

The mercaptans (IV) used in the thioether condensations were obtained from the β -chloroalkylamine hydrochlorides via the *iso*-thiuronium salts (III) according to Albertson and Clinton². Although this procedure is the most convenient of the available methods²⁻⁴, it has been shown in the present work that rather large amounts of the corresponding sulfide is formed simultaneously with the mercaptan, just as is the case in the direct hydrosulfide-halide condensation³. The formation of sulfide has been explained as a reaction between already formed mercaptan and unreacted halide⁴, an explanation which is untenable for the alkaline hydrolysis of recrystallized *iso*-thiuronium salts. The simultaneous appearance of mercaptan and sulfide might however result from a nucleophilic attack of a hydroxyl ion at the carbon atom of the urea moiety in the former case and of a nucleophilic attack of mercaptide ion at the β -carbon of the aminoalkyl moiety in the latter.

The dialkylaminoethyl mercaptans, in the form of their sodium mercaptides, were condensed with β -chloroalkylamines of identical or nonidentical structure in conventional fashion, preferably in a nonpolar solvent to minimize side reactions and polymerization of the chloroamine.*

In agreement with the findings of Lawson and Reid⁵ difficulties were encountered in isolating and distilling bis- β -dimethylaminoethyl sulfide. In addition, some preparations of bis- β -diethylaminoethyl sulfide showed evidence of vinyl sulfide or divinyl sulfide formation.

Attempts to prepare the mercaptans by acid hydrolysis of the thiosulfates (*cf.* Peak and Watkins⁶) were unsuccessful. The other available methods for the synthesis of bis-aminoalkyl sulfides, *viz.* direct sodium sulfide-aminoalkyl halide condensation, and mercaptan-aminoalkyl halide hydrochloride condensation to give a sulfide bis-hydrochloride according to Gilman *et al.*³ were employed in a few cases.

Three different sulfides and six different quaternary salts having only methyl and ethyl groups as nitrogen substituents were prepared.

The preparation of the symmetric quaternary salts by another route was also investigated briefly. The reaction of bis- β -chloroethyl sulfide with tertiary amines as described by Lawson and Reid⁵, who prepared the lowest homologue, bis-trimethylammoniummethyl sulfide chloride, of this series more than twenty-five years ago, proceeded much more smoothly than the corresponding reaction involving β -chloro ether. The method requires, however, the use of mustard gas, which is unpleasant to prepare and handle. The products were obtained in satisfactory yield.

A report on the pharmacological properties of the quaternary salts will appear elsewhere.

EXPERIMENTAL

β -Diethylaminoethyl-*iso*-thiuronium chloride hydrochloride (III, $R_1 = C_2H_5$)

Prepared according to Albertson and Clinton² from 860 g of diethylaminoethyl chloride hydrochloride (5 moles) and 400 g of thiourea (5.25 moles). No precipitation with ethyl acetate-ligroin was employed; the reaction mixture was evaporated *in vacuo* and the

* Note added in proof: Swedish Pat. 137,019 (F. Hofmann-La Roche & Co.) discloses similar sulfides prepared by condensation in ethanol-sodium ethylate.

second and third crop of crystals removed *. Yield: 1st crop 852 g, m. p. 188–192° C; 2nd crop 150 g, m. p. 185–187° C; 3rd crop 202 g, m. p. 178–185° C. Total yield 1 204 g (98 %). Crystallization from ethanol-ether raises m. p. to 196° C (Ref.³ 195° C). Yield after recrystallization 1 165 g (94 %).

β -Dimethylaminoethyl-*is*-thiuronium chloride hydrochloride (III, $R_1 = CH_3$)

Prepared as above from 288.2 g of dimethylaminoethyl chloride, HCl (2 moles) and 160 g of thiourea. Total yield after recrystallization 395 g (90 %). M. p. 173–175° C.

β -Diethylaminoethyl mercaptan (IV, $R_1 = C_2H_5$)

Prepared essentially as described³ from 248 g of *is*thiuronium salt (1 mole). Yield 71 g (53 %). B. p. 58° C at 12 mm Hg. n_D^{25} 1.4661. There was further obtained 41 g of bis- β -diethylaminoethyl sulfide (V), b. p. 147–150° C at 12–14 mm Hg. n_D^{25} 1.4736.

A solid, crystalline residue m. p. 201–203° C, is sometimes seen in the mercaptan-sulfide mixture before distillation. The residue was identified as dicyandiamide.

β -Dimethylaminoethyl mercaptan (IV, $R_1 = CH_3$)

Prepared exactly as above from 385 g (1.75 mole) of thiuronium salt. Yield 41 g (31 %). B. p. 40° C at 12 mm Hg. n_D^{25} 1.4682.

Bis- β -diethylaminoethyl sulfide (V, $R_1 = R_2 = C_2H_5$)

Prepared according to the directions given for the corresponding ether¹ from 133.2 g of α -diethylaminoethyl mercaptan (1 mole), 23 g of sodium and 172.1 g of β -diethylaminoethyl chloride, HCl. The solvent was benzene in this case. There was obtained 207 g (88 %) of the desired sulfide, slightly yellow oil, b. p. 144–150° C at 12–16 mm Hg. n_D^{25} 1.4738. (Litt.^{1,2,3,4} b. p. 64.0° C at 0.4 mm Hg, b. p. 104–106° C at 0.3 mm Hg, b. p. 139–140° C at 9 mm Hg, b. p. 106–110° C at 2 mm Hg; n_D^{20} 1.4740, n_D^{20} 1.4470).

The product was also obtained by condensation of dehydrated sodium sulfide from 14 g of sodium sulfide, 9H₂O (0.05 mole) with β -diethylaminoethyl chloride, obtained from 17.2 g of the hydrochloride in anhydrous ethanol. Yield 4.2 g (36 %), b. p. 144–146° C at 15 mm Hg.

The bis-hydrochloride was prepared by adding dry HCl gas to the amine dissolved in dry ether. The mass formed was crystallized from acetone-methanol (1 : 1), m. p. 243–245° C (decomp.) (Ref.^{3,4} 252–254° C, 246–248° C). Picrate, m. p. 174–176° C.

Bis-methiodide (As-7150) obtained from 23.2 g of sulfide (0.1 mole) and 42.6 g methyl iodide (0.3 mole) in 400 ml dry acetone and 50 ml anhydrous ethanol at room temperature for 24 hours (violent reaction to begin with). Yield 40 g (48 %), m. p. 261° C (recrystallized twice from anhydrous methanol). C₁₄H₃₄N₂SI₂ (516.3) Calc. I 49.19; found 48.18.

Bis-ethobromide (As-7102) Prepared as the bis-methiodide from 23.2 g of sulfide and 32.7 g of ethyl bromide (0.3 mole). After 3 days at room temperature, ether addition precipitates an oil which can be brought to crystallization by repeated dissolution and precipitation. Yield 10 g (22 %), m. p. 223–225° C (methanol-ether (1 : 1)). C₁₆H₃₆N₂SBr₂ (450.4) Calc. Br 35.5; found Br 35.5.

Bis- β -dimethylaminoethyl sulfide (V, $R_1 = R_2 = CH_3$)

Condensation of 105 g of dimethylaminoethyl mercaptan (1 mole) with chloride from 144 g of dimethylaminoethyl chloride, HCl, and 23 g of sodium gave 64.5 g (36.5 %)

* All melting and boiling points are uncorrected. The nitrogen and halogen values are macro determinations by Mrs. G. Speggers of this laboratory. Carbon and hydrogen values are micro determinations by Mr. A. Grossmann, University of Copenhagen.

of the sulfide, b. p. 103–107° C at 12–14 mm Hg. n_D^{25} 1.4751. $C_8H_{20}N_2S$ (176.3) Calc. C 54.36, H 11.2, N 15.52; found C 54.20, H 11.4, N 15.92.

Bis-hydrochloride, m. p. 273–276° C (from acetone-methanol (3 : 1)), $C_8H_{22}N_2S_2Cl_2$ (249.3) Calc. Cl 28.44; found Cl 28.61. The bis-hydrochloride was also obtained by a condensation of mercaptan with chloride HCl as described³, mixed m. p. with authentic sample showed no depression. Picrate m. p. 180–182° C.

Bis-methoide (As-4366). Yield 43.5 %, m. p. 276° C (from methanol). $C_{10}H_{26}N_2SI_2$ (460.1) Calc. I 55.17; found I 53.92.

Bis-ethobromide (As-4374). Yield 50.6 %, m. p. 245–248° C (from ether-methanol (1 : 1)). $C_{12}H_{30}N_2SBr_2$ (394.2) Calc. Br 40.54; found Br 39.02.

Bis-(β -dimethyl- β' -diethyl)aminoethyl sulfide (V, $R_1 = CH_3$; $R_2 = C_2H_5$)

Prepared as directed from 133.2 g of diethylaminoethyl mercaptan, 23 g of sodium, and 144 g of dimethylaminoethyl chloride, HCl. Yield 160 g (78.5 %), b. p. 125–127° C at 14 mm Hg. n_D^{25} 1.4688. $C_{10}H_{24}N_2S$ (204.3) Calc. C 58.75, H 11.8, N 13.72; found C 58.83, H 11.7, N 13.66.

Bis-Hydrochloride, m. p. 252–254° C (from acetone-methanol (1 : 1)). $C_{10}H_{26}N_2S_2Cl_2$ (277.4) Calc. Cl 25.56; found Cl 25.66.

Condensation of diethylaminoethyl mercaptan and dimethylaminoethyl chloride, HCl by heating them together (cf. Gilman *et al.*³) gave a hydrochloride-mixture, m. p. 96° C, from which could be isolated the bis-hydrochloride of bis-diethylaminoethyl sulfide, m. p. 298° C, in small yield after 8 recrystallizations from acetone-methanol (1 : 1), but no bis-hydrochloride of the asymmetric sulfide. Picrate, m. p. 158–160° C.

Bis-methoiodide (As-7277). Yield 56.1 %, m. p. 271–273° C (methanol). $C_{12}H_{30}N_2SI_2$ (488.4) Calc. I 52.01; found I 50.88.

Bis-ethobromide (As-7207). Yield 43.7 %, m. p. 227° C (from acetone-ethanol (2 : 1)) $C_{14}H_{34}N_2SBr_2$ (422.4) Calc. Br 37.87; found Br 37.45.

SUMMARY

A series of bis-quaternary alkylammonium ethyl sulfide salts prepared by reaction of bis- β -dialkylaminoethyl sulfide with alkyl halide is described. The preparation of the precursors by various routes is described.

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