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Abstract

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SYNTHESIS OF 2,3-DIMERCAPTOPROPYLAMINE AND ITS N-MONO- AND N,N′-DIALKYL DERIVATIVES

(Presented by Academician A. N. Nesmeyanov on 18 VI 1962)

Vicinal dithiols attract attention as compounds possessing considerable biological activity, for example, in antidote therapy and in the prophylaxis of radiation injury (2,3-dimercaptopropanol (^{1}), α,β-dimercaptopropionic acid (^{2}), 2,3-dimercaptopropylamine (^{3})). 2,3-Dimercaptopropylamine in the form of the base has been obtained by several authors by similar methods ($^{5-7}$)

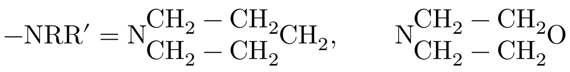
$$CH_2BrCHBrCH_2NH_2 \cdot HCl \xrightarrow{NH_4SH} CH_2(SH)CH(SH)CH_2NH_2.$$

The reaction of 2,3-dibromopropylamine hydrochloride with ammonium hydrosulfide was carried out in methyl alcohol with heating in a closed vessel to 80-90°; only the reaction time was varied, from 12 hr (^{6}) to 16 hr (^{7}). The yield of the dithiol in the best case (^{7}) reached 40% of theory, whereas in another work (^{6}) the yield of 2,3-dimercaptopropylamine did not exceed 20%. Stoken (^{7}) indicated that, to obtain 2,3-dimercaptopropylamine, mercaptation must be carried out with ammonium hydrosulfide and that the use of sodium or potassium hydrosulfide does not lead to the desired results. There are no data in the literature on the preparation of salts of 2,3-dimercaptopropylamine. Of the derivatives of 2,3-dimercaptopropylamine, only N-2,3-dimercaptopropylphthalimide and certain 2,3-dimercaptopropylsulfamides are known (^{4}).

We investigated the mercaptation reaction of 2,3-dibromopropylamine hydrobromide in methyl alcohol at room temperature using potassium hydrosulfide. When the reaction was carried out for 12 days, the hydrochloride salt of 2,3-dimercaptopropylamine was obtained in a yield of 60% of theory. Study of the kinetics of mercaptation of 2,3-dibromopropylamine hydrobromide by paper radiochromatography using the isotope S^{35} (^{8}) showed that the reaction proceeds in two stages and that complete replacement of bromine by mercapto groups under these conditions is completed already on the ninth day. A series of N-alkyl- and N,N′-dialkyl-2,3-dimercaptopropylamine derivatives, as well as N-2,3-dimercaptopropylpiperidine and N-2,3-dimercaptopropylmorpholine, was also obtained for the first time

$$CH_2BrCHBrCH_2NRR' \cdot HBr \xrightarrow{KSH} CH_2(SH)CH(SH)CH_2NRR',$$

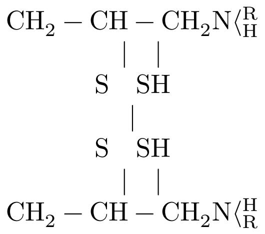
$$R = R' = H; \quad R = H,\ R' = n\text{-}C_5H_{11},\ C_6H_{13}; \quad R = R' = C_2H_5,\ n\text{-}C_3H_7,\ n\text{-}C_4H_9;$$



$$-NRR' = N{\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}}CH_2, \qquad N{\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}}O$$

The mercaptation reaction of 2,3-dibromopropylamine and its N-derivatives was carried out in methanolic solution, using a molar ratio of dibromide to potassium hydrosulfide equal to 1 : 9. The reaction time was varied from 12 to 20 days. The yield of dithiols reached 50–75% of theory. All the dithiols obtained, except N-*n*-amyl-2,3-dimercaptopropylamine, are colorless liquids with a characteristic mercaptan odor. In the case

From the compound of N-*n*-amyl-2,3-dimercaptopropylamine the compound was isolated in crystalline form and, as shown by a qualitative reaction, had free mercapto groups. However, it is possible that this is a product of incomplete oxidation of the dithiol, having the following structure



$$\begin{array}{c}CH_2-CH-CH_2N\langle{}^{R}_{H}\\ \quad\ \ |\quad |\\ \ \ S\quad SH\\ |\\ \ \ S\quad SH\\ \quad\ \ |\quad |\\ CH_2-CH-CH_2N\langle{}^{H}_{R}\end{array}$$

The results of elemental analysis do not make it possible to draw a final conclusion about the structure of the compound.

Experimental Part

Hydrochloride of 2,3-dimercaptopropylamine. 42 g (0.14 mole) of 2,3-dibromopropylamine hydrobromide (^{9}) was treated with 87.4 g (1.2 mole) of potassium hydrosulfide in 800 ml of methyl alcohol at room temperature for 20 days. Then, with a stream of dry hydrogen chloride, the excess potassium hydrosulfide was decomposed, the precipitated inorganic salt was filtered off, and the solvent was removed in vacuo. The residue was extracted with anhydrous ethyl alcohol, the extract was evaporated in vacuo, and white crystals were obtained. Yield 13.6 g (60% of theory). All operations were carried out in an atmosphere of nitrogen. The substance is very hygroscopic, has a characteristic mercaptan odor, is readily soluble in water, methyl and ethyl alcohols, and insoluble in ether and chloroform. M.p. 245° (dec.).

Found %: C 22.67, 22.75; H 6.67, 6.40
$C_3H_{10}NS_2Cl$. Calculated %: C 22.79; H 6.31

N-*n*-amyl-2,3-dimercaptopropylamine. The starting dibromide was obtained by a procedure analogous to ([9]). White crystals, stable in air, m.p. 212° (from isopropyl alcohol), yield 91% of theory.

Found %: C 26.12, 26.18; H 5.00, 4.91; N 3.89, 3.90
$C_8H_{18}NBr_3$. Calculated %: C 26.13; H 4.94; N 3.80

30.6 g of N-*n*-amyl-2,3-dibromopropylamine hydrobromide was treated with 53.5 g of potassium hydrosulfide in 800 ml of methyl alcohol for 30 days. Then the excess hydrosulfide was decomposed with conc. hydrochloric acid, and the solvent and water were distilled off in vacuo. The remaining oil was neutralized under a layer of benzene with conc. ammonia, and the base was extracted with benzene until the reaction for mercapto groups disappeared in subsequent portions of the extract. The benzene solution was evaporated under reduced pressure, and N-*n*-amyl-2,3-dimercaptopropylamine was obtained as a dark-red oil, which was distilled in vacuo. All operations were carried out in a stream of nitrogen. B.p. 65–68°/0.009 mm. Already during distillation the product began to crystallize. White crystals, unstable in air, with a specific mercaptan odor, m.p. 37°, yield 6.5 g (35% of theory).

Found %: C 49.66, 49.91; H 9.98, 9.98
$C_8H_{19}NS_2$. Calculated %: C 49.68; H 9.95

N-*n*-hexyl-2,3-dimercaptopropylamine. The starting hydrobromide of N-*n*-hexyl-2,3-dibromopropylamine was obtained by the method

analogous to (9). Colorless crystals, m.p. 182° (from water), yield 93% of theory.

$C_9H_{19}NBr_3$.	Found, %:	C 28.38, 28.28; H 5.38, 5.13; N 3.51, 3.53
	Calculated, %:	C 28.37; H 4.91; N 3.67

The dithiol was obtained by the method described above, from 31.8 g of dibromide and 53 g of potassium hydrosulfide. Reaction time 20 days. Colorless liquid with a characteristic mercaptan odor, yield 4.6 g (27% of theory), n_D^{20} 1.5108, d_4^{20} 0.9990, MR_D 62.46, calculated 62.12.

$C_9H_{21}NS_2$. Found, %: C 51.94, 51.89; H 10.09, 10.27
Calculated, %: C 52.12; H 10.21

N,N′-diethyl-2,3-dimercaptopropylamine. The hydrobromide of N,N′-diethyl-2,3-dibromopropylamine was obtained by method (10), m.p. 89-90° (from ethanol), yield 85%. The dithiol was obtained, as described above, from 48.9 g of dibromide and 86 g of potassium hydrosulfide. Duration of standing of the reagents 20 days. Colorless liquid with an unpleasant mercaptan odor, unstable in air; yield 18.6 g (74% of theory), b.p. 51-53°/0.003 mm, n_D^{20} 1.5211, d_4^{20} 1.0388, MR_D 52.8, calculated 53.3.

$C_7H_{17}NS_2$. Found, %: C 46.82, 46.78; H 9.27, 9.42; N 7.79, 7.90
Calculated, %: C 46.86; H 9.49; N 7.81

N,N′-dipropyl-2,3-dimercaptopropylamine. The hydrobromide of N,N′-dipropyl-2,3-dibromopropylamine was obtained by a method analogous to (9). White crystals, m.p. 78-80° (from methanol), yield 89% of theory.

$C_9H_{20}NBr_3$. Found, %: C 28.59, 28.46; H 5.35, 5.40; N 3.65, 3.54
Calculated, %: C 28.30; H 5.24; N 3.67

The dithiol was obtained by the method described above, from 54 g of dibromide and 86 g of potassium hydrosulfide. Duration 20 days. Colorless liquid with a mercaptan odor, unstable in air; yield 17.2 g (61% of theory), b.p. 65°/0.005 mm, n_D^{20} 1.5021, d_4^{20} 0.9750, MR_D 63.76, calculated 64.1.

$C_9H_{21}NS_2$. Found, %: C 52.07, 52.19; H 9.91, 9.87; N 6.99, 6.92
Calculated, %: C 52.13; H 10.02; N 6.76

N,N′-dibutyl-2,3-dimercaptopropylamine. The hydrobromide of N,N′-dibutyl-2,3-dibromopropylamine was obtained by a method analogous to (9). A noncrystallizing, chromatographically pure oil was used in the reaction. The dithiol was obtained by the method described above, from 57.5 g of dibromide and 86 g of potassium hydrosulfide. Duration of standing 20 days. Colorless liquid with an unpleasant mercaptan odor, yield 15 g (45.5% of theory), b.p. 61-65°/0.003 mm, n_D^{20} 1.4991, d_4^{20} 0.9460, MR_D 72.99, calculated 72.44.

$C_{11}H_{21}NS_2$. Found, %: C 56.09, 56.19; H 10.86, 10.70; N 5.91, 5.73
Calculated, %: C 56.16; H 10.63; N 5.95

N-2,3-dimercaptopropylpiperidine. The hydrobromide of N-2,3-dibromopropylpiperidine was obtained by a method analogous to (9), with a yield of 92% of theory. Snow-white crystals, m.p. 159.5-160° (from isopropyl alcohol).

$$C_8H_{16}NBr_3. \begin{array}{ll} \text{Found, \%:} & \text{C } 26.26,\ 26.50;\ \text{H } 4.40,\ 4.57 \\ \text{Calculated, \%:} & \text{C } 26.31;\ \text{H } 4.63 \end{array}$$

The dithiol was obtained by the method described above, from 51 g of dibromide and 86 g of potassium hydrosulfide. Standing time 17 days. Colorless

liquid with an unpleasant odor, yield 21.7 g (81% of theory), b.p. 68-69°/0.002 mm, n_D^{20} 1.5330, d_4^{20} 1.0590, MR_D 57.00, calculated 56.64.

Found, %: C 49.93; 50.15; H 8.96, 9.06
$C_8H_{16}NS_2$. Calculated, %: C 50.25; H 8.89

N-2,3-dimercaptopropylmorpholine. N-2,3-dibromopropylamine bromohydrate was prepared by a procedure analogous to that in ([9]). A thick, noncrystallizing oil was introduced into the reaction. The dithiol was obtained by the method described above from 53 g of the dibromide and 86 g of potassium hydrosulfide. Standing time 22 days. A colorless liquid with an unpleasant odor, yield 23.2 g (85% of theory), b.p. 62-63°/0.007 mm, n_D^{20} 1.5416, d_4^{20} 1.4448, MR_D 53.03, calculated 53.57.

Found, %: C 43.46, 43.42; H 7.74, 7.86
$C_7H_{15}NOS_2$. Calculated, %: C 43.49; H 7.82

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