hyde was highest the proportion of the two by-products was roughly equal, but even when the Raney nickel–ester ratios were varied from 5–1 to 20–1 both products were present.

The identity of the alcohol was checked by preparation of 3α,12α-diacetoxynorcholan-23-ol by direct reduction of ethyl 3α,12α-diacetoxynorthiolcholanate with W-4 Raney nickel in alcohol at room temperature.[2] The two alcohols were identical. The compound was crystallized both from aqueous alcohol and chloroform–hexane mixture; m. p. 148.5–151°; $[\alpha]^{26}D$ + 110° (100.0 mg. in 10 ml. of $CHCl_3$, *l* 1 dm.; αD +1.10°).

Anal. Calcd. for $C_{27}H_{44}O_5$: C, 72.30; H, 9.89. Found: C, 72.49; H, 9.95.

3α,12α-Diacetoxynorcholan-23-ol refluxed for two hours in 1–1 pyridine–acetic anhydride gave a 70% yield of 3α,-12α,23-triacetoxynorcholane, m. p. 108–110° from aqueous acetic acid.

Anal. Calcd. for $C_{29}H_{46}O_6$: C, 70.98; H, 9.45. Found: C, 71.05; H, 9.38.

3α,12α-Diacetoxynorcholan-23-ol was allowed to stand seven hours in a 5% solution of potassium hydroxide in 80% alcohol at room temperature. The product was precipitated by the addition of water, chromatographed and crystallized from aqueous alcohol to give a 70% yield of 3α,23-dihydroxy-12-acetoxynorcholane, m. p. 181.5–182°.

Anal. Calcd. for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41. Found: C, 73.89; H, 10.32.

Hydrolysis of 3α,12α-diacetoxynorcholan-23-ol in 10% alcoholic potassium hydroxide under reflux for three hours gave 83% of 3α,12α,23-trihydroxynorcholane, m. p. 194–200°. On recrystallization from ethanol the compound melted at 209.5–211°.

Anal. Calcd. for $C_{23}H_{40}O_3$: C, 75.77; H, 11.06. Found: C, 75.67; H, 10.96.

The dinitrophenylhydrazones and semicarbazones reported in Table II were prepared as described in previous papers in this series.[2]

Cyanohydrins.—The preparation of the steroid aldehyde cyanohydrins listed in Table III is illustrated by the method used for **3α-acetoxycholan-24-al cyanohydrin.** A mixture of 0.500 g. of 3α-acetoxycholan-24-al, 1.5 ml. of dioxane, and 3 ml. of saturated aqueous sodium bisulfite was stirred at room temperature for thirty minutes, then 0.5 g. of solid potassium cyanide was added and the mixture was heated for five minutes on the steam-bath, then allowed to cool to room temperature for thirty minutes, with occasional stirring. The reaction mixture was poured into 50 ml. of water giving a gummy precipitate. This was crystallized from aqueous acetic acid to give 0.476 g. (85%) of crystals melting at 148–152°. After several crystallizations from aqueous acetic acid the m. p. was 154.5–156°.

Summary

3α-Hydroxycholan-24-al, its 3-acetyl and 3-formyl derivatives, 12α-acetoxycholan-24-al, 3α,-12α-diacetoxynorcholan-23-al, 3α-acetoxy-11-cholen-24-al, and 3β-formoxy-5-cholen-24-al have been prepared by the desulfurization of the corresponding thiol esters with acetone deactivated Raney nickel catalyst.

The cyanohydrins have been obtained by treating these aldehydes with sodium bisulfite and potassium cyanide in dioxane–water.

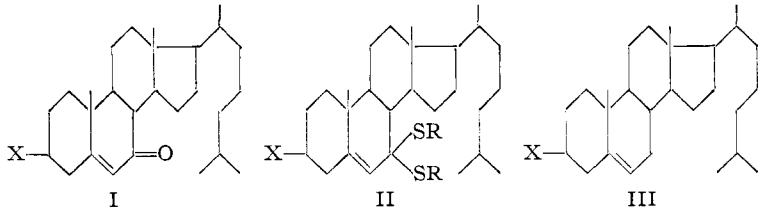
KALAMAZOO, MICHIGAN RECEIVED APRIL 28, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Addition of Mercaptans to Unsaturated Steroid Ketones

BY JACK W. RALLS,[1] R. M. DODSON[2] AND BYRON RIEGEL

Cholesterol that has been labeled with isotopic carbon in the nucleus would be useful for many biological investigations. A method for the introduction of the carbon isotopes into ring B of cholesterol (III-C) involves the intermediate 7-ketocholesterol (I-C). The final step would be the reduction of the 7-keto group to give the labelled cholesterol. This critical step was studied in some detail. Classical methods of reduction require strongly acid or basic conditions, which will cause the elimination of the group at the 3-position[3] with the formation of a second conjugated ethylenic linkage. Reduction of a carbonyl group without the simultaneous reduction of the α,β-unsaturation limits the methods that may be employed. The Wolff–Kishner reduction is unsatisfactory.



I II III

X A AcO—
B Cl—
C HO—

Recently Hauptmann[4] has prepared 4-cholestene from cholestenone by desulfurizing the dibenzyl mercaptole derivative. This method has also been used for the reduction of saturated steroid ketones[5] where the carbonyl group occupies the 3, 7, 12 and 17 positions.

The mercaptoles of 7-ketocholesteryl acetate (II-A) do not form readily. The best yield (40%) was obtained using ethanedithiol in

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(3) (a) H. Stavely and W. Bergmann, *J. Org. Chem.*, **1**, 567 (1936); (b) R. Marker, O. Kamm, G. Fleming, A. Popkin and E. Wittle, THIS JOURNAL, **59**, 619 (1937); (c) O. Wintersteiner and S. Bergstrom, *J. Biol. Chem.*, **137**, 785 (1941).

(4) H. Hauptmann, THIS JOURNAL, **69**, 562 (1947).

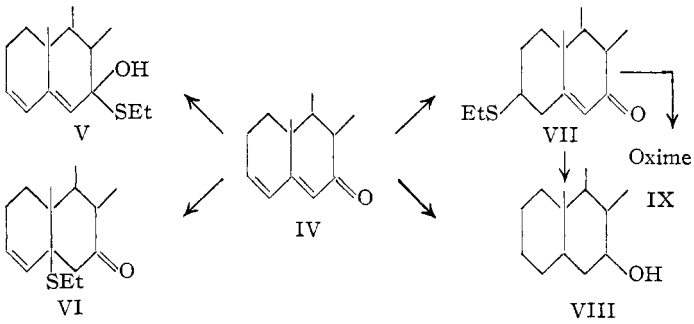
(5) (a) S. Bernstein and L. Dorfmann, *ibid.*, **68**, 1152 (1946); (b) L. Norymberska, J. Norymberski and A. Olade, *ibid.*, **70**, 1256 (1948); (c) R. H. Levin and J. L. Thompson, *ibid.*, **70**, 3140 (1948).

absolute ether with dry hydrogen chloride as the catalyst. The ethanedithiol derivative, melting at 188.2–188.8°, was reduced to cholesteryl acetate (III-A) which was isolated as the dibromide in a 40% yield. Because of the low yields on these final steps, this method did not appear feasible for the preparation of labelled cholesterol.[6]

However, when 7-ketocholesteryl acetate (I-A) was treated with ethyl mercaptan in an acetic–hydrochloric acid mixture, a good yield of a crystalline solid melting at 152–153° with a specific rotation of −106° was obtained. This compound was not the desired mercaptole. The elucidation of its structure and the course of the reaction established a new 1,6-addition.

The analytical data indicated that the substance resulted from the addition of one mole of ethyl mercaptan to 3,5-cholestadien-7-one (IV). Such a product could form if the 7-ketocholesteryl acetate had lost the elements of acetic acid to give 3,5-cholestadien-7-one which then added ethyl mercaptan. When 3,5-cholestadien-7-one was treated with ethyl mercaptan, a product identical with that from 7-ketocholesteryl acetate was obtained. The most likely compounds that would be formed by the addition of ethyl mercaptan to 3,5-cholestadien-7-one are V, VI and VII.

The presence of a carbonyl group was established when it was found that the adduct formed an oxime (IX). The addition product was unstable when heated with dilute methanolic potassium hydroxide solution. Under these conditions the adduct gave ethyl mercaptan and 3,5-cholestadien-7-one. This reversal of addition in the presence of bases is characteristic of compounds formed by 1,4-addition of mercaptans to α,β-unsaturated ketones.[7] By treating the addition product with Raney nickel in dioxane–water at 120° for twenty-four hours, complete removal of sulfur was accomplished and the product isolated was identified as 7-cholestanol (VIII). The formation of 7-cholestanol was found to be compatible with structures VI and VII when it was shown that 3,5-cholestadien-7-one gave a good yield of 7-cholestanol when reduced under the desulfuration conditions.



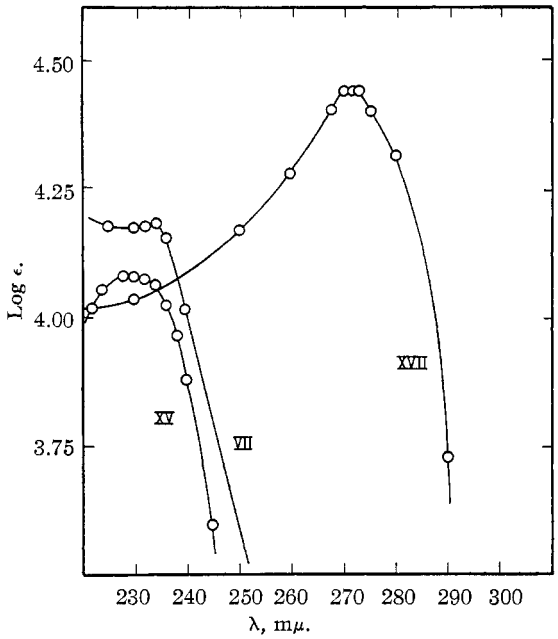


Fig. 1.—Ultraviolet absorption spectra of 3-ethylthio-5-cholesten-7-one (VII), 3-ethylsulfonyl-5-cholesten-7-one (XV), and 3-ethylthio-3,5-cholestadiene (XVII). All taken in dry ether.

An assignment of structure was made on the basis of the absorption spectrum of the adduct shown in Fig. 1. The spectrum indicates that structure VII is correct, since it is very similar to the spectra of 7-ketocholesteryl acetate and other α,β-unsaturated steroid ketones.[8] This compound, 3-ethylthio-5-cholesten-7-one (VII), would result from a 1,6-addition of ethyl mercaptan to 3,5-cholestadien-7-one. Since this type of addition has not been observed previously, a more rigorous structure proof was required.

The adduct (VII) was oxidized to a sulfone (XV) using excess hydrogen peroxide in dioxane at 100°. This compound melted at 190.0–192.0° and had a specific rotation of −64°. It would seem reasonable to expect that the sulfone (XV) would show absorption characteristics similar to VII. The absorption spectra are given in Fig. 1. The spectra are similar but the evidence was not as conclusive as we had hoped. Recently Fehnel and Carmack[9] have given an excellent presentation of the ultraviolet absorption spectra of organic sulfur compounds. However, they did not report a sulfur compound where the sulfur is attached to a bridgehead carbon atom.

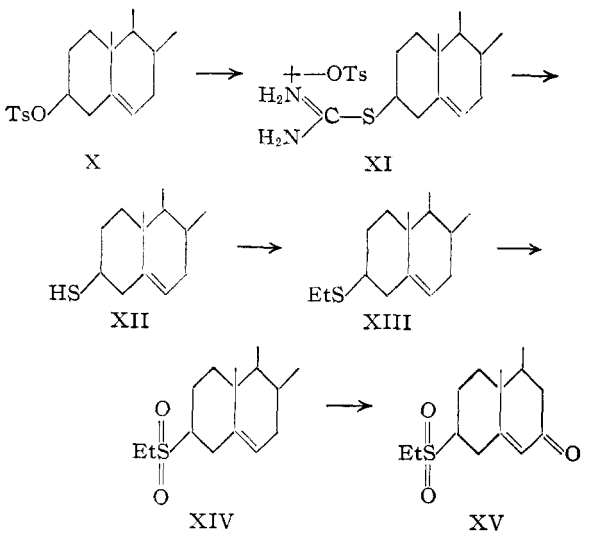
(6) Further work on these reactions was terminated when we learned from Dr. Seymour Lieberman that a similar study is in progress at the Sloan-Kettering Institute for Cancer Research.

(7) (a) B. H. Nicolet, THIS JOURNAL, **53**, 3066 (1931); (b) E. J. Morgan and E. Friedmann, *Biochem. J.*, **32**, 733 (1938).

(8) (a) H. Danneberg, *Preuss. Akad. Wiss. Math-naturw. Klasse*, No. 12 (1939); (b) I. M. Klotz, THIS JOURNAL, **66**, 88 (1944); (c) R. B. Woodward, *ibid.*, **63**, 1123 (1941).

(9) E. A. Fehnel and M. Carmack, *ibid.*, **71**, 84, 231 (1949).

To place the structure proof on a firm chemical basis, an independent synthesis of XV was carried out. The structures given in X to XV outline the method employed. By a modification of the



method of King, Dodson and Subluskey,[10] 3β-mercapto-5-cholestene (XII) was prepared. There seems to be little possible doubt that the structure of "thiocholesterol" is 3β-mercapto-5-cholestene. It has been prepared by several routes,[11-13] all of which yield the same isomer. The replacement reactions of 3β-toluenesulfonoxy-5-cholestene (X) have been studied extensively. It has been established that such replacements can lead to two isomeric products depending on the reaction conditions. Under basic (or buffered) conditions the product is predominantly the *i*-structure. Acid conditions favor replacement without inversion. In the reaction of 3β-toluenesulfonoxy-5 cholestene with thiocyanate[12] and thiourea[10] the authors have presented ample evidence that the products do not have the *i*-structure. These facts are the basis for the configurations assigned to the compounds reported in this paper. Additional evidence for these designations will be cited.

Alkyl cholesteryl sulfides are relatively unknown. The only such compound reported in the literature is the 3β-benzylthio-5-cholestene prepared by Wagner–Jauregg and Lennartz.[12] We have found that 3β-sodiothio-5-cholestene can be alkylated in excellent yield by ethyl bromide to give 3β-ethylthio-5-cholestene (XIII). This method appears to be a general one but we have not explored other possibilities. Compound XIII was prepared previously in this laboratory by the acid catalyzed rearrangement of *i*-cholesteryl methyl ether in a mixture of ethyl mercaptan and benzene.[14] Since this rearrangement is stereospecific,[15] the assignment of configuration of all the compounds reported in this paper is very probably correct.

The oxidation of 3β-ethylthio-5-cholestene (XIII) to the sulfone (XIV) was accomplished smoothly to give a compound melting at 150.8–151.6°. The sulfone when subjected to the allylic oxidation procedure[16] gave the 3β-ethylsulfonyl-5-cholesten-7-one (XV), m. p. 190.2–192.0°, $[\alpha]_D$ −64°. This material was identical with the sulfone obtained from the oxidation of the adduct formed from the addition of ethyl mercaptan to 3,5-cholestadien-7-one. Therefore, the 1,6-addition of an alkyl mercaptan to a multiple conjugated system has been established.

This type of 1,6-addition has not been observed previously. The addition of mercaptans to cinnamylideneacetophenone is stated to be a 1,4-addition,[17] although no proof of the structure of the adduct is presented. Since cinnamylideneacetophenone undergoes only 1,4-addition with a variety of reagents,[18] there is little question that the addition of mercaptans is also of this type. The 1,6-addition of ethyl mercaptan to 3,5-cholestadien-7-one is clearly a case of steric factors influencing the mode of addition. A 1,4-addition would necessitate the formation of an angular alkylthio group. Apparently the energetics of such a formation prohibit a 1,4-addition under mild conditions. This interpretation is consistent with the observation that cholestenone will not undergo a 1,4-addition of alkyl mercaptans.[4]

The generality of the reaction of 3-substituted 7-ketosteroids with ethyl mercaptan in an acetic–hydrochloric acid mixture was extended when it was found that 3β-chloro-5-cholesten-7-one (I-B) gave VII in good yield. These results suggest that this reaction may be used as a test for 7-ketosteroids which are oxygenated or halogenated in the 3-position. The applicability of this technique to mixtures has not been investigated. It has been found that cholesteryl acetate is unaffected by the reaction conditions employed. When *i*-cholestanone is treated under these conditions, only 3β-chloro-6-cholestanone results. 3-Cholestanone gives the diethyl mercaptole when the reaction time is extended. These data indicate that only the 3-ketosteroids form diethyl mercaptoles under mild conditions.

The smooth 1,6-addition of ethyl mercaptan under acid conditions was somewhat surprising. The analogous 1,4-addition of mercaptans to unsaturated ketones proceeds best when base catalyzed.[7a,19] When ethyl mercaptan was allowed to

(10) L. C. King, R. M. Dodson and L. A. Subluskey, THIS JOURNAL, **70**, 1176 (1948).

(11) H. R. Rosenberg and S. G. Turnbull, U. S. Patents 2,375,873, 2,375,874, *C. A.*, **39**, 5049 (1945).

(12) T. Wagner-Jauregg and T. Lennartz, *Ber.*, **74**, 27 (1941).

(13) A. Muller and E. Batyka, *ibid.*, **74**, 705 (1941).

(14) J. C. Colbert, Ph.D. Thesis, Northwestern University, 1946, p. 51.

(15) R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948).

(16) A. Windaus, H. Lettre and F. Schenk, *Ann.*, **520**, 98 (1935).

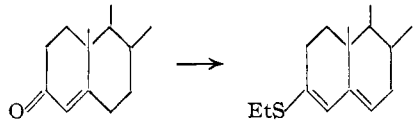
(17) S. Ruhemann, *J. Chem. Soc.*, **87**, 17, 461 (1905).

(18) E. P. Kohler and F. R. Butler, THIS JOURNAL, **48**, 1036 (1926).

(19) S. Ruhemann, *Proc. Chem. Soc.*, **20**, 251 (1904); **21**, 123 (1905).

react with 3,5-cholestadien-7-one under basic conditions, 3-ethylthio-5-cholesten-7-one was obtained but the yield was poor. Hauptmann[4] has reported that cholestenone (XVI) does not add benzyl mercaptan under basic conditions. We have found that ethyl mercaptan does not add to cholestenone under the same basic conditions which lead to 3-ethylthio-5-cholesten-7-one from the addition of ethyl mercaptan to 3,5-cholestadiene-7-one.

Under the acid conditions generally employed in this work, cholestenone (XVI) combined with ethyl mercaptan to give a good yield of the sub-



XVI XVII

stance previously reported by Bernstein and Dorfman.[5a,20] They tentatively assigned structure XVII or 3-ethylthio-3,5-cholestadiene to this material. Evidence that this structure was the correct one was obtained from the rotation and the absorption spectrum. The specific rotation of $-129°$ was that expected of a 3-substituted 3,5-cholestadiene.[21] The absorption spectrum is reproduced in Fig. 1. The auxochromic effect of the -SEt group is apparent as the maximum of 238 mμ shown by 3-acetoxy-3,5-cholestadiene[3a] is shifted toward the higher wave lengths to a degree consistent with the effect in simpler compounds.[22]

Acknowledgment.—The authors would like to express their appreciation to Professor Irving M. Klotz for helpful discussions in the determination and interpretation of the absorption spectra.

Experimental[23]

5,6-Dibromocholestanyl Acetate from 7-Ketocholesteryl Acetate.—A solution of 1.0 g. of 7-ketocholesteryl acetate[16] and 2.0 g. of ethanedithiol (b. p. 59° (30 mm.)) in 20 ml. of dry ether was prepared. A slow stream of hydrogen chloride gas was passed into the solution. A crystalline solid started to precipitate after twenty minutes. More dry ether was added to maintain a constant volume, and the addition of hydrogen chloride was continued until a red color started to develop (thirty minutes). The crystalline solid was removed by filtration and washed with cold methanol. The yield of material melting at 188.2–188.8° was 0.48 g. (40%). This compound could be crystallized from methanol without changing the m.p.; it gave a positive test for sulfur and a negative test for chlorine.

The desulfuration of this derivative was carried out in two experiments. **A.** A solution of 0.30 g. of mercaptole was prepared in 50 ml. of a two-year old Raney nickel suspension containing 9.6 g. of the catalyst. After the addition of 5 ml. of water, the mixture was heated under reflux for nine hours. The nickel components were removed by filtration and washed with ether. Removal of the solvents *in vacuo* gave a mixture of solid and gum. The solid was taken up in 20 ml. of 95% ethanol; the gum (0.037 g.) was insoluble. Diluting the ethanolic solution and cooling gave 0.065 g. of an amorphous solid which melted over a wide range (109–122°). It was thought that alcoholysis of the acetyl group had taken place. The very poor yield of organic material indicated that considerable adsorption of the steroid fraction to the catalyst had taken place. With these preliminary results available a second experiment was run.

B. A mixture of 0.178 g. of the ethanedithiol addition product, 3.0 g. of freshly prepared Raney nickel catalyst,[24] 25 ml. of purified dioxane[25] and 5 ml. of water was heated under reflux for eight hours. The catalyst was removed by filtration and washed with two portions of hot dioxane. Removal of the solvents *in vacuo* gave 0.111 g. of amorphous solid which melted at 75–95°, gave a negative test for sulfur and a positive Liebermann-Burchard reaction. A solution of 0.074 g. of this material in 5 ml. of ether–acetic acid (2:3) was treated with a dilute solution of bromine in acetic acid until a slight excess of bromine was present. Removal of the ether by evaporation, addition of a few drops of water, and cooling gave 0.052 g. of crystalline solid melting at 112–114°. The mixed m. p. with an authentic sample of cholesteryl acetate dibromide was 112–114°.

3-Ethylthio-5-cholesten-7-one (VII).—A. To a solution of 1.0 g. of 7-ketocholesteryl acetate in 25 ml. of glacial acetic acid there was added 2.0 ml. of concentrated hydrochloric acid. The steroid was precipitated. Complete solution was effected by adding 10 ml. of acetic acid and warming slightly. The solution was cooled to room temperature and 5.0 ml. of ethyl mercaptan was added. A red color developed immediately and after five minutes a crystalline solid began to deposit. After standing for thirty minutes, the solid was removed by filtration and washed with cold methanol. The dried crystalline solid weighed 0.73 g. and melted at 148–149°. Cooling the filtrate and washings gave an additional 0.10 g. melting at 146–148°. Total yield was 0.83 g. (83%). Crystallization from acetone-methanol gave long needles which melted at 152.2–152.8°; $[\alpha]^{25.4}D$ $-105.8°$ (44.6 mg. made up to 2 ml. with $CHCl_3$, $\alpha = -4.73°$, l, 2 dm.); $\lambda_{max.} = 234$ mμ ($\log \epsilon = 4.19$); solvent, dry ether.

Anal. Calcd. for $C_{29}H_{48}OS$: C, 78.32; H, 10.88; S, 7.21. Found: C, 78.25; H, 11.02; S, 7.00.

B. A solution of 0.50 g. of 3,5-cholestadien-7-one[3a] in 18 ml. of glacial acetic acid and 1.0 ml. of concentrated hydrochloric acid was treated with 2.5 ml. of ethyl mercaptan. The color immediately changed to red-orange. After five minutes a solid formed. The mixture was cooled for thirty-five minutes in an ice-bath. The solid was removed by filtration (after the solvent had melted) and washed with cold methanol. The air dried material weighed 0.53 g. (91%) and melted at 148–150°. There was no depression in melting point when this material was mixed with the product from A.

C. The preparation starting with 3β-chloro-5-cholesten-7-one[3b] was carried out as above. From 1.0 g. of the steroid there was obtained 0.95 g. of crystalline solid melting at 144–149°. This material gave a negative Beilstein test for halogen and was not depressed in melting point when mixed with the products described above. Recrystallization from methanol–acetone gave 0.84 g. (80%) melting at 147–149°.

D. A solution of 0.50 g. of 3,5-cholestadien-7-one in 20 ml. of pyridine was treated with 5.0 ml. of ethyl mercaptan. After two hours at room temperature 0.20 g. of

(20) Compare *Soc. pour l'ind. chim. à Bâle*, British Patent 554,940.

(21) (a) E. Schwenk, G. Fleischer and B. Whitman, THIS JOURNAL, **60**, 1702 (1938); (b) U. Westphal, *Ber.*, **70**, 2128 (1937).

(22) E. A. Braude, *Ann. Reports Chem. Soc.* (London), **42**, 105 (1946).

(23) Melting points are uncorrected. Microanalyses by Misses M. Hines, J. Gibbs and V. Hobbs of Northwestern University and Mr. C. W. Beazley of Micro-Tech. Laboratories, Skokie, Illinois.

(24) The catalyst was prepared according to the directions of R. Mozingo, *Org. Syn.*, **21**, 15 (1941), except after the addition of the alloy the mixture was allowed to stand at 25–30° for fourteen to sixteen hours before washing. The alkali-free catalyst was dried by azeotropic distillation with purified dioxane.

(25) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath & Co., New York, N. Y., 1941, p. 368.

commercial sodium methoxide powder was added. After an additional two and one-half hours of standing, the orange mixture was poured onto cracked ice. The orange solid was taken up in ether and the ether layer washed with three portions of water. The ether layer was dried over anhydrous sodium sulfate and the ether removed. The yellow gummy solid was dissolved in 40 ml. of methanol-acetone (3:1). On cooling, a deposit of small crystals formed; these were collected and washed with cold methanol. The yield was 0.20 g. (36%), m. p. 141–146°. The filtrate and washings gave some additional material on concentration and cooling. This melted at 95–105° and was apparently a mixture of starting material and adduct.

Desulfuration of 3-Ethylthio-5-cholesten-7-one.—A. A mixture of 0.50 g. of 3-ethylthio-5-cholesten-7-one, 3.0 g. of Raney nickel catalyst, 40 ml. of purified dioxane, and 2 ml. of water was heated under reflux for three hours. The catalyst was removed by filtration and washed with warm dioxane. Removal of the solvents *in vacuo* gave 0.498 g. of white solid which melted at 106–135°. This material was dissolved in 125 ml. of boiling methanol. After standing for twenty-four hours at room temperature 0.24 g. of crystalline solid (m. p. 148–149°) had deposited. After standing at −10° for twenty-four hours, the filtrate deposited 0.050 g. of crystals melting at 142–145°. The filtrate was evaporated to a volume of 30 ml. When cooling to room temperature produced no precipitate, the solution was heated to boiling and water added to the point of turbidity. Cooling the solution gave 0.18 g. of white solid which melted at 100–108°. Crystallization of this material from methanol-butanone gave 0.10 g. of white solid which melted at 104–110°. Later observations indicated the more soluble fraction consisted largely of 7-cholestanol (m. p. 119–120°) mixed with 3-ethylthio-5-cholesten-7-one. On the basis of the recovery of 60% of relatively pure 3-ethylthio-5-cholesten-7-one, it was estimated that only about 25% desulfuration had taken place under these conditions.

B. A mixture of 0.500 g. of 3-ethylthio-5-cholesten-7-one, 5 g. of Raney nickel catalyst, 35 ml. of purified dioxane, and 1.0 ml. of water was sealed in an 100-ml. Carius tube. The mixture was heated in a bomb furnace at 120 ± 1° for twenty-four hours. There was a slight positive pressure on opening the tube. The nickel components were removed by filtration and the solvent removed *in vacuo*. A white solid remained. This was taken up in ether, the ether solution dried over anhydrous sodium sulfate and the ether removed. The crystalline solid which remained weighed 0.424 g. (96.5%) and melted at 109–112°. This material was sulfur free. Recrystallization of 0.40 g. from ethanol gave 0.227 g. (55%) of needles melting at 119–120° which had an $[\alpha]^{26}D$ + 38.1°. This substance gave a negative Liebermann-Burchard reaction. These constants were somewhat different from those reported by Heilbron and co-workers[26] who give the melting point of 7-cholestanol as 119° and the rotation as +50.6°. The identity was proven by oxidation of the alcohol to 7-cholestanone following the directions of Marker, *et al.*[3b] From 0.20 g. of the alcohol there was obtained 0.16 g. of shiny plates which melted at 116.2–117.0°. This ketone was reduced to 7-cholestanol by the method of Heilbron, *et al.* The material was difficult to purify and after several crystallizations the needles obtained melted at 116.2–116.8°. This substance showed a marked depression in melting point when mixed with the starting ketone. A mixture with the alcohol (m. p. 119–120°) melted at 116.4–118.8°.

Stability of 3-Ethylthio-5-cholesten-7-one to Acid Conditions.—A. A mixture of 0.20 g. of 3-ethylthio-5-cholesten-7-one, 30 ml. of 95% ethanol, and five drops of concentrated hydrochloric acid was heated under reflux for three hours. When cooled the solution deposited long needles (0.20 g.) which melted at 150.8–151.8°. A mixed melting point with the starting material gave no depression.

(26) I. Heilbron, W. Shaw and F. Spring, *Rec. trav. chim.*, **57**, 529 (1938).

B. A mixture of 0.20 g. of 3-ethylthio-5-cholesten-7-one, 15 ml. of 95% ethanol and 5 ml. of concentrated hydrochloric acid was heated under reflux for six hours. The mixture had a faint red tinge and a mercaptan odor. After cooling 0.16 g. (80%) of starting material was recovered.

3-Ethylthio-5-cholesten-7-one Oxime (IX).—A mixture of 0.335 g. of 3-ethylthio-5-cholesten-7-one, 5 ml. of pyridine, 5 ml. of dry ethanol, and 0.50 g. of hydroxylamine hydrochloride was heated under reflux. Complete solution was effected when the mixture reached reflux temperature. After an eight-hour reflux period, considerable solid had formed. The mixture was cooled and the solid removed by filtration. This was washed with water and cold methanol and crystallized from dioxane–water to give 0.32 g. (92%) of crystalline solid which melted at 146–147°. The mixed melting point with the starting material was 119–129°. Recrystallization from 2-propanol gave micro needles which melted at 147.2–148.0°. The oxime gave a positive test for sulfur.

Anal. Calcd. for $C_{29}H_{49}OSN$: N, 3.05. Found: N, 3.22.

Reversal of Mercaptan Addition by Base.—A suspension of 0.40 g. of 3-ethylthio-5-cholesten-7-one in a solution of 0.50 g. of potassium hydroxide in 25 ml. of methanol was prepared. After standing for fourteen hours at room temperature, the mixture was heated under reflux. Complete solution was effected after one and one-half hours. The orange solution smelled strongly of ethyl mercaptan. After an additional one and one-half hours of heating, the solution was poured onto cracked ice and the organic material extracted with ether. The ether layer, after washing, drying, and evaporation yielded an orange solid. This substance was crystallized from methanol to give as a first crop (0.203 g.) of yellow crystalline material which melted at 105–107°. The mixed melting point with 3,5-cholestadien-7-one was 105–109°. The reversal was not complete under these conditions. The mixture was proven to be composed of the mercaptan adduct and 3,5-cholestadien-7-one when it was found that 0.190 g. of the mixture gave 0.189 g. of pure 3-ethylthio-5-cholesten-7-one melting at 150–151.5°. A second crop of 0.056 g. melting at 100–104° was obtained but was not investigated further.

7-Cholestanol.—The reduction of 3,5-cholestadien-7-one was carried out as described for 3-ethylthio-5-cholesten-7-one. The crude alcohol was recrystallized from ethanol and gave 0.30 g. (60%) of crystalline solid which melted at 119.2–120.2°. When the filtrate was evaporated and the residue crystallized from acetone, an additional 0.145 g. (29%) was obtained. This material melted at 115.5–117.0°. When mixed with the first fraction, the melting point was 116.0–117.5°. The total yield was 0.445 g. (89%).

Cholesterylisothiouronium *p*-Toluenesulfonate (XI).[10]—A suspension was prepared from 10.8 g. (0.02 mole) of 3β-*p*-toluenesulfonoxy-5-cholestene, 8.0 g. (0.105 mole) of thiourea and 140 ml. of 99% 2-propanol. The mixture was heated under reflux for four hours. Water (50 ml.) was added to the clear boiling solution at a rate which maintained ebullition. The resulting suspension was cooled to room temperature and then allowed to stand overnight in the cold room. The crystalline product was removed by filtration and washed with two 25-ml. portions of acetone (25°). The solid was dried for one hour in the air and for four hours *in vacuo* over phosphorus pentoxide at room temperature (30°). The yield of material melting at 227.5–229.0° was 11.8 g. (96%).

3β-Mercapto-5-cholestene (XII) was prepared according to the directions of King, Dodson and Subluskey.[10] From 9.84 g. of cholesterylisothiouronium *p*-toluenesulfonate there was obtained 6.10 g. (95%) of 3β-mercapto-5-cholestene, m. p. 88–95°. This material gave satisfactory results in the following preparation.

3β-Ethylthio-5-cholestene (XIII).—A solution of sodium ethoxide was prepared from 1.0 g. of sodium metal dissolved in 50 ml. of absolute ethanol. To this solution

there was added 4.10 g. (0.010 mole) of 3β-mercapto-5-cholestene. The mixture was heated to reflux temperature and the resulting solution cooled. Cold ethyl bromide (20 ml., 0.126 mole) was added and the resulting mixture heated under reflux for two hours. The mixture was poured onto 500 g. of ice and the resulting suspension extracted with ether. The ether layer was washed with water, 1.2 *N* hydrochloric acid, water, 5% sodium bicarbonate, and water. The dried ether layer was evaporated and the solid crystallized from acetone–ethyl acetate (4:1). The yield of material melting at 129.8–131.6° was 4.30 g. (98%). Recrystallization from acetone gave an analytical sample, m. p. 131.6–132.6°, $[\alpha]^{30}D$ −30.1° (0.0369 g. made up to 2.0 ml. with chloroform, αD −1.11°).

Anal. Calcd. for $C_{29}H_{50}S$: C, 80.85; H, 11.70. Found: C, 81.08; H, 11.76.

3β-Ethylsulfonyl-5-cholestene (XIV).—A solution of 2.15 g. (0.005 mole) of 3β-ethylthio-5-cholestene in 50 ml. of purified dioxane was prepared. The solution was cooled and 5.0 ml. of 30% hydrogen peroxide was added. The mixture was allowed to stand at room temperature for twenty-three hours and then heated under reflux for eight hours after the addition of 3.0 ml. of 30% hydrogen peroxide. The resulting solution was cooled and poured onto cracked ice. The suspension was extracted with two 200-ml. portions of ether. The ether layer was washed with 5% sodium bicarbonate and then with water. The solid resulting from the removal of the ether was dissolved in 110 ml. of 95% ethanol. Cooling produced a crystalline solid which melted at 149–152°. The yield was 1.4 g. (60%). Recrystallization from acetone gave an analytical sample, m. p. 150.8–151.6°, $[\alpha]^{33}D$ −18.9° (0.0456 g. made up to 2.0 ml. with chloroform, α −0.86).

Anal. Calcd. for $C_{29}H_{50}SO_2$: C, 75.27; H, 10.91. Found: C, 75.68; H, 10.98.

3β-Ethylsulfonyl-5-cholesten-7-one (XV): A. Oxidation of the Adduct.—A solution of 0.37 g. (0.864 mmole) of the adduct in 39 ml. of purified dioxane was prepared. After the addition of 3.0 ml. of 30% hydrogen peroxide, the mixture was allowed to stand for twenty-three hours at room temperature and then heated under reflux for nine hours. The resulting solution was poured onto ice. After standing overnight, the solid was removed by filtration. Crystallization from acetone–methanol gave 0.21 g. (52%) of solid melting at 186.5–188.5°. Another crystallization gave the analytical sample m. p. 190.0–192.0°, $[\alpha]^{27}D$ −64.2° (0.0340 g. made up to 2.0 ml. with chloroform, α −2.18°).

Anal. Calcd. for $C_{29}H_{48}SO_3$: C, 73.06; H, 10.15. Found: C, 72.91; H, 10.05, $\lambda_{max.}$ = 229 mμ, log $\epsilon_{max.}$ = 4.08 (in dry ether).

B. Oxidation of 3β-Ethylsulfonyl-5-cholestene.—A suspension of 1.00 g. (2.2 mmole) of 3β-ethylsulfonyl-5-cholestene in 15 ml. of glacial acetic acid was stirred vigorously and maintained at 55–58° while a solution of 0.75 g. of chromic oxide in 0.5 ml. of water and 1.5 ml. of glacial acetic acid was added over a period of forty minutes. The mixture was stirred and heated for an additional three hours. After addition of ethanol (1 ml.) to destroy the excess oxidizing agent, the warm solution was carefully diluted with 10 ml. of water. After standing overnight at 5°, the suspension was filtered and the solid washed with small portions of cold methanol until it was nearly colorless. The slightly grey solid was crystallized from acetone–methanol (1:2) to yield 0.25 g. (24%) of solid melting at 190.2–192.0°. The mixed melting point with the product from A gave no depression. The rotation was $[\alpha]^{33}D$ −64.2° (0.0385 g. made up to 2.0 ml. with chloroform, α −2.47°).

Reaction of Other Steroids with Ethyl Mercaptan in Acetic Acid–Hydrochloric Acid: A. Cholesteryl Acetate.—One gram of cholesteryl acetate was dissolved in a mixture of 35 ml. of acetic acid and 2 ml. of concentrated hydrochloric acid. Then 5 ml. of ethyl mercaptan was added to the cooled solution and the mixture allowed to stand for two hours at 0°. The solid was removed by filtration and washed with cold methanol. The dry solid (0.90 g., 90%) melted at 113–115°. Mixed melting point with starting material was 114–115°.

B. *i*-Cholestanone (3β-Chloro-6-cholestanone).—A solution of 0.105 g. of *i*-cholestanone[27] in 10 ml. of acetic acid and 0.5 ml. of ethyl mercaptan was prepared. Twenty drops of concentrated hydrochloric acid were added to the cold solution. After fifteen minutes, 5 ml. of methanol was added and the solution cooled. When no solid resulted from this treatment, water was carefully added. This resulted in the separation of a white solid. The mixture was cooled for two hours and the solid was removed by filtration and washed with cold methanol. After air drying, the solid melted at 127–129°. The mixed m. p. with 3β-chloro-6-cholestanone[15] was 127–128°. The yield was 0.090 g. (80%).

C. 3-Cholestanone (3-Cholestanone Diethyl Mercaptole).—A mixture of 0.49 g. of 3-cholestanone, 18 ml. of acetic acid, and 1.0 ml. of ethyl mercaptan was prepared. Addition of five drops of concentrated hydrochloric acid gave a cloudy suspension. Cooling for forty minutes gave a solid mixture. Addition of 15 ml. of methanol caused the solid to change to an oil. Cooling for an hour and scratching produced a solid. This was removed by filtration and washed with cold methanol. The air dried solid weighed 0.56 g. (93%) and melted at 76–78°. This was 3-cholestanone diethyl mercaptole.[5a]

D. Cholestenone (3-Ethylthio-3,5-cholestadiene).—Ten drops of concentrated hydrochloric acid was added to a mixture of 20 ml. of acetic acid, 2 ml. of ethyl mercaptan, and 1.10 g. of cholestenone. The solution soon became cloudy. Scratching and cooling gave a white solid. The mixture was cooled for one-half hour. The solid was removed by filtration and washed with three 5-ml. portions of cold methanol. The finely divided solid weighed 1.08 g. (88%) and melted at 94–95°. Recrystallization from 35 ml. of acetone gave 0.95 g. (78%) of crystalline solid melting at 97.4–98.2°. The analysis of the material corresponded to that reported by Bernstein and Dorfman[5a] when calculated on the basis of the correct formula, $C_{29}H_{48}S$; $[\alpha]^{26.4}D$ −128.8° (69.3 mg. made up to 4.93 ml. with $CHCl_3$, α −4.93°, *l*, 2 dm.); $\lambda_{max.}$ = 272 mμ (log ϵ = 4.41), taken in dry ether.

Summary

1. The keto group of 7-ketocholesteryl acetate has been reduced by converting to the ethylene mercaptole and desulfurizing.

2. In an acetic–hydrochloric acid solution, 7-ketocholesteryl acetate, 7-ketocholesteryl chloride and 3,5-cholestadien-7-one react with ethyl mercaptan to give 3-ethylthio-5-cholesten-7-one. 3,5-Cholestadien-7-one is the common intermediate for this reaction.

3. The reaction of ethyl mercaptan with 3,5-cholestadien-7-one is a new 1,6 addition.

4. The structure of 3-ethylthio-5-cholesten-7-one was established by conversion to 3-ethylsulfonyl-5-cholesten-7-one which was prepared by an independent synthesis.

5. Improved procedures are described for the preparation of 7-cholestanol, diethyl mercaptole of 3-cholestanone and for 3-ethylthio-3,5-cholestadiene (from cholestenone).

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