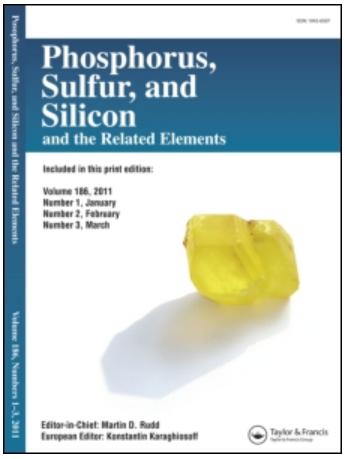

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CHOLESTERYL DELTA-AMINOBUTYL SULFIDES FROM CYCLIC SULFONIUM SALTS

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CHOLESTERYL DELTA-AMINOBUTYL SULFIDES FROM CYCLIC SULFONIUM SALTS

by

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In the course of studies with cholesterol sulfur derivatives, cholesteryl 3β-sulfonium salts were observed to act as alkylating agents toward amines.[1] 3β-Dimethylsulfonio-5-cholestene salts and aniline gave *N*-methylaniline, and not *N*-cholesterylaniline. Thus, the reaction seemed to be controlled more by steric requirements than by stabilizing factors involved in incipient formation of the homoallylic carbonium ion.

It seemed of interest to determine the course of the reaction with cyclic sulfonium salts, such as 3β-tetramethylenesulfonio-5-cholestene tosylate,[2] as δ-aminobutyl sulfides might be produced. Amino sulfides are known to form complexes with heavy metal ions.[3] Such complexes are important in biochemical processes, in analytical separations, and in drug design. The main route to amino sulfides with the two functional groups appropriately spaced for cyclic complexes involves nucleophilic displacement of halogen from the corresponding halo sulfides or halo amines. These methods often use toxic substances. Furthermore, the preparation of the starting materials usually involve selective displacement of one halogen atom from a dihalide with consequent low yields.

3β-Tetramethylenesulfonio-5-cholestene tosylate was found to react with primary and secondary aliphatic and aromatic amines by opening the five-membered heterocyclic ring to give δ-aminobutyl sulfides as the predominant products. The reaction was driven to completion through the use of excess amine. Cholesteryl amines were not isolated in the present work, although there was some indication that basic steroids were formed in minor yields as byproducts. The assigned structures as 3β-cholestene derivatives were confirmed by molecular rotation measurements, which were between −24° and −32° for all the aminobutylcholestenes prepared in the present study. The sidechain structure was consistent with nuclear magnetic resonance and infrared data and the products gave acceptable elemental analyses.

Studies are continuing on the applicability of the method to the preparation of other aminoalkyl sulfides. Apparently the method is adaptable for the preparation of a variety of aminoalkyl sulfides according to the equation, where R′ is relatively large:

$$(CH_2)_xS{-}R'^{+} + R_2NH \rightarrow R_2N(CH_2)_xSR'$$

Experimental Section

General procedure for the preparation of 3β-(δ-aminobutylthio)-5-cholestenes. 3β-(δ-Diethylaminobutylthio)-5-cholestene. A solution of 1.17 g of 3β-tetramethylenesulfonio-5-cholestene tosylate and 5 ml diethylamine in 50 ml absolute ethyl alcohol was refluxed for five hours. The mixture was then diluted with an equal volume of water and 0.5 g of sodium bicarbonate was added. The resultant mixture was distilled to remove alcohol and excess amine. (In experiments with higher boiling amines such as aniline, sufficient water was added to remove the excess amine by steam distillation.) The residue was extracted with methylene chloride. The product was recovered by addition of ethanol and concentration of the resultant solution by evaporation. The product was recrystallized from ethanol to give 480 mg. (48%) 3β-(δ-diethylaminobutylthio)-5-cholestene, mp 53–55°, $[\alpha]_D^{23}$ −30° ($CHCl_3$, c 1), as colorless platelets. In comparison to the nmr spectrum of cholesterol, the nmr spectrum showed extra signals in the 2.2 to 2.7 δ range (CH_2 protons adjacent to N and S) and around 1.0 δ (methyl protons of the ethyl groups). The *C*-6 proton signal appeared at 5.28 δ.

Anal. Calcd. for $C_{35}H_{63}NS$: C, 79.32; H, 11.98. Found: C, 79.34; H, 11.86.

3β-(δ-*n*-Butylaminobutylthio)-5-cholestene was obtained similarly in 65% yield from *n*-butylamine and 3β-tetramethylenesulfonio-5-cholestene tosylate as a waxy solid, sintering at 90°, $[\alpha]_D^{23}$ −24° ($CHCl_3$, c 1), after precipitation from methylene chloride-ethanol.

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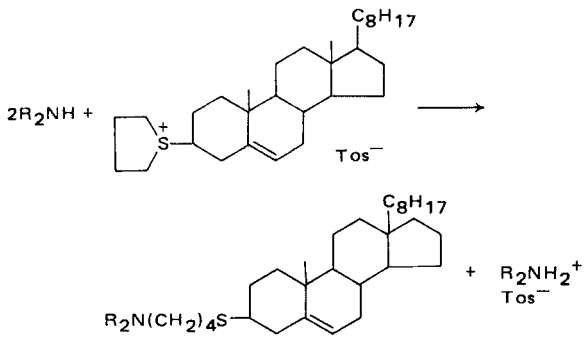
[3] E. E. Reid, Organic Chemistry of Bivalent Sulfur, Vol. II, Chemical Publishing Co., Inc., New York, N.Y., 1960, p. 294.



Anal. Calcd. for $C_{35}H_{63}NS$: C, 79.32; H, 11.98. Found: C, 78.89; H, 11.65.

3β-(δ-Anilinobutylthio)-5-cholestene was prepared from aniline as above in 67% yield as colorless needles, mp 51–52°, $[\alpha]_D^{23}$ −32° ($CHCl_3$, c 1), after recrystallization from acetone-ethanol. The nmr spectrum was compared with that of cholesterol and showed additional signals, attributed to $C_6H_5(f)NH(e)CH_2(d)CH_2(a)CH_2(a)CH_2(b)SCH(c)$, centered at 1.67 δ (*a*), 2.25 δ (*b*), 2.51 δ (*c*), 3.03 δ (*d*), 3.40 δ (*e*), and 6.8 δ (*f*) relative to tetramethylsilane. The cholesterol signals at 3.20 δ (*C*-6 H) was still present. Infrared analysis showed the N–H stretching band at 2.9 μ and aromatic patterns.

Anal. Calcd. for $C_{37}H_{59}NS$: C, 80.81; H, 10.81. Found: C, 81.07; H, 10.99.

3β-(δ-*N*-Methylanilinobutylthio)-5-cholestene was isolated similarly using *N*-methylaniline in 63% yield as colorless platelets, mp 89–90°, $[\alpha]_D^{23}$ −24° ($CHCl_3$, c 1), after recrystallization from acetone.

Anal. Calcd. for $C_{38}H_{61}NS$: C, 80.93; H, 10.90. Found: C, 80.95; H, 10.72.

3β-(δ-Morpholinobutylthio)-5-cholestene was obtained from excess morpholine as colorless needles, mp 64–66°, $[\alpha]_D^{23}$ −25° ($CHCl_3$, c 1), after recrystallization from methylene chloride-methanol.

Anal. Calcd. for $C_{35}H_{61}NOS$: C, 77.28; H, 11.30. Found: C, 77.05; H, 11.12.