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Synthesis of Bridged Steroids. II.[1] Steroids having a Bridged Bicyclo[3.2.1]octane Ring System of the Kaurene Type

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Some steroidal compounds having a bridged bicyclo[3.2.1]octane ring system of the kaurene type were syntheiszed starting from the bridged compound (VIa) of the phyllocladene type by two different routes. The major subject of this work is to convert the bridged system of the phyllocladene type into that of the kaurene tupe. The Wagner–Meerwein type rearrangement was successfully applied for this purpose as exemplified by the coversions XVd—XIV and XXII—XXIII. The allylic alcohol function was also successfully introduced into the bridged five-membered ring.

In the preceeding paper,[1] we reported the synthesis of steroids having a bridged bicyclo [3.2.1]octane system of the phyllocladene type. As a continuation of this work, synthesis of related steroids having the kaurene-type bridged ring was carried out. The present paper is an investigation of this subject.

Since kaurene (I) contains a C/D-*cis* bridged ring system, it seems quite reasonable to use 5β-cyanocholestan-3-one[3,4] as a starting material, as evident from the preceding work[1] in which 5α-cyanocholestan-3-one was used for the construction of the phyllocladene ring system. However, it was necessary to examine a possibility to construct the kaurene-type bridged ring system starting from *trans*-cyano ketones such as II, because, in a parallel study aimed at synthesizing *Garrya* alkaloids, veatchine (III) and garryine (IV) containing the kaurene-type C–D bridged ring system, our key intermediate was the *trans*-cyano ketone (II). For this reason, 5α-cyanocholestan-3-one (V) was selected as the starting material instead of its 5β-epimer. The four-step synthesis of the bridged compound (VI) starting from V was already described in the preceeding paper.[1] The major problem in the present work was, therefore, to convert the phyllocladene-type bridged ring in VI into the opposite bridged ring system. The problem did not appear to be difficult, because in gibberellin chemistry a similar conversion was already recorded in which allogibberic acid (VII) was rearranged to gibberic acid (VIII) by treatment with hydrochloric acid.[5]

With this principle in mind, conversion of the ketol (VIa) into the bridged olefins (XIIa) and (XIIb) was undertaken. The ketol (VIa) was smoothly reduced to the 1,3-diol (IXa) with sodium borohydride in 95% yield. The *endo* configuration of the newly introduced hydroxyl group was deduced from the generally accepted view that reagents attack the

1) For Part I of this series, W. Nagata and M. Narisada, *Chem. Pharm. Bull.* (Tokyo), **16**, 867 (1968).
2) Location: *Fukushima-ku, Osaka.*
3) W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *J. Org. Chem.*, **26**, 2413 (1961).
4) *a*) W. Nagata, M. Yoshioka, and S. Hirai, *Tetrahedron Letters*, **1962**, 461; *b*) W. Nagata and M. Yoshioka, Proceedings of the 2nd International Congress of Hormonal Steroids, Milan, Italy, May 1966, Excerpta Medica Foundation, Amsterdam, 1966, p. 327.
5) A.J. Birch, R.W. Rickards, H. Smith, J. Winter, and W.B. Turner, *Chem. Ind.* (London), **1960**, 401; *cf.* N. Takahashi, H. Kimura, A. Kawarada, Y. Seta, M. Takai, S. Tamura, and Y. Sumiki, *Bull. Agr. Chem. Soc. Japan*, **19**, 267 (1955).

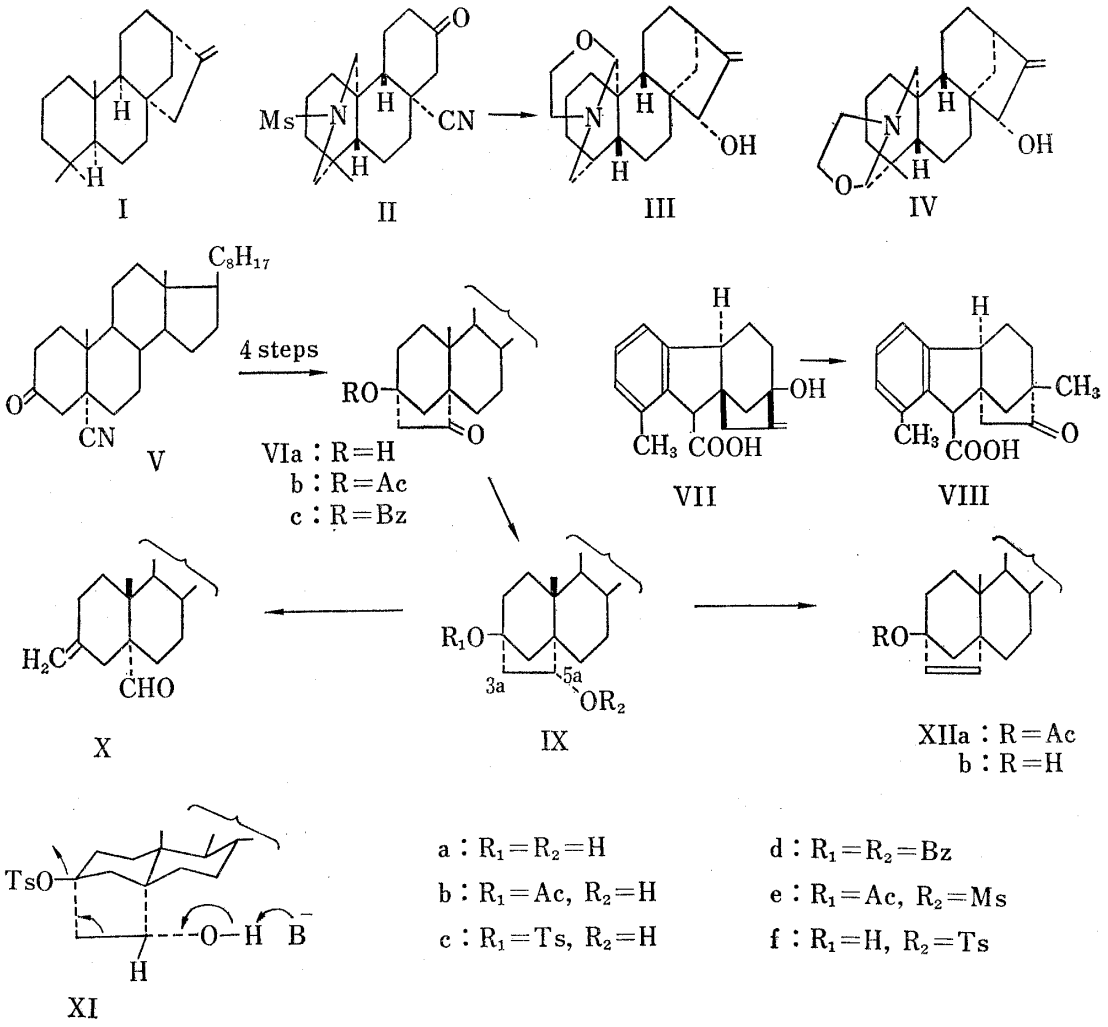


Chart 1

substrate from the less hindered *exo* side[6] in such a bicyclo[3.2.1] ring system. This configuration is confirmed by nonidentity of this diol with the 5α–epimeric 1,3–diol (XVI) derived by hydroboration of the olefin (XIIa) and subsequent oxidation (*vide infra*). The 1,3–*endo* diol was then treated with *p*–toluenesulfonyl chloride in pyridine in the hope of obtaining the monotosylate (IXf). However, the product actually formed was found to be the unexpected monotosylate (IXc), in which the *tert*–hydroxyl group at the bridge head was tosylated in place of the secondary one. The structure of IXc was substantiated by the formation of 3–vinyl–5α–formylcholestane (X) on treatment of IXc with a base. The structural assignment of X is based upon the bands at 2670 and 1719 cm^{-1} and those at 3070, 1650, and 895 cm^{-1}, ascribable to a formyl and an exomethylene group, respectively. The formation of X from compound (IXc)is understandable only when the latter possesses the assigned structure (IXc) and the 1,4–fragmentation mechanism[7] depicted in XI operates in this reaction. The tosylation of the bridged head hydroxyl group in preference to the secondary *endo* one is well rationalized by recognizing that, whereas the bridged head hydroxyl group, though tertiary, is free from steric hindrance,[8] the secondary one greatly suffers hindrance arising from the *endo* orientation at the backside of both the A and B rings. Next, the diol (IXa) was benzoylated with benzoyl chloride in pyridine to give an oily bisbenzoate (IXd). Attempted

6) For instance, R. Henderson, and R. Hodges, *Tetrahedron*, **11**, 226 (1960); *cf.* E.J. Corey, R. Hartmann, and P.A. Vatakencherry, *J. Am. Chem. Soc.*, **84**, 2611 (1962) and references cited therein.
7) C.A. Grob, *Experientia*, **13**, 126 (1957).
8) *cf.* P.D. Bartlett and L.H. Knox, *J. Am. Chem. Soc.*, **61**, 3184 (1939).

pyrolysis of this compound to the olefinic compound (XIIa) (R=Bz instead of Ac) resulted in recovery of the unchanged material. Therefore, the hydroxyl group at the bridge head of the ketol (VIa) was initially acylated with acetic anhydride or benzoyl chloride in pyridine to the keto acetate (VIb) or the keto benzoate (VIc). Compound (VIb) was reduced with sodium borohydride giving the acetoxy *endo* alcohol (IXb).[6] Smooth sulfonylation of the highly hindered, secondary *endo* hydroxyl group of IXb was effected under mild conditions by using reactive methanesulfonyl chloride instead of *p*-toluenesulfonyl chloride to give the acetoxy mesylate (IXe). This compound was finally converted into the desired acetoxy olefin (XIIa) by refluxing with collidine. The 70% over-all yield of XIIa from the ketol (VIa) by four steps is excellent. The hydroxy olefin (XIIb) prepared from XIIa was found to be identical with the solvolysis product of the acetoxy mesylate (IXe) as described in a subsequent paper.[9]

An attempt to rearrange this hydroxy olefin (XIIb) to another bridged ketone (XIV) of the kaurene type by a treatment similar to that used for allogibberic acid (VII) (*vide supra*) was unsuccessful probably owing to formation of an insufficient amount of the necessary 3a-carbonium ion (XIII) which is convincingly less stable than another possible 5a-carbonium ion having a reduced steric hindrance at C_5. We, therefore, planned to place a suitable leaving group at the 3a-position in order to definitely produce a plus charge at the same position.

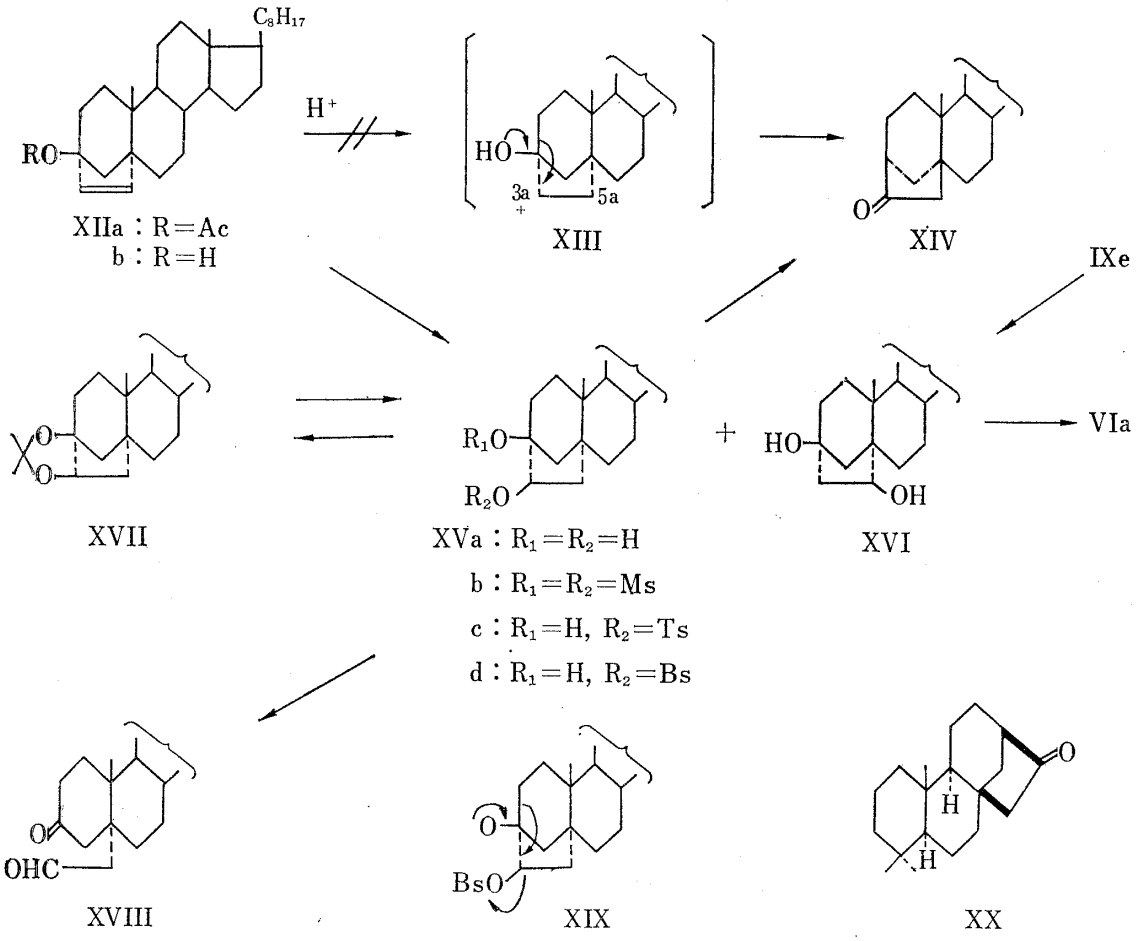


Chart 2

Hydroboration of XIIa with diborane[10] followed by oxidation with hydrogen peroxide, hydrolysis, and separation of the product by alumina chromatography gave the 1,2- and

9) See our subsequent paper.
10) H.C. Brown and B.C. Subba Rao, *J. Am. Chem. Soc.*, **81**, 6428 (1959).

1,3-diols (XVa) and (XVI) in yields of 23% and 13%, respectively. The newly introduced hydroxyl groups of both diols can be assigned an *exo* configuration from the standpoint of the *exo* attack of diborane and no configurational change at the relevant 3a and 5a carbon atoms during subsequent treatment.[11] The structural assignment of both diols was confirmed in the following way. The 1,2-diol (XVa) was converted smoothly into its acetonide (XVII) and regenerated from the latter by treatment with aqueous acetic acid. The fact that the keto aldehyde (XVIII) was obtained by cleavage of XVa with periodic acid again supports the 1,2-diol structure. The isomeric 1,3-diol (XVI) which was not identical with the diol (IXa) (*vide supra*) and also obtained from the solvolysis[9] of the acetoxy mesylate (IXe) was oxidized with chromic anhydride to the known ketol (VIa). For raising the yield of the desired 1,2-diol (XVa), the sterically controlled hydroboration process of Brown and Zweifel[12] was applied to the acetoxy olefin (XIIa). Thus, treatment of this compound with bis(3-methyl-2-butyl)borane, subsequent oxidation, and alkaline hydrolysis gave a crude diol mixture, from which the 1,2-diol (XVa) was isolated *via* its acetonide (XVII) in 41% yield together with 17% yield of the 1,3-diol (XVI). An oily monotosylate (XVc) was obtained by treatment of the 1,2-diol with *p*-toluenesulfonyl chloride in pyridine at 40° for 24 hr. In contrast to this reagent, methanesulfonyl chloride reacted with the diol very rapidly even at room temperature and the dimesylate (XVb) was obtained with failure of selective mesylation. *p*-Bromobenzenesulfonyl chloride, however, proved to be suitable, and treatment of the 1,2-diol with the chloride at room temperature gave the monobrosylate (XVd), which without purification was subjected to a base-induced, Wagner-Meerwein type rearrangement[13] represented by arrows in formula (XIX). Refluxing an aqueous methanolic dioxane solution of a crude material of XVd with potassium hydroxide expectedly gave the ketone (XIV) (mp 125—126°) in 53% over-all yield from the diol (XVa). The same ketone was formed also by applying the solvolysis method of Winstein[14] using lithium perchlorate in tetrahydrofuran, but the rate was very slow as compared with the former process. The assignment of the formula (XIV) to this ketone is based on the band at 1744 cm^{-1} corresponding to a five-membered keto group in the infrared and a negative Cotton effect in the ORD curve. The negative Cotton effect observed for XIV is in good accordance with the fact that while phyllocladene nor-ketone (XX) shows a positive Cotton effect, gibberic acid (VIII) shows a negative one. The main reason for this facile rearrangement obviously is that the leaving brosyloxy group is orientated *anti*-parallel to the migrating C_2–C_3 bond.

Although conversion of the phyllocladene-type bridged ring into the kaurene-type was thus accomplished, an alternative route was also studied. As will be recognized later, this method may serve in the construction of the C-D bridged ring of grayanotoxins,[15] for instance, XXI. The hydroxy olefin (XIIb) was epoxidized with perbenzoic acid to afford the epoxide (XXII) in 71% yield. The *exo* configuration of the epoxy function suitable for the rearrangement is based likewise on the preferable attack of the reagent from the less hindered *exo* side.

Treatment of this epoxide with boron trifluoride etherate[16] gave rise to rearrangement giving the ketol (XXIII), mp 173—178°, in about 40% yield. Substitution of diethylaluminum chloride for boron trifluoride etherate in this reaction markedly raised the yield and the purity of the product; the ketol (XXIII) of mp 182.5—184° was obtained in 75% yield. The superiority of the former reagent over the latter may be due to the lower acidity of the former

11) H.C. Brown, "Hydroboration," **1962**, W.A. Benjamin Inc., New York, 230.
12) *a*) H.C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 3222 (1962); *b*) G. Zweifel, N.R. Ayyanger, and H.C. Brown, *J. Am. Chem. Soc.*, **85**, 2072 (1963).
13) *cf.* Y. Mazur and M. Nussim, *J. Am. Chem. Soc.*, **83**, 3914 (1961).
14) S. Winstein, S. Smith, and D. Darwish, *J. Am. Chem. Soc.*, **81**, 5511 (1959).
15) T. Kozima, K. Nakanishi, M. Yanai, and H. Kakisawa, *Tetrahedron Letters*, **1964**, 1329; W.H. Tallent, *J. Org. Chem.*, **29**, 2756 (1964).
16) *cf.* G. Büchi and W.D. MacLeod, *J. Am. Chem. Soc.*, **84**, 3205 (1962).

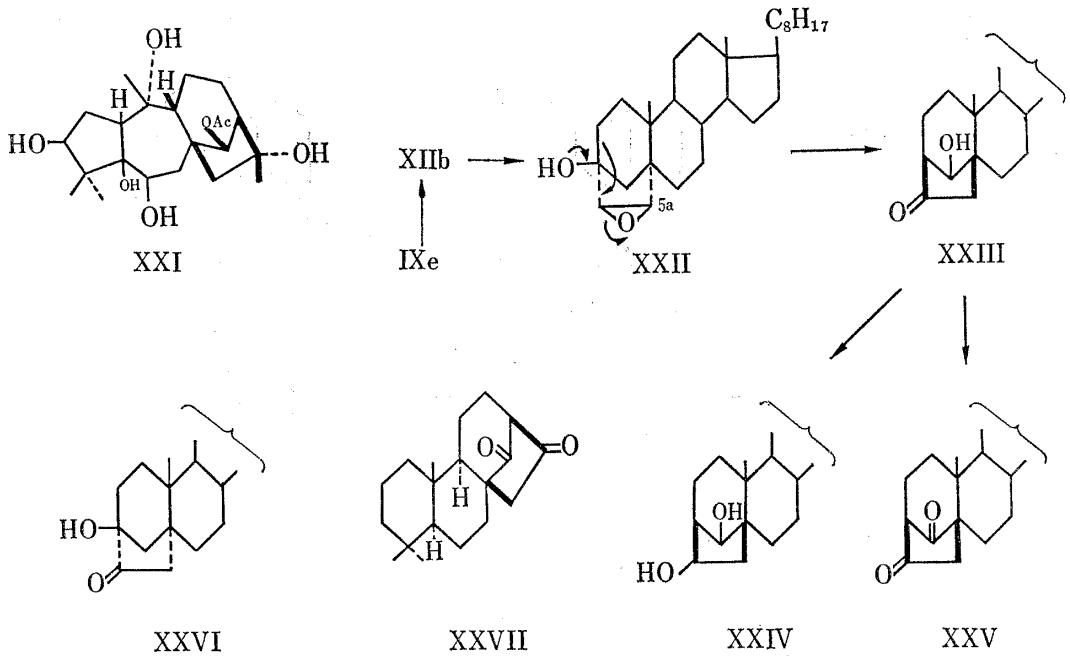
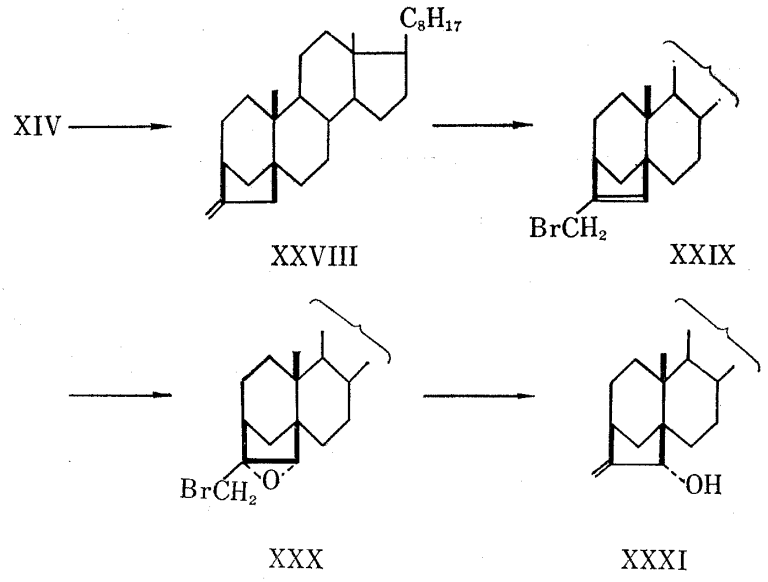


Chart 3

facilitating the migration of electrons from the bridged head oxygen in a metalated intermediate. When the process was carried out continuously without purification of the products of each step, this ketol (XXIII) was obtained in 78% over-all yield from the acetoxy mesylate (IXe) in three steps. The structure and the stereochemistry of this compound as depicted in the formula are based upon the band at 1735 cm^{-1} due to a five-membered keto group, the negative Cotton effect in the ORD curve, and a reasonable assumption that no configurational change takes place at the carbon 5a during the rearrangement. The ketol (XXIII) was reduced with sodium borohydride to the diol (XXIV), which could not be cleaved by periodic acid oxidation. Failure in the cleavage excludes a possible assignment of the 1,2-ketol structure (XXVI) to the rearranged product. The 1,3-diketone (XXV) was also derived from the ketol (XXIII) by chromic anhydride oxidation. The bands of this diketone in the infrared appeared at 1767 and 1729 cm^{-1} are in good coincidence with 1765 and 1730 cm^{-1} reported by Bell, *et al.* for *dl*-norphyllocladenedione (XXVII).[17]

Finally, elaboration was made for introducing an allylic alcohol function into the bridged five-membered ring. The allylic alcohol function is present commonly in the *Garrya* alkaloids. Here, the same method as that explored for the synthesis of the bicyclo[2.2.2]octane ring of the atisine type[9] was used. The ketone (XIV) was treated with methylenetriphenylphosphorane[18] to give the *exo*-olefin (XXVIII) in 82% yield. Wohl-Ziegler bromination[19] of the latter compound with N-bromosuccinimide in the presence of a trace of benzoyl peroxide gave the rearranged allylic bromide (XXIX). Such facile migration of the double bond from the *exo* to *endo* position is well recognized in diterpene chemistry.[20] The crude bromide (XXIX) was epoxidized with perbenzoic acid giving the *exo* epoxide (XXX) of mp 107—108° in an over-all yield of 65% from XXVIII. Employment of the epoxidation reaction is advantageous to introduce an oxygen atom into the 5a position from the requisite *exo* orientation. The epoxy bromide (XXX) was finally treated with zinc in refluxing ethanol giving the allylic alcohol (XXXI) with the desired stereochemistry in 55% yield. The presence of

17) R.A. Bell, R. E. Ireland, and R.A. Partyka, *J. Org. Chem.*, **27**, 3741 (1962).
18) G. Wittig and U. Schöllkopf, *Chem. Ber.*, **87**, 1318 (1954).
19) L. Horner and E.H. Winkelmann, *Angew. Chem.*, **71**, 349 (1959).
20) For instance, L.H. Briggs, B.F. Cain, R.C. Cambie, and B.R. Davis, *J. Chem. Soc.*, **1962**, 1850.



XXVIII XXIX XXX XXXI

Chart 4

both the hydroxyl and the exomethylene groups was proven by the bands at 3627 cm^{-1}, 3073, 1663, and 899 cm^{-1} in the infrared spectrum. The objective of this work was thus accomplished and the reaction sequence explored was successfully applied to our total synthesis of the *Garrya* alkaloids, veatchine and garryine.[21]

Experimental

3α,5α-Ethanocholestane-3β,5aα-diol (IXa)——To a solution of the ketol (VIa) (1.500 g) in dry MeOH (60 ml) were added at room temperature ten 1.5 g portions of $NaBH_4$ over 10 hr period. The product obtained by the usual work-up of the reaction mixture was found to contain a small amount of the starting material. Then, a solution of the product in tetrahydrofuran (60 mg), and water (15 ml) was treated with $NaBH_4$ (2 g) added in several portions. After the mixture was kept at room temperature for 9 hr, the bulk of the solvent was removed at reduced pressure, and the residue was extracted with ether. Crystallization of the product from MeOH–ether gave the diol (IXba) (1.432 g, 95%), mp 179—181°. An analytical sample, obtained by further recrystallization from the same solvent mixture melts at 181—182°. *Anal.* Calcd. for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.80; H, 11.68. IR ν_{max}^{Nujol} 3423 cm^{-1}. $[\alpha]_D^{26.5}$ $-3.3\pm2°$ ($c=1.095$, $CHCl_3$).

3α,5α-Ethanocholestane-3β,5aα-diol 3-Tosylate (IXc)——To a cooled solution of the diol (IXa) (801 mg) in pyridine (8 ml) was added tosyl chloride (1.06 g, 3 molar euqiv.). After being let stand for 38 hr at room temperature, the reaction mixture was poured into ice-water and extracted with ether. The colloidal residue was crystallized from $CHCl_3$–ether to give IXc (808 mg) as an amorphous powder. An analytical sample, obtained by further recrystallization from CH_2Cl_2–MeOH, melts at 144—145°. *Anal.* Calcd. for $C_{36}H_{56}O_4S$: C, 73.92; H, 9.65; S, 5.48. Found: C, 73.96; H, 9.69; S, 5.42. IR ν_{max}^{Nujol} cm^{-1}: 3543, 3531, 1600, 1332, 1168. $[\alpha]_D^{25.5}$ $0\pm2°$ ($c=0.984$, $CHCl_3$).

3-Methylene-5α-formylchloestane (X)——To a suspension of the monotosylate (IXc) (42.5 mg) in dry MeOH (2 ml) was added KOH (329 mg), and the mixture was refluxed for 1 hr. Ice-water was added to the mixture. The precipitate was collected by filtration, washed with water, and dried to give 18.4 mg of the vinyl aldehyde (X), mp 88—95°. An analytical sample, obtained by recrystallization from acetone–water, melts at 98—101°. *Anal.* Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.39; H, 11.74. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2670, 1719, 3070, 1650, 894. $[\alpha]_D^{25.5}$ $+3.4\pm2°$ ($c=0.523$, $CHCl_3$).

3α,5α-Ethanocholestane-3β,5aα-diol 3,5a-Dibenzoate (IXd)——A solution of the *endo* 1,3-diol (IXa) (37 mg) in pyridine (0.3 mg) was mixed with benzoyl chloride (0.1 ml), and the mixture was kept at room temperature for 14 hr, mixed with water (0.1 ml), and allowed to stand at room temperature for 30 min. The reaction mixture was then heated at 100° for 15 min to decompose excess benzoyl chloride poured into ice-water, and extracted with ether. The ethereal layer was washed with 2 N HCl water, 2 N K_2CO_3 and water,

21) W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *J. Am. Chem. Soc.*, **86**, 929 (1964); *ibid.*, **89**, 1499 (1966).

dried, and evaporated. There was obtained the dibenzoate (IXa) (49 mg) as an oil whose infrared spectrum did not show a hydroxyl band.

Atetmpted Pyrolysis of the Dibenzoate (IXd)——The crude dibenzoate (IXd) (35 mg) was heated at 300—310° under reduced pressure furnished by a water aspirator for 1 hr. The residue was found to be unchanged IXd by an inspection of the infrared spectrum.

3α,5α-Ethanocholestan-3β-ol-5a-one 3-Acetate (VIb)——To a solution of 4.900 g of the ketol (VIa) in pyridine (40 ml) was added acetic anhydride (10 ml), and the resulting mixture was refluxed for 80 min. The solvent was removed by codistillation with toluene at reduced pressure. Crystallization of the residue from CH_2Cl_2–MeOH gave the ketol acetate (VIb), (4.821 g, 89%) mp 127—128°. An analytical sample melts at 129—130°. *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. $[\alpha]_D^{27}$ $-18.6\pm2°$ ($c=0.9667$, $CHCl_3$).

3α,5α-Ethanocholestane-3β,5aα-diol 3-Acetate (IXb)——To a refluxing solution of the ketol acetate (VIb) (4.446 g) in tetrahydrofuran (180 ml) and water (36 ml) was added with stirring $NaBH_4$ (4.5 g) in six portions at 1 hr intervals. The mixture was poured into water and extracted with ether:chloroform (3:1). The residue from the extract was crystallized from CH_2Cl_2–MeOH to give the *endo* 1,3-diol monoacetate (IXb) (4.154 g, 93%), mp 138—139°. An analytical sample melts at 139—141°. *Anal.* Calcd. for $C_{31}H_{52}O_3$: C, 78.76; H, 11.09. Found: C, 78.98; H, 11.14. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3644, 3520, 1735, 1721, 1253. $[\alpha]_D^{23.5}$ $-4.8\pm2°$ ($c=0.966$, $CHCl_3$).

3α,5α-Ethanocholestane-3β,5aα-diol 3-Acetate 5a-Mesylate (IXe)——To a well-stirred solution of the *endo*-1,3-diol monoacetate (IXb) (3.862 g) in pyridine (35 ml), mesyl chloride (2.89 ml) was added dropwise at 0° and the resulting mixture was kept at room temperature for 14 hr. A few pieces of ice were added to the reaction mixture which was allowed to stand for 30 min, poured into 2 N HCl–ice (350 ml), and extracted with ether:$CHCl_3$ (3:1). The residue from the extract was crystallized from ether–MeOH to give the mesyl acetate (IXe) (4.277 g, 95%), mp 126—133°. An analytical sample melts at 134—135°. *Anal.* Calcd. for $C_{32}H_{54}O_4S$: C, 69.77; H, 9.88; S, 5.82. Found: C, 69.39; H, 8.91; S, 5.78. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1738, 1370, 1178. $[\alpha]_D^{23.5}$ $-23.2\pm2°$ ($c=0.868$, $CHCl_3$).

3α,5α-Ethenocholestan-3β-ol Acetate (XIIa)——A solution of the mesyl acetate (IXe) (2.00 g) in collidine (20 ml) was refluxed in a nitrogen atmosphere for 14 hr. The mixture was poured into 2 N HCl–ice (200 ml) and extracted with ether. The residue from the extract was crystallized from ether–MeOH to give the allyl acetate (XXIIa) (1.451 g, 89%), mp 49—51°/68—70°. The analytical sample melts at 50—52°/68—70°. Another sample melted at 97—98° (dimorphism). *Anal.* Calcd. for $C_{30}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 82.07; H, 11.10. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3050, 1738. $[\alpha]_D^{24}$ $-28.9\pm2°$ ($c=1.094$, $CHCl_3$).

3α,5α-Ethenocholestan-3α-ol (XIIb)——To a solution of the allyl acetate (XIIa) (100 mg) in ethanol (15 ml) was added 2 N KOH (5 ml), and the mixture was refluxed for 3 hr. The reaction mixture was concentrated *in vacuo* and extracted with ether. The residue from the extract was crystallized from ether–MeOH to give an analytically pure sample of the allyl alcohol (XIIb) (40 mg), mp 132.5—133°. *Anal.* Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.60; H, 11.79. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3606, 3042, 1598. $[\alpha]_D^{27}$ $-13.1\pm2°$ ($c=1.050$, $CHCl_3$).

3α,5α-Ethanocholestane-3β,3aβ-diol (XVa) and 3α,5α-Ethanocholestane-3β,5aβ-diol (XVI)——Into a solution of the allyl acetate (XIIa) (1.027 g) in dry tetrahydrofuran (20 ml) was introduced at 0° over a period of 40 min diborane gas which was generated from BF_3–ether (2.97 ml) and $NaBH_4$ (392 mg). After being let stand at room temperature for 3 hr, the reaction mixture was mixed successively with water (2.3 ml), 3 N NaOH (4.6 ml), and 30% H_2O_2 (4.6 ml). The resulting mixture was stirred for 3 hr at room temperature and extracted with $CHCl_3$–MeOH–tetrahydrofuran. The organic layer was washed with satd. NaCl, dried and evaporated. The residue was mixed with ethanol (150 ml) and 2 N KOH (30 ml). After being refluxed for 2 hr, the mixture was concentrated at reduced pressure, poured into satd. NaCl, neutralized with acetic acid (3.6 ml), and extracted with chloroform. The residue (853 mg) from the extract was chromatographed on Woelm alumina (activity II, 30 g). Elution with benzene:chloroform (1:1) followed by crystallization from $CHCl_3$–ether gave the *exo*-1,3-diol (XVI) (128 mg, 13%), mp 227—228°. An analytical sample, obtained by recrystallization from $CHCl_3$ melts at 229—231°. *Anal.* Calcd. for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.53; H, 11.68. IR ν_{max}^{Nujol} cm^{-1}: 3315. $[\alpha]_D^{24.5}$ $+30.2°$ ($\pm2°$) ($c=0.933$,CHC l_3–MeOH=4:1). The fractions eluated with benzene:$CHCl_3$ (1:1)–$CHCl_3$–MeOH (9:1) were crystallized from CH_2Cl_2–AcOEt to give the *exo*-1,2-diol (XVa) (219 mg, 23%). An analytical sample melts at 220—222°. *Anal.* Calcd. for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 81.08; H, 11.72. IR ν_{max}^{Nujol} cm^{-1}: 3403, 3314. $[\alpha]_D^{24.5}$ $+24.6\pm2°$ ($c=1.131$, $CHCl_3$).

Solvolysis of 2α,5α-ethanocholestane-3β,5aα-diol 3-Acetate 5α-Mesylate (IXe)——A solution of mesyl acetate (IXe) (22.8 g) in methanol (450 ml) and dioxane (120 ml) was mixed with 20% KOH (400 ml), and the resulting mixture was stirred under reflux for 5 hr in a nitrogen atmosphere. The mixture was concentrated under reduced pressure, poured into ice–water, and extracted with ether. The residue (19.05 g) from the extract was chromatographed on Woelm alumina (activity II, 250 g). The fractions eluated with $CHCl_3$–MeOH (9:1) were crystallized from $CHCl_3$ to afford the 1,3-exodiol (XVI) (829 mg, 5%), mp 221—224°. This sample was proved to be identical with XVI prepared by the hydroboration of XIIa by mixed mp and comparison of IR spectra.

3α,5α-Ethanocholestane-3β,3aβ-diol Acetonide (XVII)——A solution of the allylacetate (XIIa) (100 mg) in dry ether (10 ml) was added dropwise to an ethereal solution of bis(3-methyl-2-butyl)borane (prepared from BF_3-ether (0.73 ml), 2-methyl-2-butene (1.25 ml) in dry ether (10 ml) and $LiAlH_4$ (160 mg) in dry ether (10 ml)). After being kept at room temperature for 18 hr, the reaction mixture was mixed with a small amount of water, poured into water, and extracted with ether. To a solution of the residue in tetrahydrofuran (10 ml) were added 3 N NaOH (5 ml) and 30% H_2O_2 (5 ml) at 0°. The mixture was stirred at 0° for 2.5 hr, poured into ice-water, and extracted with ether. The organic layer was evaporated to give the residue (69 mg). The colloidal aqueous alkaline phase was mixed with 30% H_2O_2 (5 ml), after being stirred for 2 hr at room temperature, the mixture was extracted with chloroform. The $CHCl_3$ layer was washed with water, 2 N HCl, and water, and evaporated to furnish the residue (37 mg), the thin-layer chromatogram of which shows that the product is the *exo*-1,2-diol. To a solution of the combined residues (67 mg+37 mg) in ethanol (30 ml) was added 2 N KOH (6 ml). The mixture was refluxed for 2 hr, mixed with acetic acid (1 ml), and extracted with $CHCl_3$. The dried residue (103 mg) from the extract was mixed with dry acetone (30 ml) and *p*-toluenesulfonic acid monohydrate (35 mg). The mixture was refluxed for 3 hr, poured into cold 1% $NaHCO_3$, and extracted with $CHCl_3$. The residue (180 mg) obtained from the extract by washing with water and evaporation was chromatographed on Woelm alumina (activity II, 4 g). Elution with petroleum ether-benzene (2:1) afforded the acetonide (XVII) (52.8 mg, 5%), mp 143—146°. An analytical sample melts at 146—147°. *Anal.* Calcd. for $C_{32}H_{54}O_2$: C, 81.64; H, 11.56. Found: C, 81.73; H, 11.64. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1065. $[\alpha]_D^{28}$ +15.8±2° (c=1.019, $CHCl_3$). The fractions eluted with $CHCl_3$ was crystallized from $CHCl_3$-ether to give the *exo*-1,3-diol (XVI) (15.7 mg, 17%), mp 227—229°, which was proved to be identical with the sample obtained before.

A suspension of the acetonide (XVII) (25.7 mg) in 90% AcOH (2 ml) was heated at 100° for 30 min. The solvent was removed by codistillation with toluene, and the residue was crystallized from CH_2Cl_2-acetone to afford the *exo*-1,2-diol (XVa) (19.1 mg, 81%), mp 227—229°, the IR spectrum of which is identical with that of an authentic sample. The mixed melting point showed no depression.

Oxidation of Exo-1,3-diol (XVI)——To the suspension of the *exo*-1,3-diol (XVI) (1.222 g) in acetone (200 ml) the Jones reagent (2 ml) was added dropwise with stirring at 0° over a period of 10 min. The precipitate was removed by decantation, and the acetone layer was diluted with water, and extracted with ether. The extract was washed with water, 2 N KOH, and water dried, and evaporated. The residue was crystallized from CH_2Cl_2-MeOH to afford the ketol (VIa) (992 mg), mp 176.5—178°. This compound was proved to be identical with an authentic sample by mixed mp and comparison of IR spectra.

5α-(2-Oxoethyl)cholestan-3-one (XVIII)——To a solution of the *exo*-1,3-diol (XVa) (180 mg) in tetrahydrofuran (18 ml) was added a solution of periodic acid dihydrate (190 mg, 2 molar equiv.) in water (9 ml). The mixture was kept in a dark place at room temperature for 70 min, mixed with water, and extracted with ether. The residue was crystallized from acetone to give the keto aldehyde (XVIII) (153 mg), mp 149—151°. An analytical sample melts at 151—153°. *Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.42; H, 11.21. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2736, 1720. $[\alpha]_D^{22}$ +17.0±2°(c=1.124, $CHCl_3$). ORD: $[\phi]_{270\,m\mu}^{28}$ −1571, $[\phi]_{312\,m\mu}^{28}$ +2696 (c=0.376, dioxane).

3α,5α-Ethanocholestane-3β,3aβ-diol 3a-Tosylate (XVc)——To a solution of 50 mg of the *exo*-1,2-diol (XVa) (50 mg) in pyridine (1 ml) was added tosyl chloride (89 mg, 4 molar equiv.). The mixture was kept at room temperatre for 38 hr and then warmed at 35—40° for 24 hr. A few pieces of ice were added to the mixture to decompose an excess of the reagent. After being allowed to stand for 1 hr, the resulting mixture was poured into 2 N HCl (10 ml)-ice and extracted with ether. The infrared spectrum of the residue (70 mg) from the extract shows that the main portion is the 3a-monotosylate. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3604, 1602, 1367, 1173.

3α,5α-Ethanocholestane-3β,3aβ-diol Dimesylate (XVb)——To a solution of the *exo*-1,2-diol (XVa) (50 mg) in pyridine (1 ml) mesyl chloride (0.049 ml) was added at 0°. The mixture was kept at room temperature for 37 hr and mixed with a few pieces of ice to decompose an excess of the reagent. After 1 hr, the resulting mixture was poured into 2 N HCl-ice and extracted with ether. The residue (58 mg) from the extract was crystallized from CH_2Cl_2-ether to afford the dimesylate (XVb) (49 mg, 72%), mp 160—162°. An analytical sample melts at 162—165°. *Anal.* Calcd. for $C_{31}H_{54}O_6S_2$: C, 63.44; H, 9.28; S, 10.93. Found: C, 63.21; H, 9.20; S, 10.94. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1359, 1170. $[\alpha]_D^{26}$ +5.0±3° (c=0.780, $CHCl_3$).

3β,5β-Ethanocholestan-3a-one (XIV)

a) By rearrangement of 3α,5α-Ethanocholestane-3β,3aβ-diol 3aβ-mono-*p*-bromobenzenesulfonate(XVd): To a solution of the *exo*-1,2-diol (XVa) (542 mg) in pyridine (7 ml), brosyl chloride (912 mg, 3 molar equiv.) was added at 0°. The mixture was allowed to stand at room temperature for 155 hr and then treated with a few pieces of ice at room temperature for 1 hr to decompose an excess of the reagent. The resulting mixture was poured into 2 N HCl (70 ml)-ice and extratced with $CHCl_3$. The infrared spectrum of the extract (820 mg) shows that the major portion is the monobrosylate (XVd), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3605, 1580, 1368, 1175. To a solution of the crude material obtained above in dioxane (90 ml) and methanol (90 ml) was added a solution of KOH (9 g) in water (30 ml). The mixture was refluxed for 3 hr, concentrated under reduced pressure, poured into ice-water, and extracted with $CHCl_3$. The residue (569 mg) was chromatographed on Woelm alumina (activity II, 15 g). The fractions eluted with petroleum ether:benzene (9:1)—(4:1) on crystallization

from MeOH afforded the five membered ketone (XIV) (266 mg, 53%), mp 124—125°. An analytical sample melts at 125—126°. *Anal.* Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.36; H, 11.82. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1744. $[\alpha]_D^{27.5}$ +3.3±2° (c=1.055, $CHCl_3$). ORD: $[\phi]_{288\,m\mu}^{30}$ +7753, $[\phi]_{312\,m\mu}^{30}$ −3534, $[\phi]_{315\,m\mu}^{30}$ −2941, $[\phi]_{323\,m\mu}^{30}$ −6946 (c=0.193, dioxane).

b) By solvolysis of XVd: A mixture of the crude monobrosylate (XVd) (47 mg), $LiClO_4$ (113 mg), and dry tetrahydrofuran (7 ml) was refluxed for 14 hr. The product obtained by the usual work-up was found to be *ca.* 1:1 mixture of the ketone (XIV) and the starting material (XVd) by an investigation of the IR spectrum.

3aβ,5aβ-Epoxy-3α,5α-ethanocholestan-3β-ol (XXII)——To a solution of the allyl alchohol (XIIb) (690 mg) in dry benzene (8.9 ml) was added a solution of perbenzoic acid in benzene (7.4 ml, 1.5 molar equiv.). After being kept in dark for 16 hr. in a closed vessel, the mixture was poured into 2 N NaOH–ice and extracted with ether. The residue from the extract was chromatographed on Woelm alumina (30 g). The fractions eluted with benzene:$CHCl_3$ (4:1) were crystallized from acetone to give the epoxy alcohol (509 mg, 71%), mp 164.5—166.5°. An analytical sample melts at 166—167°. *Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.30; H, 11.31. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3601, 3463. $[\alpha]_D^{27.5}$ +21.4±2° (c=1.058, $CHCl_3$).

3β, 5β-Ethanocholestan-4β-ol-3a-one (XXIII)

a) By rearrangement of XII with diethylaluminum chloride: To a solution of the epoxy alcohol(XXII) (519 mg) in tetrahydrofuran (10 ml) was added a solution of diethylaluminum chloride (1.23 g, 8.5 molar equiv.) in tetrahydrofuran (2.6 ml) at 0° under nitrogen. After being allowed to stand at room temperature for 15 hr in a closed vessel, the mixture was poured into diluted NaOH and extracted with ether. The residue (533 mg) was chromatographed on neutral alumina (15 g). The fractions eluted with benzene—benzene: $CHCl_3$ (19:1) was crystallized from acetone to give the ketol (XXIII) (386 mg, 75%), mp 182.5—184°. An analytical sample melts at 183—184°. *Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.36; H, 11.30. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3626, 3460, 1737. $[\alpha]_D^{28}$ −15°±2° (c=1.009, $CHCl_3$).

b) By rearrangement of XII with boron trifluoride: To a solution of the epoxy alcohol (XXII) (50 mg) in dry ether (5 ml) was added $BF_3 \cdot Et_2O$ (0.5 ml) at 0°. After being let stand for 16 hr at room temperature, the mixture was poured into ice–water and extracted with ether. The residue from the extract was crystallized from CH_2Cl_2–acetone to afford the ketol (XXIII) (22 mg), mp 173—178°. The infrared spectrum of the product was identical with that of the ketol (XXIII) obtained in a).

3β,5β-Ethanocholestane-3aβ,4β-diol (XXIV) and Attempted Oxidation with Periodic Acid——To a refluxing solution of the ketol (XXIII) (22 mg) in tetrahydrofuran (5 ml) and water (2 ml) was added $NaBH_4$ (23 mg) in three portions at 1 hr intervals. The mixture was concentrated under reduced pressure, mixed with water, and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated under reduced pressure. The residue was crystallized from CH_2Cl_2–acetone to afford the diol (XXIV) (7.1 mg), mp 215—221°. IR ν_{max}^{Nujol} cm^{-1}: 3480, 3220. A solution of the diol (XXIV) (5.4 mg) in tetrahydrofuran (0.4 ml) was mixed with a solution of periodic acid (21 mg) in water (0.2 ml), and the mixture was kept at room temperature for 15 hr. The usual work-up (ether extraction) and crystallization of the product from acetone afforded crystals (4.0 mg), mp 215—221°, the infrared spectrum of which was identical with that of the starting material (XXIV). The identity was cofinrmed by mixture melting point determination.

3β,5β-Ethanocholestane-3a,4-dione (XXV)——To a solution of the ketol (XXIII) (1.000 g) in 150 ml of acetone was added the Jones reagent until an orange-brown color persisted. After being stirred at 0° for 15 min, the mixture was poured into ice–water and extracted with ether. The residue from the extract was crystallized from CH_2Cl_2–acetone to afford the diketone (XXV) (866 mg, 87%), mp 203—205.5°. An analytical sample melts at 203—206°. *Anal.* Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.56; H, 10.82. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1767, 1729. $[\alpha]_D^{27}$ −16.6°±2° (c=1.017, $CHCl_3$). ORD: $[\phi]_{275\,m\mu}^{28}$ +10863, $[\phi]_{290\,m\mu}^{28}$ −7455, $[\phi]_{315\,m\mu}^{28}$ −4507, $[\phi]_{319\,m\mu}^{28}$ −4651 (c=0.120, dioxane).

3β-Methylene-3β,5β-ethanocholestane (XXVIII)——Triphenylmethylphosphonium bromide (1.17 g) was added at 0° to a mixture of 1.16 N ethereal butyl lithium (2.81 ml) and dry ether (10 ml). The resulting mixture in a stoppered flask was stirred for 2 hr at room temperature. To this yield solution was added a solution of the ketone (XIV) (250 mg) in dry tetrahydrofuran (15 ml). After the ether was removed by distillation, the mixture was refluxed for 4 hr, poured into ice–water, and extracted with ether. The extract (526 mg) was chromatographed on neutral alumina (15 g). Elution with petroleum ether and crystallization of the fractions from ether–MeOH afforded the *exo*-olefin (XXVIII) (204 mg, 82%), mp 75—75.5°. An analytical sample melts at 78—79°. *Anal.* Calcd. for $C_{30}H_{50}$: C, 87.73; H, 12.27. Found: C, 87.53; H, 12.21. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3070, 1658, 874. $[\alpha]_D^{27.5}$ +44.9±2° (c=1.064, $CHCl_3$).

3aβ-Bromomethyl-3aα,5aα-epoxy-3β,5β-ethanocholestane (XXX)——A solution of the *exo*-olefin (XXVIII) (73 mg) in dry CCl_4 (3 ml) was mixed with N-bromosuccinimide (38 mg) and benzoylperoxide (2 mg), and the mixture was refluxed for 30 min. The reaction mixture was poured into ice–water and extracted with CCl_4. The infrared spectrum of the product in which the 874 cm^{-1} band almost disappeared showed that the major portion was the allyl bromide (XXIX). To a solution of the product obtained above in dry benzene (1 ml) was added 0.92 ml of a 0.29 M solution of perbenzoic acid in benzene. The mixture was allowed to stand in a dark place for 51 hr, poured into 2 N KOH–ice and extracted with ether. The residue (92 mg) was chromatographed on neutral alumina (4 g). Elution with petroleum ether and crystallization of the fractions from

ether–MeOH afforded an analytically pure sample of the epoxy bromide (XXX) (58.7 mg, 65%), mp 107—108°. *Anal.* Calcd. for $C_{30}H_{49}OBr$: C, 71.26; H, 9.77; Br, 15.81. Found: C, 71.50; H, 9.78; Br, 15.58. $[\alpha]_D^{25}$ +25.6±4° (c=0.645, $CHCl_3$).

3a-Methylene-3β,5β-ethanocholestan-5aα-ol (XXXI)——A solution of the epoxy bromide (XXX) (30 mg) in dry ethanol (6 ml) was mixed with zinc powder (300mg), and the mixture was stirred under reflux for 4 hr. After being cooled, the reaction mixture was diluted with ether, and the organic layer was separated by decantation and evaporated. The residue was chromatographed on neutral alumina (1 g). Crystallization of the fractions eluted with petroleum ether (4:1)—(2:1) gave the allylic alcohol (XXXI) (13.8 mg, 55%), mp 97—100°. An analytical sample melts at 101—104°. *Anal.* Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.33; H, 11.76. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3627, 3037, 1663, 899. $[\alpha]_D^{24.5}$ +63.8±4° (c=0.669, $CHCl_3$).