The Action of Bases on 1-Mercaptopropyltrimethylammonium Iodide[1]

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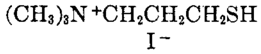
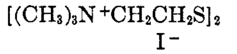
1-Mercaptopropyltrimethylammonium iodide (A) is unaltered by aqueous sodium hydroxide at 90° or by potassium *t*-butoxide in refluxing *t*-butyl alcohol; with dry potassium *t*-butoxide at 180° 1-methylmercapto-3-dimethylaminopropane (C) is formed. Aqueous sodium hydroxide at 150° gave propionic acid, trimethylamine, methanol, and a polymer corresponding to $(CH_2CH_2CH_2S)_x$. Trimethylene sulfide is not an intermediate in the reaction. The 1-mercaptoethyltrialkylammoniumthiols G-1 and G-2 gave the trialkylamine when heated with dry potassium *t*-butoxide at 130°. The S-alkyl compound was not formed.

In connection with studies on the kinetics of aminothiol oxidation by air, we have prepared the quaternary aminothiol A from the disulfide B. It was expected that the quaternary aminothiol would be rapidly converted with base, by inter- or intramolecular alkylation,[3] to the tertiary amino sulfide C. Analogous reactions are known in alcohols containing a quaternary ammonium group; thus the *cis*-quaternary ammonium compound D yields, at 150°, 17% of the methyl ether E[4] (see eq 1). Internal displacement of tertiary amine by alkoxide ion to form oxygen heterocycles has been well documented,[5] although this displacement is different from the process occurring in the transformation of D to E.



$$\underset{I^-}{(CH_3)_3N^+CH_2CH_2CH_2SH}$$

A

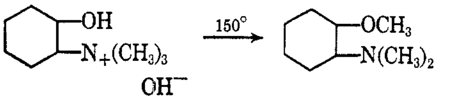


$$[\underset{I^-}{(CH_3)_3N^+CH_2CH_2S}]_2$$

B

$(CH_3)_2NCH_2CH_2CH_2SCH_3$

C

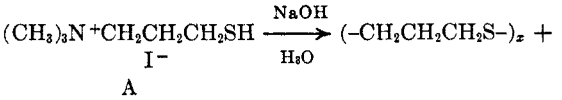


(1)

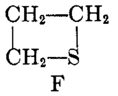
cis D *cis* E

It was surprising, therefore, to recover the quaternary ammoniumthiol A unchanged, even after heating with strong aqueous alkali at 90°; the amount of thiol present was determined by titration with N-ethylmaleimide (NEM),[6] and paper chromatography showed only the thiol and a little disulfide.

Under still more drastic conditions, with 25% sodium hydroxide at 150°, the products detected included propionic acid, isolated as the piperazinium salt. Vpc of the aqueous solution demonstrated the presence of methanol, trimethylamine, and a small amount of allyl disulfide (see eq 2). Hydrogen sulfide was also present; neither trimethylene sulfide nor the S-methyl compound C was detected by vpc. C was shown to be stable to the reaction conditions. The bulk of the product was an amorphous material; its analysis indicated that it was an impure polymer of the $-CH_2CH_2CH_2S-$ unit. It could not be purified because of its insolubility. The polymer appears not to be formed from trimethylene sulfide (F), because the latter does not polymerize appreciably under the reaction conditions. As a further test for the intermediacy of F, the quaternary ammoniumthiol was refluxed with concentrated aqueous alkali, and no F could be detected.



$$\underset{\text{A}}{\underset{I^-}{(CH_3)_3N^+CH_2CH_2CH_2SH}} \xrightarrow[H_2O]{NaOH} (-CH_2CH_2CH_2S-)_x + CH_3CH_2COOH + (CH_3)_3N + CH_3OH + H_2S \quad (2)$$



F

The formation of the polymer is probably the result of a series of intermolecular displacement steps, with the chain-propagating step shown in eq 3. A similar polymer might be formed by preliminary formation of allyl mercaptan, or its disulfide, followed by vinyl polymerization of the double bonds. This seems unlikely, because of the well-known action of mercaptans as chain-transfer agents.

$$(CH_3)_3N^+(CH_2)_3S^- + (CH_3)_3N^+N(CH_2)_3S^- \longrightarrow (CH_3)_3N + (CH_3)_3N^+(CH_2)_3S(CH_2)_3S^- \quad (3)$$

A further examination of the behavior of the quaternary thiol A with strong bases in nonaqueous systems showed that very drastic conditions were necessary to bring about the conversion of A to the S-methyl compound C. Thus, reflux of A with sodium methoxide–methanol for 18 hr gave none of the S-methyl compound detectable by thin layer chromatography (tlc). Similar results were obtained by refluxing the thiol for 2 hr with potassium *t*-butoxide in *t*-butyl alcohol. Refluxing the thiol for 48 hr with potassium *t*-butoxide in a mixture of *t*-butyl alcohol and DMF gave only a trace of C. Heating the thiol A with dry potassium *t*-butoxide at 180° for 0.5 hr gave a 49% yield of the S-methyl compound; this was identified by a comparison of its infrared, nmr, and tlc properties with those of a known sample. A similar result was obtained by heating A with dry sodium methoxide.

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[2] To whom inquiries should be addressed.

[3] For examples of the high nucleophilicity of mercaptide ion, see A. Streitwieser, *Chem. Rev.*, **56**, 582 (1956).

[4] A. C. Cope, E. Ciganek, and J. Lazor, *J. Am. Chem. Soc.*, **84**, 2591 (1962); *cf.* V. J. Traynelis and J. G. Dadura, *J. Org. Chem.*, **26**, 686, 1813 (1961).

[5] Epoxide formation is described by P. Rabe and J. Hallensleben, *Ber.*, **43**, 884 (1910), and in later papers listed by A. Rosowsky, "Heterocyclic Compounds with Three- and Four-membered Rings," Part I, Interscience Publishers, Inc., New York, N. Y., 1964, pp 171–173. Formation of tetrahydrofuran rings by a similar displacement process are reported by N. R. Easton and V. B. Fish, *J. Am. Chem. Soc.*, **77**, 1776 (1955), and by J. G. Godfrey, D. S. Tarbell, and V. Boekelheide, *ibid.*, 3342 (1955), among others. The formation of episulfides by a similar process from 1,2-aminothiols is indicated by J. S. Dix and C. R. Bresson, *J. Org. Chem.*, **32**, 282 (1967).

[6] J. D. Gregory, *J. Am. Chem. Soc.*, **77**, 3922 (1955).

The behavior of the mercaptoethyl compounds G-1 and G-2 toward base was also examined. The methyl quaternary salt G-1 gave trimethylamine (32% yield)

$$\underset{I^-}{HSCH_2CH_2N^+R_3} \xrightarrow{\text{base}} (SCH_2CH_2)_x + R_3N \qquad (4)$$

$$\text{G-1, R} = CH_3$$
$$\text{G-2, R} = C_2H_5$$

when heated with dry potassium *t*-butoxide at 125–130° for 30 min, along with an insoluble residue whose elementary analysis indicated that it was a polymer of ethylene sulfide. The triethyl compound behaved similarly; there was no evidence in either case for the alkylation of the thiol group to form sulfides of the type $RSCH_2CH_2NR_2$ (R = CH_3 or C_2H_5) (see eq 4).

Experimental Section

3-Dimethylamino-1-propyl Disulfide.—A solution of 3-dimethylamino-1-chloropropane (50 g, 0.41 mole, Aldrich Chemical) in methanol (480 ml) was refluxed with a solution of sodium thiosulfate (65 g, 0.41 mole) in water (480 ml). A solution of iodine (45 g, 0.18 mole) was added dropwise during 2 hr; the resulting solution was evaporated and cooled, and sodium hydroxide (40 g) in water (200 ml) was added. The resulting solution was extracted with several 50-ml portions of chloroform, and the combined chloroform extracts were taken to dryness. The weight of crude disulfide[7] was 32 g (66%).

Methiodide B.—The crude disulfide (16 g, 0.068 mole) in methanol (100 ml) was refluxed with methyl iodide (24 g). A yellow solid remained after solvent removal, which was recrystallized from ethanol; the yield was 28 g (79%) of material melting at 226–227°.

Anal. Calcd for $C_{12}H_{30}N_2S_2I_2$: C, 27.83; H, 5.69. Found: C, 27.60; H, 5.97.

1-Mercaptopropyltrimethylammonium Iodide (A).—The methiodide (8.0 g) was dissolved in 20 ml of water and 15 ml of 48% hydriodic acid was added. The disulfide was reduced to the thiol electrolytically,[8] and excess water and hydriodic acid were removed in a freeze dryer. The residue was recrystallized several times from absolute ethanol. The yield of material melting at 187–188° was 4 g (50%).

Anal. Calcd for $C_6H_{16}NSI$: C, 27.71; H, 6.19. Found: C, 27.62; H, 6.07; free thiol, 98 and 99% by NEM.[6]

3-Dimethylamino-1-methylmercaptopropane Hydriodide (C).—3-Dimethylamino-1-chloropropane hydrochloride (16 g, 0.10 mole) in water (50 ml) was mixed with solution of sodium hydroxide (4 g) in water (20 ml); ethanol was added until the oil that formed was redissolved. Methanethiol (4.8 g, 0.10 mole) in a solution of sodium hydroxide (4 g) in water (50 ml) at 0° was added to the solution prepared above, and the whole was refluxed for 30 min. The solution was acidified with hydrochloric acid and evaporated to dryness, and the white crystalline residue was extracted several times with hot ethanol. The combined alcohol extracts were taken to dryness to give 17 g (100%) of the crude hydrochloride as a white solid; this was dissolved in water (50 ml) and made alkaline with 20% aqueous sodium hydroxide. The alkaline solution was extracted with three 50-ml portions of ether, and the combined ether extracts were extracted with three 50-ml portions of 20% hydriodic acid. The aqueous extracts were taken to dryness in a freeze dryer and the yellow residue was recrystallized several times from absolute ethanol; the yield was 17 g (65%), mp 78–79°.[9]

Anal. Calcd for $C_6H_{16}NSI$: C, 27.60; H, 6.20. Found: C, 27.69; H, 6.08.

Stability of 1-Mercaptopropyltrimethylammonium Iodide (A) in Alkaline Solution.—Thiol (980 mg) and sodium hydroxide (142 mg) in distilled water (11.0 ml) were left for 48 hr at room temperature. An NEM determination showed no change in thiol concentration. A small aliquot was acidified with dilute hydriodic acid. Ascending paper chromatography on Whatman No. 4 paper at 27°, using either butanol–water (upper phase) or butanol–water (upper phase)–acetic acid (50:1) showed only one spot identical in R_f value with the starting thiol.

The alkaline thiol solution was heated for 18 hr on a steam bath. An NEM determination indicated 95% of the thiol remained. A chloroform extract showed no residue on evaporation. After acidification with dilute hydriodic acid, the aqueous solution was taken to dryness. Ascending paper chromatography showed spots identical in R_f value with those of the starting thiol and its disulfide. A spot corresponding the the expected S-methyl compound was not observed.

Alkaline Decomposition of 1-Mercaptopropyltrimethylammonium Iodide (A).—The thiol A (261 mg, 0.001 mole) and 1.60 ml (0.01 mole) of 25% aqueous sodium hydroxide were heated in a sealed tube at 150° for 5 hr. Vpc of the liquid phase using a 5-ft Ucon Polar column at 135° showed peaks corresponding to authentic samples of methanol, trimethylamine, and allyl disulfide in relative areas of 8:32:1, respectively. No peak was detected corresponding to authentic samples of trimethylene sulfide or the S-methyl compound C.

The alkaline solution was acidified with dilute hydriodic acid; the smell of hydrogen sulfide was immediately obvious. A confirmatory test using lead acetate paper was positive. The aqueous acidic mixture was chromatographed on paper as previously described. Spots identical in R_f value with those of authentic samples were found for the quaternary thiol A, its disulfide, and trimethylamine (all as hydriodides). No spot appeared at an R_f value corresponding to authentic 3-dimethylaminopropylmethyl sulfide hydriodide.

The acid solution was centrifuged and the supernatant liquid was decanted from a dark amorphous solid. This solid was triturated with large amounts of water, then with a copious amount of acetone, leaving 68 mg (90%) of a white solid. The solid was insoluble in all organic solvents, which precluded further purification. This solid showed no definite melting point on heating. Microscopic examination showed that the material was truly amorphous and not entirely homogeneous.

Anal. Calcd for C_3H_6S: C, 48.64; H, 8.16; N, 0.00; S, 43.20. Found: C, 45.58, 45.76, 46.01; H, 7.90, 7.93, 8.03; N, 0.74, 0.77; S, 40.29, 40.34.

The aqueous solution was extracted continuously with ether for 48 hr. The ether layer was removed and dried, and the ether was removed by distillation. The liquid residue was identified as propionic acid by comparison of the piperazinium salt, mp and mmp 123–124° (lit.[10] 124–125°).

Attempted Trapping of Trimethylene Sulfide.—The quaternary thiol (261 mg) was refluxed in 1.6 ml of 25% sodium hydroxide for 24 hr with a continuous, slow stream of nitrogen passing through the mixture. The nitrogen stream was led through a trap containing a saturated solution of mercuric chloride. No precipitate formed. Runs using known amounts of trimethylene sulfide showed that extremely small amounts of this material gave a voluminous precipitate. In addition, a blank run using authentic trimethylene sulfide and concentrated alkali at 150° failed to produce much polymeric material.

Stability of C under Basic Conditions.—The S-methyl compound C (133 mg) and 25% aqueous sodium hydroxide (1 ml) were heated in a sealed tube at 150–160° for 5 hr and allowed to cool. The thioether layer did not disappear; no basic gases could be detected, and acidification with 10% hydriodic acid did not give evolution of hydrogen sulfide. Tlc of the reaction mixture on silica gel using different solvents showed no spots other than that of the starting material.

In a separate run treated as above, 98.7% of the thioether was recovered as 1-methylmercaptopropyltrimethylammonium iodide[9] melting at 222–224°.

Thermal Decomposition of 3-Mercaptopropyltrimethylammonium Iodide.—The thiol A (50 mg) was sealed in a 3 × 30 mm Pyrex tube, and the tube was heated carefully using a microburner. The solid melted, and then decomposed, as shown by some darkening and foaming of the melt. A white crystalline material was slowly deposited on the cool upper surface of the tube. After several minutes of heating, the foaming had subsided and the tube was cooled and opened; the crystalline material melted at 205–222°. Recrystallization from 95% ethanol did

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[7] F. Y. Rachinskii, *et al.* [*Zh. Obshch. Khim.*, **28**, 2998 (1958); *Chem. Abstr.*, **53**, 9045 (1959)], prepared the disulfide; they reported the hydrochloride to melt at 207°.

[8] D. S. Tarbell, P. P. Brownlee, D. A. Buckley, R. Thomas, and J. S. Todd, *J. Org. Chem.*, **29**, 3314 (1964).

[9] The free base is described by F. K. Kirchner, A. E. Soria, and C. J. Cavallito, *J. Am. Chem. Soc.*, **77**, 4599 (1955).

[10] C. D. Pollard, *et al.*, *ibid.*, **56**, 1759 (1934).

not give sharp melting material. Paper chromatography of the white crystalline material gave essentially one spot identical in R_f value with that of authentic trimethylamine hydriodide.

The nonvolatile material from the decomposition was insoluble in water and all common organic solvents. It was amorphous and not characterized further.

Action of Sodium Methoxide–Methanol on the Quaternary Thiol A.—The thiol (1 g), dissolved in 19 ml of methanol containing 0.0899 g of sodium, was refluxed under nitrogen for 18 hr. The cooled solution showed on tlc examination no spot corresponding to authentic S-methyl compound C.

The methanolic solution was evaporated, the residue was dissolved in 10 ml of water and was acidified with dilute hydriodic acid. Evolution of traces of hydrogen sulfide and formation of a small amount of black precipitate were noted. After filtration and boiling, the solution was examined by tlc; the only spots observed were those corresponding to the thiol A and the disulfide B.

Similar results were obtained using potassium *t*-butoxide and refluxing for 2 hr in *t*-butyl alcohol.

Action of Potassium *t*-Butoxide on the Quaternary Thiol A. 1. In DMF–*t*-Butyl alcohol.—The thiol (1.0 g) was refluxed with potassium *t*-butoxide (0.43 g) in equal volumes of DMF–*t*-butyl alcohol for 48 hr. Fractional distillation indicated the absence of the S-methyl compound.

In a similar run, the reaction products were diluted with water and acidified with dilute hydriodic acid. The resulting solution was passed through a Dowex-50 W column, and the effluent *t*-butyl alcohol–water–DMF was discarded. The resin was then eluted with 50 ml of 10% hydriodic acid and washed with water until neutral. The effluent was evaporated, made basic, and extracted with carbon tetrachloride; the extract was dried and concentrated to about 1 ml, the solution gave an infrared spectrum identical with that of the S-methyl compound C. Consideration of the intensity of absorption of the N–CH_3 band at 2770 cm^{-1} showed that not more than 5 mg of C was present. Compound C obeyed Beer's law in the 0–5% range in CCl_4. The feasibility of the ion-exchange method of isolation was shown by a run on known amounts of the quaternary thiol A and the S-methyl compound C.

2. **Without Solvent.**—An intimate mixture of the thiol A (5.20 g) and dry potassium *t*-butoxide (2.30 g) was distilled under reduced pressure in a nitrogen stream. Reaction started when the oil bath had reached 180°; 0.87 g of *t*-butyl alcohol was obtained[11] and was identified by its infrared spectrum. Then 1.29 g of the S-methyl C compound distilled over, identified by comparison with authentic material.

1-Mercaptoethyltrimethylammonium iodide (G-1) was prepared by electrolytic reduction of the disulfide;[12] the product was isolated by filtering off and discarding a precipitate, concentrating *in vacuo* and adding anhydrous ethanol. The product was recrystallized from ethanol and melted at 164–165°; an NEM determination[6] showed the calculated amount of thiol.

Reaction with Potassium *t*-Butoxide.—An intimate mixture of the thiol G-1 and the base (20 mmole of each) was heated under nitrogen in an oil bath at 125–130° for 30 min to give *t*-butyl alcohol, identified by its infrared spectrum. Trimethylamine was identified by its infrared spectrum and by the picrate and chlorplatinate salts, which showed no depression on mixed melting point with known samples. In a quantitative run, 1 g of the thiol was heated with an equimolar (twice molar in another run) amount of potassium *t*-butoxide at about 150°, and the gases evolved were swept into a known amount of dilute sulfuric acid with a current of nitrogen. The yield of trimethylamine amounted to 31–33% of the theoretical.

The residue in the flask was a yellowish brown material which was insoluble in the common solvents; it was washed with water repeatedly and dried under vacuum to constant weight.

Anal. Calcd for $(CH_2CH_2S)_n$: C, 39.99; H, 6.71; S, 53.3. Found: C, 38.99; H, 6.13; S, 47.17; residue, 3.11.

1-Mercaptoethyldiethylamine[13] was oxidized to the disufide with sodium hypoiodite; the product was quaternized by refluxing with excess ethyl iodide. The bisquaternary salt (disulfide of G-2) melted, after recrystallization from ethanol, at 220–222°; the yield was 77%.

The corresponding thiol, G-2, was obtained in 95% yield by electrolytic reduction of the disulfide. It melted at 195–196° after recrystallization from ethanol, and was stored under dry nitrogen, because it blackened on exposure to air.

Anal. Calcd for $C_8H_{20}INS$: C, 33.23; H, 6.97. Found: C, 33.09; H, 6.80.

Action of Potassium *t*-Butoxide on 1-Mercaptoethyltriethylammonium Iodide (G-2).—An equimolar mixture of the two (20 mmoles each) was heated at 180° under nitrogen for 1 hr. The distillate was found, by vpc on a di-*n*-decylphthalate column, to be a mixture of *t*-butyl alcohol and triethylamine; no other product could be detected. The picrate of the amine did not depress the melting point of an authentic sample.

A homogeneous sample of constant weight could not be obtained from the nonvolatile residue from the reaction mixture.

Registry No.—A, 13448-87-8; B, 13448-88-9; C hydriodide, 13448-89-0; G-1, 7161-73-1; G-2, 13448-91-4.

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[11] For *t*-butyl alcohol in solid potassium *t*-butoxide, see S. M. McElvain and L. R. Morris, *J. Am. Chem. Soc.*, **73**, 206 (1951); H. Feuer, *et al.*, *ibid.*, **78**, 4364 (1956).

[12] J. Fakstorp, *Acta Chem. Scand.*, **10**, 15 (1956).

[13] Prepared by the method of N. F. Albertson and R. O. Clinton, *J. Am. Chem. Soc.*, **67**, 1222 (1945).