dil. HCl and extracted with $CHCl_3$:ether (3:1). The usual work-up gave an acidic product (544 mg, 55%), which was recrystallized from MeOH to give crystals of mp 195—199°. IR ν_{max}^{Nujol} cm^{-1}: 2680 (broad), 2228, 1709.

3,3-Ethylenedioxy-5α-hydroxymethylcholestane Tosylate (XVIb)——A solution of XVIa[13] (500 mg) in pyridine (10 ml) was mixed with tosyl chloride (1 g), and the mixture was kept stand 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 H_3PO_4 (50 ml)–ice, and extracted with ether:$CHCl_3$ (3:1). The organic layer was washed with H_2O, 2 N Na_2CO_3, and H_2O, dried and evaporated. The residue was recrystallized from ether to give XVIb (583 mg, 88%), mp 106—107° (decomp.). $[\alpha]_D^{23.5}$ −17.0±2° ($CHCl_3$, c=0.996). *Anal.* Calcd. for $C_{37}H_{58}O_5S$: C, 72.27; H, 9.51; S, 5.21. Found: C, 72.34; H, 9.54; S, 5.30. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1602, 1372, 1188, 1178, 1090.

3,3-Ethylenedioxy-5α-hydroxymethylcholestane Acetate (XVIc)——A mixture of XVIa (2.146 g), pyridine (40 ml), and Ac_2O (20 ml) was let stand for 2 days at room temperature. The residue obtained by the usual work-up was recrystallized from acetone–MeOH to give XVIc (2.068 g, 89%), mp 106—107°. A pure sample melts at 107—108°, $[\alpha]_D^{22}$ +1.8±2° ($CHCl_3$, c=1.022). *Anal.* Calcd. for $C_{32}H_{54}O$: C, 76.44; H, 10.83. Found: C, 76.29; H, 10.82. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1741, 1246, 1900.

5α-Hydroxylmethylcholestan-3-one Acetate (XVIIc)——A solution of XVIc (2.050 g) in 90% HOAc (110 ml) was heated at 100° for 30 min. The usual work-up and recrystallization of the residue from MeOH gave XVIIc (1.694 g, 91%), mp 116—117°. A pure sample melts at 117—118°, $[\alpha]_D^{22}$ +30.7±2° ($CHCl_3$, c=1.022). *Anal.* Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.71; H, 11.04. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1745, 1712, 1233. ORD: $[\phi]_{271}^{26}$ −1790; $[\phi]_{315}^{26}$ +2340 (dioxane, c=0.509).

Reaction of XVIIc with Triethyl Phosphonoacetate——To a stirred suspension of NaH (122 mg) in 1,2-dimethoxyethane (10 ml) was added dropiwse 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 XVIIc (1.552 g) in 1,2-dimethoxyethane (18 ml), and the mixture was heated at 80° for 2 hr. (XVIIc did not react at room temperature). The reaction mixture was poured into ice–water and extracted with $CHCl_3$:ether (1:4). The ether layer was washed with 2 N NaOH and H_2O, dried and evaporated. The residue was chromatographed on neutral Al_2O_3 (60 g). Fractions No. 5—9 eluted with petroleum ether–benzene (2:1) were recrystallized from ether–MeOH to give XVIII (254 mg, 14%), mp 107.0—109.5. *Anal.* Calcd. for $C_{34}H_{56}O_4$: C, 77.22; H, 10.67. Found: C, 77.73; H, 10.84. UV λ_{max}^{EtOH} mμ (ε): 226 (16500). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1743, 1715, 1642, 1240. Fractions No. 10—18 eluted with petroleum ether–benzene (2:1)—(1:2) were recrystallized from ether–MeOH to give XIX (213 mg, 16%), mp 134—137°. $[\alpha]_D^{24}$ +11.5±2° ($CHCl_3$, c=1.125). *Anal.* Calcd. for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.32; H, 11.59. UV λ_{max}^{EtOH} mμ (ε): 209 (6400), 276 (39). UV $\lambda_{max}^{n\text{-heptane}}$ mμ (ε): 195 (7700), 269 (128). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3093, 1690, 855. ORD: $[\phi]_{264}^{24}$ +6820, $[\phi]_{308}^{24}$ −4220, $[\phi]_{313}^{24}$ −3990, $[\phi]_{315}^{24}$ −4089, (dixoane, c=0.541), $[\phi]_{301}$ −5100, $[\phi]_{260}$ +10450, $[\phi]_{250}$ +10450, (MeOH, c=0.400). NMR (in $CHCl_3$): no olefinic H. Fraction No. 20 (35 mg) eluted with benzene consists of XVIIc (confirmed by mixed mp and comparison of IR-spectra). Fractions No. 24—25 eluted with benzene–$CHCl_3$ (1:1)—$CHCl_3$ were recrystallized from $CHCl_3$–MeOH to give XXI (98 mg, 6%), mp 251—255°, $[\alpha]_D^{22}$ +31.1±2° ($CHCl_3$, c=1.050). *Anal.* Calcd. for $C_{32}H_{54}O_3$: C, 78.96; H, 11.18 (for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99). Found: C, 78.96; H, 11.02. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3609, 1762. NMR (in $CDCl_3$) τ: *ca.* 5.6 (2H, quartet, $-\overset{|}{C}-CH_2OH$). Fraction No. 26—28 eluted with $CHCl_3$ were recrystallized from ether–MeOH to give XX[13] (79 mg, 5%), mp 203—208°.

Deketalization of XVIb to XVIIb and XIX——A mixture of XVIb (508 mg), tetrahydrofuran (25 ml), and 2 N H_2SO_4 (2.5 ml) was refluxed for 15 min. The mixture was concentrated *in vacuo*, poured into ice–water, and extracted with ether:$CHCl_3$ (4:1). The orgainc layer was washed with 2 N Na_2CO_3 and H_2O, dried and evaporated. Fractional crystallization of the residue (371 mg) from ether gave XVIIb (51 mg, 11%), mp 116—117°, and XIX (70 mg, 21%), mp 132—134.5°. XVIIb, $[\alpha]_D^{22}$ +5.8±2° ($CHCl_3$, c=1.041). *Anal.* Calcd. for $C_{35}H_{54}O_4S$: C, 73.64; H, 9.54; S, 5.62. Found: C, 73.65; H, 9.53; S, 5.64. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1714, 1601, 1377, 1191, 1179. ORD: $[\phi]_{279}^{25.5}$ −1620, $[\phi]_{318}^{25.5}$ +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 $Pt_2O \cdot 2H_2O$ (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:$CHCl_3$ (4:1). The residue (177 mg) obtained by the usual work-up of the extract was dissolved in ether–$CHCl_3$ and methylated with ethereal diazomethane in the usual way. The residue (180 mg) containing the methyl esters (XXII) and (XXIII) was chromatographed on neutral Al_2O_3 (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 $\nu_{max}^{CCl_4}$ cm^{-1}: 3630, 3500, 1741. Fractions eluted with benzene:$CHCl_3$ (2:1) were recrystallized from ether–MeOH to give XXIII (50.5 mg, 24%), mp 157—158°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3630, 3520, 1734.

3α,5α-Ethano-3a-carbethoxycholestane (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 $CHCl_3$: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 $C_{31}H_{52}O_2$: C, 81.52; H, 11.48. Found: C, 81.36; H, 11.36. UV: end absorption at 210—350 mμ. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1749. Color reaction with tetranitromethane: negative.

Methyl 5α-Tosyloxymethylcholestan-3α-ylacetate 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°. $[\alpha]_D^{23.5}$ −9.0±2° ($CHCl_3$, c=0.997). *Anal.* Calcd. for $C_{38}H_{60}O_5S$: C, 72.57; H, 9.62; S, 5.16. Found: C, 72.30; H, 9.68; S, 5.13. UV λ_{max}^{EtOH} mμ (ε): 226 (11800), 256 (435), 262 (570), 268 (529), 273 (483). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740, 1601, 1371, 1181, 1176.

3,3-Ethylenedioxy-5α-acetiminocholestane (XXX)——To XXIX (2.000 g) dissolved in abs. ether (40 ml) was added 0.69 M ethereal CH_3Li (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°/123—130° (double mp). $[\alpha]_D^{25.5}$ +35.4±2° ($CHCl_3$, c=1.004). *Anal.* Calcd. for $C_{31}H_{53}O_2N$: C, 78.92; H, 11.32; N, 2.97. Found: C, 78.87; H, 11.34; N, 2.85. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3238 (weak), 1635, 1109. NMR (in $CDCl_3$) τ: 8.07 (3H, singlet CH_3–C=NH).

5α-Acetylcholestan-3-one (VII)——A mixture of crude XXX (946 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: $CHCl_3$ (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 Al_2O_3 (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°. $[\alpha]_D^{24}$ +34.8 (±2°) ($CHCl_3$, c=1.076). *Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.66; H, 11.38. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1171. ORD: $[\phi]_{270}^{24}$ −4100, $[\phi]_{311}^{24}$ +3320, $[\phi]_{319}^{24}$ +3840, (dioxane, c=0.309).

2α,5α-Ethanocholestan-3β-ol-5a-one (VIIIa) and Its Acetate (VIIIb)——A suspension of VII (499 mg) in EtOH (25ml) 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:$CHCl_3$ (3:1). The residue from the extract was recrystallized from CH_2Cl_2–MeOH to give VIIIa (469 mg, 94%), mp 174.5—176.5°. This was again recrystallized from CH_2Cl_2–MeOH using active-charcoal to afford a pure sample, mp 176—177°. $[\alpha]_D^{23.5}$ −9.9±2° ($CHCl_3$, c=1.066). *Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 80.98; H, 11.25. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3612, 3454, 1731. ORD: $[\phi]_{290}^{27}$ +2810, $[\phi]_{321}^{27}$ −1710, $[\phi]_{331}^{27}$ −2720, (MeOH, c=0.394). A mixture of VIIIa (4.900 g), pyridine (40 ml), and Ac_2O (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 CH_2Cl_2–MeOH to give VIIIb (4.821 g, 89%), mp 127—128°. A pure sample melts at 129—130°, $[\alpha]_D^{27}$ −18.6±2° ($CHCl_3$, c=0.967). *Anal.* Calcd. for $C_{31}H_{50}O_3$: C, 79.10; H, 10.71. Found: C, 79.28; H, 10.65. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740, 1230. ORD: $[\phi]_{289\,m\mu}^{29}$ +3890, $[\phi]_{319\,m\mu}^{29}$ −1960, $[\phi]_{321\,m\mu}^{29}$ −1760, $[\phi]_{330\,m\mu}^{29}$ −4150, (dioxane, c=0.361).

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