mole) of 4,6-dichloropyrimidine[2] was mixed with 21.5 g. (0.20 mole) of benzylamine. The mixture became hot and a solid separated. The mixture was then heated on the steam-bath for 3 hours. The resulting solid was dissolved in hot alcohol and cooled to yield 6.5 g. (46%) of 4,6-bis-benzylaminopyrimidine, m.p. 234–235°.

Anal. Calcd. for $C_{18}H_{18}N_4$: C, 74.45; H, 6.25; N, 19.30. Found: C, 74.09; H, 6.52; N, 19.54.

4-Benzylamino-6-chloropyrimidine.—The alcohol filtrate from the above crystallization was concentrated and the solid residue was recrystallized from a mixture of ethyl acetate and petroleum ether; yield 2 g. (18.2%), m.p. 121°.

Anal. Calcd. for $C_{11}H_{10}ClN_3$: N, 19.13. Found: N, 18.74.

4,6-Bis-*n*-butylaminopyrimidine.—Six and seven-tenths grams of 4,6-dichloropyrimidine was treated with 14.6 g. of *n*-butylamine in the manner described above; yield 6.7 g. (67%), m.p. 154°.

Anal. Calcd. for $C_{12}H_{22}N_4$: C, 64.82; H, 9.97; N, 25.20. Found: C, 64.63; H, 9.93; N, 25.05.

4-Chloro-6-β-phenoxyethylaminopyrimidine.—To a solution of 6.85 g. (0.05 mole) of β-phenoxyethylamine in 60 ml. of 20% alcohol was added 3.95 g. (0.026 mole) of 4,6-dichloropyrimidine. The solution was heated on the steam-bath for 12 hours. Upon cooling 4-chloro-6-β-phenoxyethylaminopyrimidine crystallized and was recrystallized from a mixture of ethyl acetate and petroleum ether; m.p. 98–100°, yield 6 g. (90%).

Anal. Calcd. for $C_{12}H_{12}ClN_3O$: N, 16.83. Found: N, 16.37.

4-Chloro-6-furfurylaminopyrimidine.—A mixture of 5.9 g. (0.06 mole) of furfurylamine and 4.46 g. (0.03 mole) of 4,6-dichloropyrimidine in 50 ml. of water was heated on the steam-bath for several hours. An oil separated that readily crystallized upon cooling. This was recrystallized from a mixture of ethyl acetate and petroleum ether; yield 3.5 g. (58%), m.p. 130°.

Anal. Calcd. for $C_9H_8ClN_3O$: N, 20.05. Found: N, 20.25.

4-Chloro-6-piperidinopyrimidine was prepared by the procedure described above; yield 93%, m.p. 78°.

Anal. Calcd. for $C_9H_{12}ClN_3$: C, 54.68; H, 6.12; N, 21.26. Found: C, 54.82; H, 5.97; N, 21.35.

4,6-Bis-*n*-butylamino-3-methylpyrimidinium Iodide.—One gram each of 4,6-bis-*n*-butylaminopyrimidine and methyl iodide was added to 25 ml. of ethyl acetate. After refluxing for one hour, a crystalline solid was collected from the cooled solution. Recrystallization from ethanol gave 1.2 g. (43%) of solid, m.p. 121°.

Anal. Calcd. for $C_{13}H_{25}IN_4$: C, 42.80; H, 6.92; N, 15.37. Found: C, 43.16; H, 6.78; N, 15.38.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Studies in the Synthesis of the Antirachitic Vitamins. VI. The Synthesis of 2-Cholestanylidene-ethan-1-al

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Several methods for the synthesis of 2-cholestanylidene-ethan-1-al, a key intermediate in the synthesis of biologically active vitamin D homologs, have been studied. Of all these, the method in which the Grignard of ethoxyacetylene is allowed to react with cholestanone with subsequent partial hydrogenation followed by acid-catalyzed rearrangement gives the best yields and minimum by-products.

In the synthesis of biologically active vitamin D homologs[2] one of the key intermediates is 2-cholestanylidene-ethan-1-al (IX). It is the purpose of this communication to describe the various methods used for the synthesis of this intermediate.

The first method used for the synthesis of 2-cholestanylidene-ethan-1-al is outlined in a sequence of reactions shown in Fig. 1. The reaction between cholestanone[3,4] and lithium acetylide in liquid ammonia was studied under a variety of conditions before optimum yields of the acetylenic carbinol II were obtained. Only negligible quantities of this carbinol were obtained when cholestanone was added as a solid or in ether solution to liquid ammonia containing only 10% excess of lithium acetylide. A 22% yield was realized when toluene was substituted for ether and a fourfold excess of lithium acetylide used. Optimum yields of 75–80% of the acetylenic carbinol were obtained when cholestanone was added in a 50–50 mixture of ether–toluene to liquid ammonia containing sevenfold excess of lithium acetylide. Girard reagent P was advantageous in removing the unreacted ketone.

The acetylenic carbinol was partially hydrogenated in ethanol to 3-ethenylcholestan-3-ol (III) in quantitative yields using palladium-on-calcium carbonate as the catalyst. Both compounds II and III gave, upon catalytic hydrogenation using platinum oxide, 3-ethylcholestan-3-ol (IV). Following the method of Dimroth[6] and Grab and Rumpf[7] the carbinol III was treated with phosphorus tribromide in pyridine to yield a mixture consisting of 82% of 1-bromo-2-cholestanylidene-ethane (V) and 18% of 3-ethenylcholest-3-ene (VI). The bromide V was difficult to purify so the mixture was treated directly with potassium acetate in acetic acid to produce another mixture consisting of 67% of 1-acetoxy-2-cholestanylidene-ethane (VII) and an additional 33% of the diene VI through a dehydrobromination reaction. The over-all yield of the ester for the two reactions was 55%. Most of the diene could be separated by crystallization, but the ester was obtained free from the diene only by chromatography in efficiencies of 25–30%.

An attempt then was made to by-pass the bro-

(1) From the Ph.D. Thesis of C. P. Priesing, M.I.T., April, 1957.

(2) N. A. Milas and C. P. Priesing, THIS JOURNAL, **79**, 3610 (1957); also presented before the 132nd Meeting of A.C.S., New York, N. Y., September 8–13, 1957.

(3) W. F. Bruce and J. O. Ralls, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 191.

(4) W. F. Bruce, ref. 3, p. 139.

(5) A. Girard and G. Sandulesco, *Helv. Chim. Acta*, **19**, 1105 (1936).

(6) K. Dimroth, *Ber.*, **71**, 1333, 1346 (1938); *cf.* W. L. Alderson, Jr., Ph.D. Thesis, M.I.T., Nov., 1939.

(7) C. A. Grab and J. A. Rumpf, *Helv. Chim. Acta*, **27**, 1479 (1954).

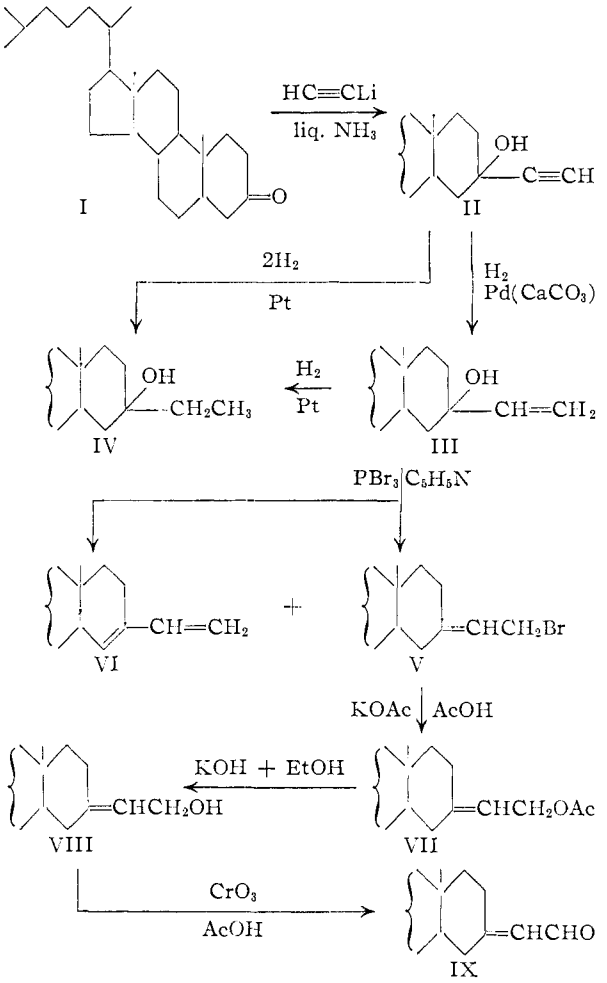


Fig. 1.—Reaction flowsheet.

mide intermediate V and prepare the ester VII by a direct rearrangement–acetylation[8] of 3-ethenylcholestan-3-ol (III). When III was heated for one hour at 110–140° in acetic anhydride with an equivalent of pyridine hydrobromide a mixture was obtained which contained 75% of the ester VII and 25% of the diene VI. However, at lower temperatures (110–120°) the yield of the diene increased to 63% while that of the ester decreased to 37%. These observations seem to indicate that the diene, formed at lower temperature by a dehydration or dehydrobromination, underwent at higher temperatures a 1,4-addition of acetic acid to give a higher yield of the ester.

In view of these results the possibility of 1,4-addition was investigated using the pure diene VI in cyclohexane with an equivalent of pyridine hydrobromide in water-free acetic acid. The reaction was studied by comparing the ultraviolet absorption extinction coefficient of the diene before and after the reaction. After shaking the mixture in nitrogen at room temperature for four days no appreciable conversion was observed. However, under reflux conditions at 110–125° for 8.5 hours, a 38% conversion of the diene to the ester was observed. This reaction was also studied in methyl Cellosolve at 100–110° with a mixture containing 63.8% diene and 36.2% ester with the purpose of increasing the ester concentration. The course of the reaction was followed spectroscopically at intervals of one hour for a period of nine hours. After five hours of heating, the concentration of the ester increased from 36.2% to a maximum of 57.8%, then it began to decrease and, after nine hours, it had reached a concentration of 46%. These results seems to indicate that under the conditions of our experiment both 1,4-addition and 1,4-elimination of acetic acid proceeded simultaneously but at somewhat different rates.

The ester VII, produced by any of the experiments outlined above, was freed from the diene by chromatography and hydrolyzed with ethanolic potassium hydroxide to give 2-cholestanylidene-ethan-1-ol (VIII) in yields of 75%.

A shorter route to the primary allylic alcohol was sought in the acid-catalyzed rearrangement of the tertiary alcohol III. No trace of the desired rearrangement product was found when a solution of III in petroleum ether was shaken for four days with an equal volume of 1% sulfuric acid solution. A similar experience was encountered by Grab and Rumpf[7] when they attempted to rearrange 2-methyl-2-carbethoxy-1-ethenylcyclohexan-1-ol to the corresponding primary alcohol in a 10% sulfuric acid solution in dioxane.

Finally, 2-cholestanylidene-ethan-1-al was obtained in yields of 50% by the chromic acid oxidation of the primary alcohol VIII in benzene solution. When the direct method of rearrangement–oxidation employed in the cyclohexane series[9] was used, a yield of 50% of the aldehyde was obtained from the alcohol III in one step. A summary of all the reactions involved in the first synthetic route of the aldehyde IX is illustrated in Fig. 2. When the aldehyde was prepared from the alcohol III *via* the bromide V the over-all yield was 20%. This yield was increased to 30% when the bromide step was eliminated and III was converted directly to the ester VII. In both cases the yield was increased 5 to 10% when the diene by-product VI was utilized. However, the best procedure was the one-step rearrangement–oxidation of III which gave a yield of 50% of the aldehyde.

A second route which makes use of the Grignard of ethoxyacetylene (X) was also investigated and ultimately proved superior to the first. However, early endeavors to prepare 3-ethoxyethynylcholestan-3-ol (XI) by this method from cholestanone yielded repeatedly ethyl cholestanylidene acetate (XII) and unreacted cholestanone. It was then discovered that traces of mineral acids present in the atmosphere of the laboratory during recovery and purification of the carbinol XI were sufficient to cause its rapid rearrangement to ethyl cholestanylidene acetate (XII). When these difficulties were overcome nearly quantitative yields of the carbinol XI were obtained.

The carbinol XI was then partially hydrogenated in ethanol using palladium-on-calcium carbonate.

(8) N. A. Milas, P. Davis and M. T. Burgess, unpublished results; N. A. Milas, "The Vitamins, Chemistry, Physiology and Pathology," edited by W. Sebrell, Jr., and R. S. Harris, Academic Press, Inc., New York, N. Y., Vol. 1, 1954, p. 39.

(9) N. A. Milas and C. P. Priesing, THIS JOURNAL, **79**, 6295 (1957).

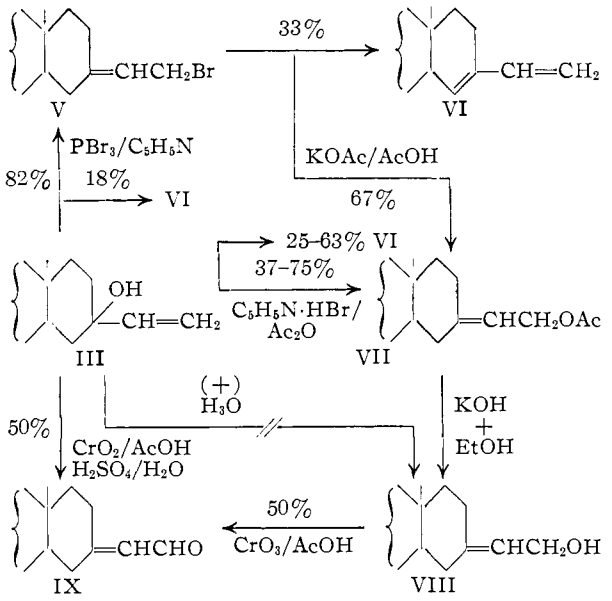


Fig. 2.—The synthesis of cholestanylidene-ethan-1-al, route 1.

The absorption of hydrogen was very rapid and the yields of XIII were quantitative. Without further purification a petroleum ether solution of XIII was shaken in nitrogen with a dilute solution of sulfuric acid thereby producing 2-cholestanylidene-ethan-1-al in nearly quantitative yields. The sequence of these reactions is shown in Fig. 3.

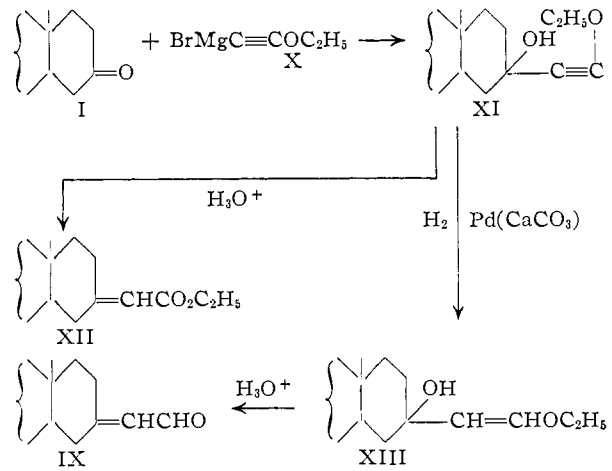
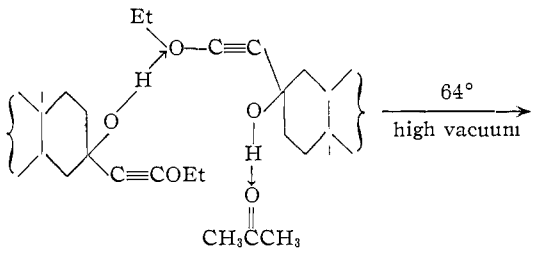
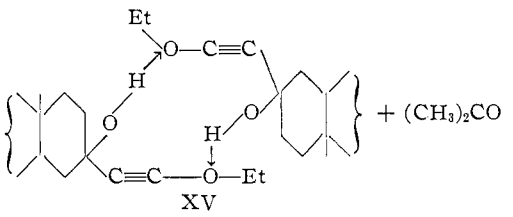


Fig. 3.—Synthesis of 2-cholestanylidene-ethan-1-al, route 2.

An interesting observation on hydrogen bonding made during the purification of 3-ethoxyethynylcholestan-3-ol (XI) is worth recording here. This carbinol always was obtained as a brownish gum from all common solvents except dry acetone from which it crystallized every time in white crystalline clusters. In spite of repeated crystallizations from acetone followed by prolonged pumping under high vacuum at room temperature, elemental analyses and infrared spectra of the crystals gave the same results, and confirmed our suspicion that acetone was bound to the ethoxyacetylenecarbinol in the ratio of one mole to two of the carbinol. The infrared spectrum of the crystals was determined in carbon tetrachloride (10%) and showed a carbonyl band at 1705 cm.$^{-1}$ with a sharp band at 3480 cm.$^{-1}$, attributed to the single hydrogen bridge of the complex probably involved in the dimeric association, and a wide intense band ranging from 3370 to 3200 cm.$^{-1}$ attributed to a stronger hydrogen bonding with the carbonyl group of the acetone.[10] When the crystals were heated at 64° overnight at high vacuum, a white gum was obtained the elemental analysis of which indicated the absence of acetone and the infrared spectrum showed a very weak band at 1705 cm.$^{-1}$, a sharp band of about the same intensity, as observed with the crystals at 3480 cm.$^{-1}$, and a narrow, much less intense, band between 3400 and 3250 cm.$^{-1}$. No unassociated hydroxyl absorption band was found in either case. These observations are consistent with the making and breaking of an intermolecular bridge between one of the hydroxyl groups of XV and the carbonyl of acetone in XIV.



XIV



XV

A somewhat similar case[11] was encountered in the literature when Δ^5-3β-acetoxy-17β-hydroxy-17α-ethoxyethynylandrostene was recrystallized from hexane–acetone. Although the compound had a good m.p. no analysis or infrared spectra were given. The fact that it was found necessary to heat this product at 65° for 60 hr. under high vacuum before an acceptable analysis was obtained led us to suspect that the original acetone-recrystallized product was an acetone complex of the type we have observed.

Since, with the exception of cholestanone, all of the compounds discussed above are new, their infrared spectra are recorded in Tables I and II.

Experimental

One-half liter of dry liquid ammonia was saturated with dry acetylene and treated with 3.2 g. (0.455 mole) of finely cut lithium allowing time for decoloration after each addition.

While acetylene was allowed to bubble through the above mixture, 25.0 g. (0.065 mole) of cholestanone in the minimum quantity of a 50–50 ether–toluene mixture was added

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954; K. Dobriner, E. R. Katzenellenbogen and R. N. Jones, "Infrared Absorption Spectra of Steroids," Interscience Publishers, Inc., New York, N. Y., 1953.

(11) H. Heuser, K. Eichenberger and P. A. Plattner, *Helv. Chim Acta*, **33**, 370 (1950).

TABLE I

INFRARED SPECTRA OF COMPOUNDS IN THE CHOLESTANE SERIES, ROUTE 1 (10% IN CARBON TETRACHLORIDE)

Compound	Group	Infrared bands, cm.$^{-1a}$
Cholestanone (I)	—C=O	1712vs, 1227s, 1250r, 1208w
	—CH_2CO	1435pm
3-Ethynylcholestan-3-ol (II)	—OH	3650p, 3460qm, 1336p, 1265qm, 1164m, 1143m, 1120m, 1034vs
	—C≡CH	3320vp
3-Ethenylcholestan-3-ol (III)	—OH	3620p, 3480q, 1340w, 1235w, 1168m, 1150m, 1129m, 1022m
	$RCH=CH_2$	3090wp, 1850vw, 1642w, 1415p, 996m, 926vs
3-Ethylcholestan-3-ol (IV)	—OH	3620p, 3500q, 1336p, 1232w, 1168m, 1150m, 1130m, 1240w, 1032m
3-Ethenylcholest-3-ene (VI)	$RCH=CH_2$	3095pr, 1610p, 1412w, 992s, 897vs
	$R_2C=CHR$	1640p, 955m, 926s, 863vw, 834w
1-Acetoxy-2-cholestanylidene-ethane (VII)	—C=O	1730s
	CH_3CO_2R	1260s, 1232s, 1204rw
	—CH_2OC=O	1017qs, 1093qm
	R_2C=CHR	3060r, 1665m, 952mq, 930w, 862w, 849w
2-Cholestanylidene-ethan-1-ol (VIII)	—OH	3640w, 3420q, 1335w, 1228w, 1164r, 1145s, 1133r, 1023m
	$R_2C=CHR$	1668w, 843m

[a] vs = very strong; s = strong; m = medium; w = weak; vw = very weak; p = sharp; q = wide; r = shoulder

TABLE II

INFRARED SPECTRA OF COMPOUNDS IN THE CHOLESTANE SERIES, ROUTE 2 (10% IN CARBON TETRACHLORIDE)

Compound	Group	Infrared bands, cm.$^{-1a}$
3-Ethoxyethynylcholestan-3-ol (XI)	—OH	3480w, 3400–3280w, 1332w, 1220s, 1142m, 1027vs, 1002s
	—C≡C—	2250s
	—C≡COC_2H_5	1286w, 1178m, 1164m, 1116–1102qm, 1090m, 1070m
Ethyl cholestanylideneacetate (XII)	R_2C=CHR	1650s, 860m
	=CHC(O)O—	1283m, 1256–1247dw, 1232rm, 1220m, 1187rw, 1165s, 1150vs, 1136r, 1120r, 1100w
	—CH_2OC=O	1042s
	—C=O	1718vs
Cholestanylidene acetic acid	—COH	3570w, 3400–2500q, 2670r, 2572r, 935qw
	—C=O	1686vs
	R_2C=CHR	1640s, 888vw, 862m
	=CHC(O)O—	1422m, 1300r, 1283m, 1265s, 1195m, 1113qm, 1000qm
2-Cholestanylidene-ethan-1-al (IX)	—C(O)H—	1667vs, 891w
	R_2C=CHR	1624m, 852m

[a] d = doublet.

dropwise over a period of 0.5 hr. An extra 200 cc. of the ether–toluene mixture was then added to allow for evaporation losses. The flow of acetylene was stopped, the flask removed from the cooling bath and stirring was continued for 24 hr. during which time the ammonia had evaporated. The residual deep-red solution was then hydrolyzed with 100 g. of tartaric acid in 300 cc. of ice-water. The organic layer was separated and the aqueous layer extracted three times with ether and the non-aqueous portions combined, washed once with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. When the solvent was evaporated 25 g. of a yellowish-brown solid separated which was subjected to a high vacuum for one hr. at 90–100°. No unreacted cholestanone was recovered by treatment of the residue with the Girard Reagent P indicating that quantitative conversion to the acetylenic carbinol had taken place. The product gave an immediate precipitate with alcoholic ammoniacal silver nitrate reagent. Finally, the yellowish-brown solid was recrystallized from ligroin, m.p. 163°, $[\alpha]^{25}D$ +22.4°, $[M]^{25}D$ +9300 (in chloroform). The infrared spectrum of this compound is recorded in Table I.

Anal. Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.70; act. H, 2.00. Found: C, 84.25; H, 11.66; act. H, 1.76.

Hydrogenation in ethyl acetate using Adams catalyst consumed 2 mole-equivalents of hydrogen to give 3-ethylcholestan-3-ol (IV), m.p. 139°. The infrared spectrum is recorded in Table I.

Anal. Calcd. for $C_{29}H_{52}O$: C, 83.35; H, 12.58. Found: C, 82.61; H, 12.23.

3-Ethenylcholestan-3-ol (III).—Palladium hydroxide (2.5 g. of 1% on calcium carbonate) was freshly reduced with hydrogen in 200 cc. of absolute ethanol and to this was added 10 g. of 3-ethynylcholestan-3-ol (II) in 100 cc. of ethanol. The mixture was allowed to absorb one mole-equivalent of hydrogen. The hydrogenation was then stopped and the mixture filtered through a Celite, analytical-filter-aid to remove the catalyst. The filtrate was diluted with water and extracted several times with ether, the combined ether extracts washed with water, dried and the ether removed. The residue was recrystallized from ligroin, m.p. 122°, yield 9.0 g. (90%). This product had an active hydrogen value of 1.02 and, when completely hydrogenated, 3-ethylcholestan-3-ol (IV), m.p. 139°, was obtained. The infrared spectrum of compound III is recorded in Table I.

1-Bromo-2-cholestanylidene-ethane (V).—An ether solution (50 cc.) containing 0.269 g. (1.0 mmole) of phosphorus tribromide was cooled to 0° and to it was added dropwise with stirring in nitrogen over a period of 0.5 hr. an ether solution (50 cc.) containing 1.0 g. (2.4 mmoles) of 3-ethenylcholestan-3-ol and 0.079 g. (1.0 mmole) of dry pyridine. The reaction mixture was stirred for one hr. at 0°, and for an additional hour at 40–50°. The ethereal solution was then decanted into a separatory funnel, washed twice with water, dried and the ether removed. The brownish residual oil was subjected to a high vacuum at room temperature for 4 hr., yield 1.0 g. With alcoholic silver nitrate this oil gave an immediate precipitate of silver bromide giving qualitative evidence for the presence of an allylic bromide. An ultraviolet absorption analysis (in cyclohexane) of the oil

revealed the presence of a maximum at 232 mμ which is characteristic for 3-ethenylcholest-3-ene (VI) obtained as a dehydrobromination by-product. Comparison of the ε value of 4130 for the oil with the ε value of 22,600 for the analytically pure diene VI indicated that the mixture contained 18% of the diene and 82% of the bromide. Since it was not possible to separate these two products at this stage, the mixture was used as such for the conversion of the bromide to the acetate.

1-Acetoxy-2-cholestanylidene-ethane (VII).—To a cyclohexane solution (100 cc.) containing 1.0 g. of the mixture obtained in the above experiment was added dropwise with stirring in nitrogen 0.3 g. of potassium acetate in 100 cc. of glacial acetic acid and the mixture heated to 60–70° for 3 hr. It was then diluted with water and extracted three times with ether, the ether extracts shaken with dilute sodium carbonate solution until neutral, washed with water, dried and the solvent removed under reduced pressure. The residue was subjected to a high vacuum for 5 hr. at room temperature and was found free from bromide. The ultraviolet spectrum had an ε (232 mμ) value of 10,100 indicating the presence of the diene VI in 45%. Since the infrared spectrum showed the presence of only the diene and the acetate it was concluded that the acetate substitution occurred to the extent of 67% and dehydrobromination 33%. The over-all yield of the acetate VII based on these measurements was therefore 55%.

The residue was treated with ethyl acetate whereby most of the diene VI crystallized out. It was recrystallized from ethanol, m.p. 84–86°. The ultraviolet spectrum gave an ε (232 mμ) of 22,600. The infrared spectrum is recorded in Table I.

Anal. Calcd. for $C_{29}H_{48}$: C, 87.84; H, 12.11. Found: C, 87.57; H, 12.03.

Acetylated Rearrangement of 3-Ethenylcholestan-3-ol (III).—To a solution of 0.5 g. (1.2 mmoles) of the carbinol III in 100 cc. of acetic anhydride was added in one portion with stirring in nitrogen 3 cc. of 0.4 *M* solution of pyridine hydrobromide in water-free acetic acid. The mixture was then heated with stirring at 110–140° for one hr., cooled and poured into 200 cc. of iced-water and extracted three times with ether. The combined extracts were washed with 5% potassium hydroxide solution, then with saturated salt solution, dried and the ether removed to give 0.48 g. of residue which was subjected to a high vacuum at 40–50° for 5 hr. When the residue was recrystallized first from isopropyl alcohol, then from ethanol, a small amount of crystalline product was obtained, m.p. 84–86°, which was identical with the diene VI.

The product from the mother liquors was recovered and an attempt to crystallize 1-acetoxy-2-cholestanylidene-ethane (VII) from it was unsuccessful in spite of the fact that infrared analysis showed mainly the presence of the acetoxy derivative. The weight distribution of the two products indicated a yield of the ester of 75–80%. When the reaction was repeated at a temperature of 110–120° for one hr. only 42.5% yield of the ester was obtained as determined spectroscopically.

Chromatographic Separation of 1-Acetoxy-2-cholestanylidene-ethane from 3-Ethenylcholest-3-ene.—A mixture (1.2906 g.) of compounds VI and VII was dissolved in 40 cc. of petroleum ether and fixed on 40 g. of ethyl acetate-washed alumina (Act. IV). Slightly positive nitrogen pressure was applied at the top of the column, and slightly reduced pressure (700 mm.) was applied at the bottom of the column to which was attached a large receiver for collecting five samples without interruption. An elution procedure was used employing 40 cc. each of petroleum ether, benzene, ether, ethyl acetate and methanol grading each change of solvent according to the ratios 9:1, 4:1 and 1:1. The progress of the chromatography was followed by ultraviolet absorption spectra. It was observed that the diene VI was most effectively eluted with petroleum ether. Eluents, petroleum ether through ethyl ether, gave mixtures of the two components while fractions eluted between ethyl ether and methanol contained only the ester component. Only about 30% of the purified ester was separated by this procedure. A further attempt to obtain the ester in the crystalline form was unsuccessful, so it was decided to hydrolyze it to the alcohol.

2-Cholestanylidene-ethan-1-ol (VIII).—The ester VII (0.6322 g.) was dissolved in 100 cc. of 95% ethanol containing 0.2 g. of potassium hydroxide and the mixture refluxed for 2 hr. It was then cooled, diluted with water and extracted with ether, the ethereal extract dried and the ether removed. The residue was subjected to a high vacuum at 90–100° for 5 hr., then recrystallized first from ligroin then from ethanol–water; yield 0.4333 g. (75%), m.p. 136.5–138°. The infrared spectrum of this compound is recorded in Table I.

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.98; H, 12.15. Found: C, 83.33; H, 12.45.

The 1,4-Addition of Acetic Acid to 3-Ethenylcholest-3-ene (VI).—A mixture (1.1208 g.) containing 63.8% of the diene VI and 36.2% of the ester VII was dissolved in 49 cc. of methyl Cellosolve and to it was added 53 cc. of water-free acetic acid, prepared by adding 15 g. of acetic anhydride to one pound of glacial acetic acid assayed at 0.5% water, and 8.0 cc. of a 0.4 *M* pyridine hydrobromide solution in water-free acetic acid. A blank was prepared simultaneously for use in ultraviolet absorption analysis. The mixture was heated with stirring in nitrogen at 100–110° while aliquot portions of 0.1 cc. were withdrawn for ultraviolet absorption analysis. Using the molecular extinction coefficient of the pure diene VI for comparison, the extent of ester formation over a given period was estimated. It was found that the ε value for the diene reached a minimum after 5 hr. showing that the ester concentration had increased from 36.2 to 57.8%, a conversion of 21.6%. Then, the ε value began to increase and, after 8 hr. of heating, the ester concentration had decreased from 57.8 to 46%.

When the reaction was repeated with the pure diene VI, using cyclohexane as the solvent instead of methyl Cellosolve and heating at 100–125°, a conversion of 38% of the diene to the ester was observed. The ester produced by this procedure was identical with that obtained by the reactions described in the previous sections, since upon hydrolysis the alcohol isolated had the same m.p. as that of 2-cholestanylidene-ethan-1-ol (VIII).

2-Cholestanylidene-ethan-1-al (IX).—To a solution of 100 cc. of benzene containing 0.31 g. of the alcohol VIII was added dropwise at 0° with stirring in nitrogen a solution of 0.075 g. of chromic acid dissolved in 2 cc. of water, 1 cc. of concentrated sulfuric acid and 20 cc. of glacial acetic acid. Stirring was continued for 0.5 hr. at 0°, 0.5 hr. at room temperature, and for one hr. at 60–70°. The mixture was then cooled and diluted with twice its volume of water, extracted with ether, the extract washed with water, dried and the ether removed to yield 0.25 g. of crude residue which was purified through its bisulfite addition product. The aldehyde was regenerated with sodium hydroxide and recrystallized from ethanol–water; yield 0.15 g. (50%), m.p. 114–115°. The 2,4-dinitrophenylhydrazone (bright red) was prepared, m.p. 243.5–244.5° (ethanol–ethyl acetate).

Anal. Calcd. for $C_{35}H_{51}N_4O_4$: C, 71.04; H, 8.69; N, 9.47. Found: C, 70.90; H, 8.57; N, 9.48.

The oxime was also prepared and purified from 95% ethanol. The m.p. was rather indistinct since it softened at 110° and finally melted at 140°.

Anal. Calcd. for $C_{39}H_{49}NO$: C, 81.46; H, 11.55; N, 3.27. Found: C, 81.43; H, 11.50; N, 3.00.

The Rearrangement–Oxidation of 3-Ethenylcholestan-3-ol (III).—To a solution of 100 cc. of benzene containing 9.0 g. (0.0215 mole) of the carbinol III was added dropwise at 0° with stirring in nitrogen a solution made up of 1 cc. of concentrated sulfuric acid, 1 cc. of glacial acetic acid and 25 cc. of water. Stirring was continued for 20 min., then 0.8 g. of chromic acid in 25 cc. of water was added over a period of 10 min. followed by 20 min. stirring. Another solution (1 cc. of concentrated sulfuric acid in 25 cc. of water) was then added and the mixture stirred for 20 min. when a second solution of 0.8 g. of chromic acid in 25 cc. of water was added in 10 min. followed by additional stirring of 20 min. at 0°. Stirring was allowed to continue at room temperature for 20 hr., then the benzene layer separated and the aqueous layer extracted several times with benzene. The benzene extracts were combined, washed with 5% solution of sodium carbonate, then with water and the benzene distilled to leave 8.0 g. of crude product.

The crude product was then digested on a steam-bath with 200 cc. of a saturated solution of sodium bisulfite with intermittent shaking, cooled and extracted with ether; the bisulfite addition product of the aldehyde was insoluble

in ether as well as in water. From the ether layer was recovered 1.5 g. of 2-cholestanylidene-ethan-1-ol (VIII), m.p. 136.5–138°. The bisulfite addition product was mixed with 50 cc. of ether and decomposed with vigorous shaking at 0° with 200 cc. of 36 *N* sodium hydroxide. After several extractions with ether, the extracts were combined, washed with water, dried and the ether removed. The crude product was recrystallized from ethanol–water; yield 4.5 g. (50%), m.p. 114–115°; ϵ (245 mμ) 30,000 (ethanol).

Anal. Calcd. for $C_{29}H_{48}O$: C, 84.39; H, 11.72. Found: C, 83.94; H, 11.90.

The 2,4-dinitrophenylhydrazone (bright red) was prepared, m.p. 243.5–245°.

3-Ethoxyethynylcholestan-3-ol (XI).—To a Grignard reagent prepared from 24 g. (0.220 mole) of freshly distilled ethyl bromide and 5.1 g. (0.210 mole) of magnesium in 300 cc. of ether was added dropwise over a period of 0.5 hr. with stirring at 0°, 16.12 g. (0.230 mole) of ethoxyacetylene[12] in 100 cc. of ether. The mixture was allowed to warm to room temperature, then refluxed gently for 0.5 hr. At this time, when the ethoxyethynylmagnesium bromide appeared as a heavy black oil finely dispersed in ether, the mixture was rapidly cooled to 0° and to it added over a period of one hr. 400 cc. of ether solution containing 40.6 g. (0.105 mole) of cholestanone previously subjected to a high vacuum for 4 hr. at 135–140°. Stirring was continued for 24 hr. at room temp. under a slow stream of nitrogen. The mixture was then hydrolyzed at 0° with 31.6 g. of tartaric acid in 200 cc. of water and the ether layer separated, washed with water, shaken with a mixture of 300 g. of chromatographic-grade basic alumina and 50 g. of magnesium sulfate, then filtered. The filtrate was further dried with magnesium sulfate, filtered and the ether removed; yield of a pale-yellow amorphous product, 44.0 g. Ultraviolet absorption analysis of this product showed no maximum at 226 mμ characteristic of ethyl cholestanylidene-acetate (XII), the by-product expected from acid-rearrangement. This product also gave a negative ketonic reaction with 2,4-dinitrophenylhydrazine reagent. Furthermore, it was not possible to crystallize this product from any of the common organic solvents except dry acetone. After several recrystallizations from this solvent, the crystals were subjected to a high vacuum at room temp. for 24 hr., m.p. 85–86°.

Anal. Calcd. for $C_{31}H_{52}O_2 \cdot {}^1/_2C_3H_6O$ (XIV): C, 80.36; H, 11.41. Found: C, 80.44; H, 11.14.

The infrared spectrum of this compound showed a sharp absorption maximum at 1705 cm.$^{-1}$ which disappeared when the compound was subjected to a high vacuum at 64° for 24 hr. leaving a non-crystalline product, $[\alpha]^{25}D$ +7.8°, $[M]^{25}D$ +3600 (in chloroform). The infrared spectrum of this compound is recorded in Table II.

Anal. Calcd. for $C_{31}H_{52}O_2$ (XI or XV): C, 81.49; H, 11.49. Found: C, 81.17; H, 11.36.

Ethyl Cholestanylidene Acetate (XII).—A petroleum ether solution (50 cc.) containing 1.0 g. of compound XI was shaken for 12 hr. with 50 cc. of water containing 3 drops of sulfuric acid. The petroleum ether was then separated, washed with water, dried over magnesium sulfate and the solvent removed to give 1.0 g. of a product which, upon recrystallization from a 50–50 mixture of methanol–ethyl acetate had a m.p. of 74°, with softening at 68°. The ultraviolet-spectrum showed an ϵ (226 mμ) of 15,800 (in ethanol). The infrared spectrum is recorded in Table II.

(12) E. R. H. Jones, G. Eglinton, B. L. Shaw and M. C. Whiting, *J. Chem. Soc.*, 1860 (1954); *Org. Syntheses*, **34**, 46 (1954); E. A. Braude and O. H. Wheeler, *J. Chem. Soc.*, 320 (1955).

Anal. Calcd. for $C_{31}H_{52}O_2$: C, 81.49; H, 11.49; $|^{=}$, 1.0. Found: C, 81.53; H, 11.56; $|^{=}$, 1.0.

Cholestanylideneacetic Acid.—When the ester XII was refluxed for 2 hr. with 10% ethanolic potassium hydroxide and the product recovered in the usual manner, a material was obtained which was recrystallized from ethanol, m.p. 226–227°. The ultraviolet spectrum showed an ϵ (224 mμ) 14000 (in ether). The infrared spectrum is recorded in Table II.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.26; H, 11.28. Found: C, 80.80; H, 11.17.

Ethyl Cholestanyl Acetate.—The ester XII was hydrogenated in ethanol using platinum oxide as catalyst and the product recovered and crystallized from ethanol–water, m.p. 62°.

Anal. Calcd. for $C_{31}H_{54}O_2$: C, 81.14; H, 11.86. Found: C, 81.25; H, 11.52.

Cholestanylacetic Acid.—Ethyl cholestanyl acetate was hydrolyzed with 10% ethanolic potassium hydroxide and, after acidification, the acid was recovered and recrystallized from ethanol, m.p. 180°.

Anal. Calcd. for $C_{29}H_{50}O_2$: C, 80.90; H, 11.70. Found: C, 80.81; H, 11.41.

3-Ethoxyethenylcholestan-3-ol (XIII).—Ten grams of palladium hydroxide (2% on calcium carbonate) catalyst was freshly reduced in 400 cc. of absolute alcohol, 44.0 g. of crystalline 3-ethoxyethynylcholestan-3-ol (XI) was then added and the mixture allowed to absorb the calculated volume of hydrogen plus 10% excess. The alcoholic solution was filtered through Celite to remove the catalyst and the filtrate diluted with saturated sodium chloride solution and extracted several times with ether. The combined ether extracts were washed with water, dried and the ether removed. The yield was nearly quantitative.

2-Cholestanylidene-ethan-1-al (IX).—A petroleum ether solution (200 cc.) containing 80.0 g. of 3-ethoxyethenylcholestan-3-ol (XIII) was shaken for 24 hr. in nitrogen with 200 cc. of 2 *N* sulfuric acid. The organic layer was then separated, washed three times with water, shaken vigorously with 200 g. of alumina (Act. III) and filtered. The alumina was washed several times with fresh portions of ether and the filtrate and washings combined, dried over magnesium sulfate, filtered and the solvent removed to give 73.0 g. of 2-cholestanylidene-ethan-1-al. This was recrystallized from ethanol–water mixture, m.p. 114–115°, $[\alpha]^{25}D$ −9.38°, $[M]^{25}D$ −3860 (in chloroform), ϵ (244.5 mμ) 30,250 (in ethanol). The infrared spectrum is recorded in Table II.

Anal. Calcd. for $C_{29}H_{48}O$: C, 84.39; H, 11.72. Found: C, 84.00; H, 11.82.

This aldehyde gave a strong purplish color with fuchsine reagent and formed a bright-red, 2,4-dinitrophenylhydrazone, m.p. 244–245° (chloroform–methanol). The ultraviolet-spectrum gave an ϵ (373 mμ) of 43,040 (in chloroform).

Anal. Calcd. for $C_{35}H_{51}N_4O_4$: C, 71.04; H, 8.69; N, 9.47. Found: C, 70.71; H, 8.63; N, 9.44.

The infrared spectrum had the expected bands for the $R_2C{=}CHCH{=}N-$ group at 1620 and 1600 cm.$^{-1}$, respectively.

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