[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE VETERANS ADMINISTRATION CENTER, WICHITA, KANSAS, AND THE UNIVERSITY OF WICHITA]

The Reaction of Dimethyl Sulfide with 3,5-Cyclosteroids

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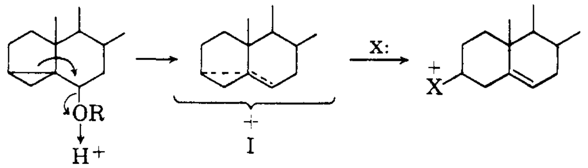
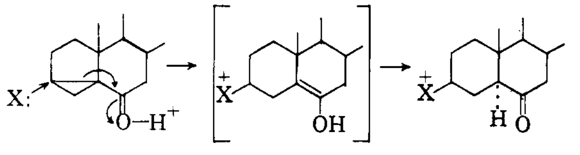
Dimethyl sulfide reacts with 3,5-cyclo-6β-hydroxycholestane and with 3,5-cyclo-6β-methoxycholestane in the presence of *p*-toluenesulfonic acid to yield 3β-dimethylsulfonio-5-cholestene *p*-toluenesulfonate. In an analogous reaction 3,5-cyclo-6-cholestanone gives 3β-dimethylsulfonio-6-cholestanone *p*-toluenesulfonate. 3β-Methylthio-6-cholestanone reacts with methylmagnesium iodide to give, subsequent to dehydration, 3β-methylthio-6-methyl-5-cholestene.

3,5-Cyclo-6-substituted steroids have been treated with pyridine and *p*-toluenesulfonic acid to give pyridinium tosylates. Similarly, such steroids react with thiourea to yield isothiouronium tosylates.[2a,b] These reactions have been described as nucleophilic attack on a hybrid carbonium ion (I)[3] in the one case and as a concerted nucleophilic attack (II)[4] in the other.

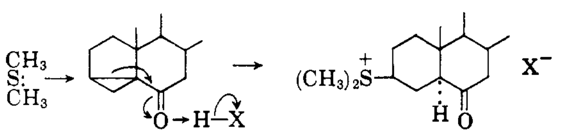




II

Our interest in sulfonium derivatives of steroids[5] prompted us to study the reaction of dimethyl sulfide on 3,5-cyclosteroids.

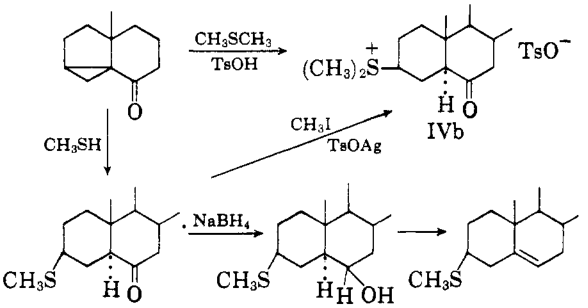
When 3,5-cyclo-6-cholestanone (III),[6] prepared from 3-chloro-6-cholestanone and potassium carbonate,[7] was treated with dimethyl sulfide and hydrogen chloride in acetonitrile, there was obtained 3β-dimethylsulfonio-6-chlolestanone chloride (IVa), m.p. 172°, in about 50% yield.



III IVa. X = Cl−
b. X = TsO−

As a by-product 3-chloro-6-cholestanone was formed in about 36% yield. As the *p*-toluenesulfonate ion (TsO−) is a poorer nucleophile[8] than chloride ion, *p*-toluenesulfonic acid was substituted for hydrogen chloride with a resultant yield of 64% of 3β-dimethylsulfonio-6-cholestanone *p*-toluenesulfonate(IVb); m.p. 184°; $[\alpha]^{25}_{D}$ 5°. The β-configuration at C-3 was established by relating the structure of IVb to the known 3β-methylthio-5-cholestene.[5]

The reaction of 3,5-cyclo-6-cholestanone with methanethiol gave 3-methylthio-6-cholestanone (V), m.p. 115°. Reduction of V with sodium borohydride yielded 3-methylthio-6-hydroxycholestane (VI), which on dehydration gave the known 3β-methylthio-5-cholestene (VII).[5] Accordingly IV, V, and VI, all have the β- or equatorial configuration at C-3.



V VI VII

In contrast to 3β-dimethylsulfonio-5-cholestene *p*-toluenesulfonate, which suffers attack at S-methyl by hydroxide ion,[5] 3β-dimethylsulfonio-6-cholestanone *p*-toluenesulfonate is attacked at C-5 giving gamma elimination with the formation of 3,5-cyclo-6-cholestanone. The latter result is attributed to the increased acidity of hydrogen at C-5 because of the presence of the carbonyl group C-6.[3,6,7]

3,5-Cyclo-6-methoxycholestane (VIII)[9] and 3,5-cyclo-6-hydroxycholestane (IX)[9] both give the previously prepared 3β-dimethylsulfonio-5-choles-

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(2) (a) L. C. King, R. M. Dodson, and L. A. Subluskey, *J. Am. Chem. Soc.*, **70**, 1176 (1948); (b) L. C. King, *J. Am. Chem. Soc.*, **70**, 2685 (1948).

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(7) F. S. Prout and Z. F. Chmielowicz, *J. Org. Chem.*, **24**, 308 (1959).

(8) C. G. Swain and C. D. Scott, *J. Am. Chem. Soc.*, **75**, 141 (1953).

(9) E. M. Kosower and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4347 (1956).

TABLE I

INFRARED ABSORPTION SPECTRA OF CHOLESTEROL DERIVATIVES

	Compound	Absorption Frequencies, Cm.$^{-1}$									
A	3,5-Cyclo-6-cholestanone	1300		1179	1131		967	922	875	811	
B	3-Methoxy-5-cholestene			1192	1111		945		837	805	740
C	3-Methylthio-5-cholestene			1161		1030	961		829	801	771
D	3-Methylthio-6-methyl-5-cholestene			1161		1031	960		825		
E	3-Methylthio-6-cholestanone	1281	1232		1161		999	925	872		
F	Cholesteryl *p*-toluenesulfonate	1370	1192	1181	1100	1030	1011		815		
G	3-Dimethylsulfonio-5-cholestene *p*-toluenesulfonate	1215	1190		1121	1031	1010		815		

tene *p*-toluenesulfonate[5] with dimethyl sulfide and *p*-toluenesulfonic acid.

Reaction of 3β-methylthio-6-cholestanone (V) with methylmagnesium iodide gave subsequent to dehydration 3β-methylthio-6-methyl-5-cholestene. The structure of the latter compound was established by comparison (mixed melting point) with the product obtained from 6-methylcholesteryl *p*-toluenesulfonate[10b] and methanethiol.

Like cholesteryl *p*-toluenesulfonate,[5] 6-phenylcholesteryl *p*-toluenesulfonate,[10a] and 6-methylcholesteryl *p*-toluenesulfonate give the corresponding sulfonium derivatives with dimethyl sulfide.

In all cases where two compounds were shown to be identical this was established by mixed melting point and comparison of infrared spectra. Table I gives the absorption peaks in the so-called finger print region for steroids (below 1350 cm.$^{-1}$).

Definitely assigned absorption peaks common to all of the compounds in Table I were: C=H stretching at 1470 cm.$^{-1}$, CH_3 absorption at 1450 cm.$^{-1}$ and 1380 cm.$^{-1}$. In addition, compounds A, E, and G showed C=O stretching absorption at 1710 cm.$^{-1}$ and CH_2 deformation at 1429 cm.$^{-1}$; compound B showed C—O absorption at 1110 cm.$^{-1}$; compounds B, C, and F, >C=C—H absorption at 819 cm.$^{-1}$

EXPERIMENTAL

3β-Chloro-6-nitro-5-cholestene. To a stirred suspension of 12 g. of 3β-chloro-5-chloestene[11] in 150 ml. glacial acetic acid was added dropwise 50 ml. of fuming nitric acid (90%). The temperature of the mixture rose to 40°. One hour later 3.5 g. of potassium nitrite was added over a period of fifteen minutes while the solution was stirred slowly. The reaction was allowed to proceed overnight in a glass-stoppered flask. The crystals, collected on a filter, were well washed with water and cold methanol to remove most of the water. They were dissolved in 350 ml. ether and precipitated by the addition of 300 ml. methanol. A further crop was obtained from the concentrated filtrates, resulting in a total yield of 19.0 g. (72%, m.p. 153°).

3,5-Cyclo-6-cholestanone.[6] 3β-Chloro-6-nitro-5-cholestene was reduced in the usual way (zinc and acetic acid) to 3β-chloro-6-cholestanone. Five grams of 3β-choloro-6-cholestanone was dissolved in 900 ml. of ethanol, and a solution of 21 g. of potassium carbonate in 45 ml. of water was added. The rapidly stirred mixture was refluxed for two hours, then distilled to remove about 300 ml. of ethanol. To the remainder, water was added well past turbidity and the mixture was shaken with chloroform (7 × 50 ml.). The crystalline residue resulting from the distillation of the solvent *in vacuo* was dissolved in hot methanol; upon cooling 4.1 g. product (89%) was obtained, m.p. 95–96°. Recrystallization from methanol raised the melting point to 97°.[6]

3β-Dimethylsulfonio-6-cholestanone chloride (IVa). To 50 ml. of acetonitrile contained in a pressure bottle were added in the order given 1.92 g. (0.005 mole) 3,5-cyclo-6-cholestanone, 7.0 ml. dimethyl sulfide, and one equivalent of hydrogen chloride dissolved in acetonitrile. Complete solution of the sterol followed on shaking the mixture, which now turned a light yellow color. After standing for two hours at room temperature, stellate aggregates of needle-shaped crystals were deposited on the inside of the flask. No perceptible heat developed in the mixture at any time. After three days the mixture was chilled and filtered. The crystals, washed with cold acetonitrile and cold ether, weighed 1.12 g., m.p. 170–172°. An additional amount of 34 mg. of product was obtained from the concentrated mother liquor, resulting in a total yield of 1.15 g. (48%). The melting point after crystallization from methanol-ether was 173°.

Anal. Calcd. for $C_{29}H_{51}OSCl$: C, 72.2; H, 10.56; Cl, 7.34. Found: C, 71.4; H, 10.34; Cl, 7.03. The mother liquor, concentrated in vacuo gave 0.75 g. needles. Crystallized from hot methanol, they melted at 131°, the melting point of 3β-chloro-6-cholestanone.

3β-Dimethylsulfonio-6-cholestanone p-toluenesulfonate (IVb) *A.* From 3,5-cyclo-6-cholestanone (III). To 1.92 g. 3,5-cyclo-6-cholestanone suspended in 50 ml. acetonitrile was added 10 ml. dimethyl sulfide, followed by 0.95 g. *p*-toluenesulfonic acid. In fifteen minutes the solids were all in solution and a clear pink tinge developed in the mixture. The solution, after standing for two hours at room temperature, was poured into 10–15 times its volume of ether and refrigerated overnight. The crystals, washed on a filter with cold ether, weighed 1.96 g. (63.4% theory), and melted at 169–170°. Recrystallization from methanol-ether three times gave a product melting at 183°. $[\alpha]^{27}_{D}$ ($CHCl_3$) −5°.

Anal. Calcd. for $C_{36}H_{58}O_4S_2$: C, 69.9; H, 9.39; S, 10.36. Found: C, 70.1; H, 9.56; S, 10.33.

B. From 3β-methylthio-6-cholestanone. One gram (2.3 mmoles) of 3β-methylthio-6-cholestanone (V) was dissolved in 5 ml. of ether and 1 ml. of methyl iodide was added. After standing for ten hours the precipitated sulfonium iodide was filtered, dissolved in methyl alcohol, and shaken with silver *p*-toluenesulfonate. Silver iodide and excess silver *p*-toluenesulfonate were removed by filtration and ether was added to the filtrate to precipitate the product. Crystallization from alcohol-ether gave 300 mg. of a product melting at 184° and identical (mixed m.p.) with the product obtained from 3,5-cyclo-6-cholestanone.

Reaction of 3β-dimethylsulfonio-6-cholestanone p-toluenesulfonate with potassium hydroxide. A mixture of 500 mg. of 3β-dimethylsulfonio-6-cholestanone *p*-toluenesulfonate and 10 ml. of 5% alcoholic potassium hydroxide was refluxed for one hour. The mixture was poured into water and extracted with ether. The ether extract was evaporated to dryness and

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[10] (a) R. A. Sneen, *J. Am. Chem Soc*, **80**, 3971 (1958); (b) *J. Am. Chem. Soc.*, **80**, 3982 (1958).

[11] E. M. Kosower and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4354 (1956).

the residue crystallized from methanol. The melting point of the product was 96°. A mixed melting point with authentic 3,5-cyclo-6-cholestanone was 96–97°.

Reaction of 3,5-cyclo-6β-methoxycholestane with dimethyl sulfide and p-toluenesulfonic acid. To 50 ml. of acetonitrile were added 2.0 g. (0.005 mole) 3,5-cyclo-6β-methoxycholestane,[9] 10 ml. dimethyl sulfide, and 0.95 g. *p*-toluenesulfonic acid monohydrate. The solids formed a cake on the bottom of the cylinder, which was shaken intermittently during 30 minutes. At the end of that time floccules began falling to the bottom while the cake of starting material was gradually diminishing in bulk. After three hours, the chilled mixture was filtered. The ether-washed crystals (1.808 g.) melted at 183°. Three crystallizations from methanol-ether raised the melting point to 202°. The dark-colored tar from the mother liquor was triturated with acetone and refrigerated for 48 hours. On filtration 0.125 g. crystals were obtained, which, after crystallization from methanol-ether melted at 200–202°. The total yield of pure product was 1.81 g. and was identified as 3β-dimethylsulfonio-5-cholestene *p*-toluenesulfonate by mixed melting point with an authentic preparation.

The filtrates and ether washings were distilled *in vacuo*, leaving a residue insoluble in cold methanol but soluble in acetone. Three crystallizations from methanol yielded a product melting at 78–80°. A mixed melting point with 3β-methoxy-5-cholestene (m.p. 84°) was 82°.

Reaction of 3,5-cyclo-6β-hydroxycholestane with dimethyl sulfide and p-toluenesulfonic acid. 3,5-Cyclo-6β-hydroxycholestane,[9] 1.933 g. (0.005 mole), was suspended in 50 ml. freshly distilled acetonitrile and dimethyl sulfide (10 ml.) was added. This was followed by 0.95 g. (one equivalent) of *p*-toluenesulfonic acid. On shaking briefly, a solid mass of crystals was precipitated, m.p. 193°. Recrystallized from methanol-ether, the compound showed no depression of melting point on mix-melting with 3β-dimethylsulfonio-5-cholestene *p*-toluenesulfonate (198°). The concentrated mother liquor yielded 0.450 g. crystals, m.p. 133°. They were identified as cholesteryl *p*-toluenesulfonate by mixed melting point with a known preparation of the compound.

3β-Methylthio-6-cholestanone (V). A mixture of 3.84 g. (0.01 mole) of 3,5-cyclo-6-cholestanone, 50 ml. of nitromethane, 10 ml. of methanethiol, and 0.1 g. of *p*-toluenesulfonic acid was placed in a pressure bottle and allowed to stand over night at room temperature. The opened bottle was heated on a steam bath for one hour, during which time an oily precipitate dissolved. The semicrystalline product which separated from the cooled solution was filtered off, washed with methanol, and crystallized from ethanol; yield 1.0 g., m.p. 115°. The filtrate and washings were evaporated *in vacuo* (water pump) and the residue was crystallized from hot methanol giving an additional 1.6 g. The total yield of product, melting at 115° was 2.6 g. or 60%. $[\alpha]_D^{25}$ −13.

Anal. Calcd. for $C_{28}H_{48}OS$: C, 77.7; H, 11.11; S, 7.41 Found: C, 77.6; H, 11.24; S, 7.22.

3β-Methylthio-6-methyl-5-cholestene. A. From 3β-methylthio-6-cholestanone. One g. (2.3 mmole) of 3β-methylthio-6-cholestanone was dissolved in 5 ml. of ether and slowly added to 5 ml. of 1*N* methylmagnesium iodide in ether. After five hours the mixture was poured into a solution of aqueous ammonium chloride. Ten ml. of ether was added and the separated ether layer was dried over sodium sulfate and distilled. The dry residue was refluxed for one hour with 75 ml. acetic acid containing 0.3 g. of *p*-toluenesulfonic acid. Water was added to incipient turbidity and the solid which separated on cooling was crystallized twice from acetone. M.p. 97°. $[\alpha]_D^{25}$ −32.

Anal. Calcd. for $C_{29}H_{50}S$: C, 81.1; H, 11.64; S, 7.44. Found: C, 80.6; H, 11.81; S, 7.32.

B. From 6-methylcholesteryl p-toluenesulfonate. A mixture of 2.75 g. (0.005 mole) of 6-methylcholesteryl *p*-toluenesulfonate,[11b] 40 ml. glacial acetic acid, and 10 ml. methanethiol was placed in a pressure bottle and allowed to stand at 35° for 48 hours. The clear solution was evaporated to dryness under vacuum and the residue was crystallized from acetone. The yield of compound melting at 97° was 1.5 g. (50%). A mixed melting point with the compound obtained in A above was 97°.

3β-Methylthio-5-cholestene (VII). A mixture of 1 g. (2.3 mmoles) of 3β-methylthio-6-cholestanone, (V) 2 g. of sodium borohydride, and 50 ml. of dioxane was allowed to stand at room temperature for three hours, diluted with water, and extracted with ether. The ether was dried over sodium sulfate and then concentrated at reduced pressure. The residue was dissolved in 75 ml. of glacial acetic acid containing 0.3 g. of *p*-toluenesulfonic acid. The mixture was refluxed for one hour and diluted to incipient turbidity with water. On cooling, the solution deposited white crystals. Several crystallizations from acetone gave a product melting at 125°. A mixed melting point with an authentic sample of 3β-methylthio-5-cholestene[5] showed no depression.

6-Phenylcholesteryl p-toluenesulfonate. This was prepared essentially as described by Sneen,[10a] except that three intermediate steps were omitted and the precurser 6β-phenylcholestan-3β,6α-diol was dehydrated directly with thionyl chloride to yield the desired compound. In this respect the procedure is similar to that employed by Sneen for the synthesis of 6-methylcholesteryl *p*-toluenesulfonate.[10b]

3β-Dimethylsulfonio-6-methyl-5-cholestene p-toluenesulfonate. To 100 ml. acetonitrile was added 1.10 g. (0.002 mole) 6-methylcholesteryl *p*-toluenesulfonate, followed by 23 ml. dimethyl sulfide. The suspended solid gradually dissolved giving a clear red-colored solution after 24 hours (30°). Four days later, the solution was chilled and the crystals were washed on a filter with ether (m.p. 162°). A further crop was isolated from the mother liquor, washings, and filtrates. Crystallized from methanol-ether, the product weighed 0.863 g. (70% theory) and melted at 168°.

Anal. Calcd. for $C_{7}H_{30}O_{3}S_{2}$: C, 72.2; H, 9.74; S, 10.4. Found: C, 72.5; H, 9.52; S, 10.41.

3β-Dimethylsulfonio-6-phenyl-5-cholestene p-toluenesulfonate. To 75 ml. of nitromethane was added 1.854 g. (0.003 mole) of 6-phenylcholesteryl *p*-toluenesulfonate.[10a] Warming the mixture to 50° caused but a slight amount of the sterol to dissolve. When 15 ml. of dimethyl sulfide was added the greater part of the sterol went into solution. After three days at 40° the solvent became water clear. The fourth day fine needle-shaped crystals began to form and continued to increase in amount until the seventh day. The crystals, weighing 2.0 g., were crystallized from methanol-ether; m.p. 200–201°; weight, 1.435 g. The filtrate on being concentrated gave a further crop of 0.210 g. product. The combined crystals were dissolved in hot nitromethane and refrigerated. The separated solids were washed with a mixture of ether nitromethane (1:1), m.p. 203–204°.

Anal. Calcd. for $C_{2}H_{62}OS_{2}$: C, 74.4; H, 9.18; S, 9.45. Found: C, 74.1; H, 0.93; S, 9.45.

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