γ-Hydroxypropyl β'-(N-Thiomorpholino)-ethyl Sulfide Hydrochloride.—To 36 g. (0.178 mole) of N-β-chloroethylthiomorpholine hydrochloride was added a mixture of 150 cc. of 10% potassium hydroxide and 200 cc. of ether. The ether layer was separated, dried over potassium hydroxide pellets, and filtered. The oil remaining after removing the ether was dissolved in 35 cc. of absolute ethanol and this solution was added with stirring to an absolute ethanol solution of sodium γ-hydroxypropyl mercaptide prepared from 27.6 g. (0.3 mole) of γ-hydroxypropyl mercaptan. After the cloudy mixture had been stirred for one hour at room temperature, it was refluxed for five hours, cooled, and filtered. The ethanol was then removed under reduced pressure and the residue shaken with a mixture of 200 cc. of ether and 50 cc. of water. The ether layer was dried, cooled on ice, and then treated with hydrogen chloride in ether to give an oil which solidified promptly. Recrystallization from absolute ethanol gave 33.2 (72.6%) of colorless crystals melting at 126–128°.

Anal. Calcd. for $C_9H_{20}ONClS_2$: N, 5.43. Found: N, 5.52 and 5.54.

The N-β-hydroxyethylthiomorpholine hydrochloride was obtained in a 40% yield by reaction of three moles of ethanolamine and one mole of β,β'-dibromoethyl sulfide in benzene. The β,β'-bromoethyl sulfide was prepared in yields of 81 and 88% from β,β'-dihydroxyethyl sulfide and hydrogen bromide.[9] The N-β-chloroethylthiomorpholine was prepared in 98% yield (m. p., 206–208°) from the N-β-hydroxyethyl thiomorpholine hydrochloride and thionyl chloride in chloroform.

1-β-Diethylaminoethylmercapto-2,3-epoxypropane.—A suspension of sodium β-diethylaminoethyl mercaptide, prepared in toluene from 0.2 mole of β-diethylaminoethyl mercaptan and 0.2-g. atom of sodium, was added portionwise to a stirred solution of 18.6 g. (0.2 mole) of epichlorohydrin in 100 cc. of toluene. The temperature of the reaction mixture was maintained below 10°, and on working up there was obtained 17.8 g. (47%) of product which boiled at 90–92° (0.5 mm.).

Anal. Calcd. for $C_9H_{19}ONS$: N, 7.40. Found: N, 7.57.

1,2-Di-γ-acetoxypropylsulfonylethane, $(CH_3COOCH_2CH_2CH_2SO_2CH_2—)_2$.—This compound was prepared in general accordance with the procedure of Ziegler and Connor.[10] Twenty-three grams (1-g. atom) of sodium was dissolved in 325 cc. of absolute ethanol and to this was added 92 g. (1 mole) of γ-hydroxypropyl mercaptan. To the mercaptide solution was added over a fifty minute period and with stirring, 110 g. (0.59 mole) of ethylene bromide in 50 cc. of absolute ethanol. The mixture was refluxed for two hours and then, after standing at room temperature for two hours, the ethanol was removed under reduced pressure. On pouring into 200 cc. of water an oily layer separated. This was combined with the ether extracts of the aqueous layer, and after drying and then removing the ether, an oily residue which soon solidified was obtained.

This 1,2-di-γ-hydroxypropylmercaptoethane was dissolved in a mixture of 160 cc. of glacial acetic acid and 160 cc. of acetic anhydride. To the stirred solution (cooled in an ice–salt-bath) was added 275 g. of 30% hydrogen peroxide over a one and one-half hour period, during which time the temperature varied between 10 and 40°. After standing at room temperature for three days, the solution was heated in a 70° bath for two hours, and then the volatile solvents were removed. The yield of solid melting at 114–119° was 160 g. (89%). A portion of the solid melted at 124–125° after recrystallizations from a chloroform–ether mixture.

Anal. Calcd. for $C_{12}H_{22}O_8S_2$: S. 17.89. Found: S. 18.18, 18.10.

Summary

Syntheses are described for γ-(6-methoxy-8-quinolylamino)-propyl β'-diethylaminoethyl sulfide and three related types in which the diethylamino group has been replaced by a piperidino, morpholino, and thiomorpholino group.

AMES, IOWA RECEIVED[11] JULY 28, 1945

---

[9] Burrows and Reid, THIS JOURNAL, 56, 1720 (1934).

[10] Ziegler and Connor, *ibid.*, 62, 2596 (1940).

[11] Original manuscript received November 1, 1944.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

β-Diethylaminoethyl Mercaptan and γ-Diethylaminopropyl Mercaptan

BY H. GILMAN, MARY ALYS PLUNKETT, L. TOLMAN, L. FULLHART AND H. SMITH BROADBENT

β-Diethylaminoethyl mercaptan has been prepared[1] from ethylene sulfide and lithium diethylamide and from β-diethylaminoethyl chloride by the isothiouronium salt synthesis. We have observed that the mercaptan can be prepared in yields up to 57% by reaction of β-diethylaminoethyl chloride with sodium hydrosulfide.

One of the by-products of the reaction is bis-(β-diethylaminoethyl) sulfide, whose dihydrochloride was obtained earlier by Cook and Kreke[2] incidental to an attempt to prepare the mercaptan from reaction of β-diethylaminoethyl bromide hydrobromide with sodium sulfide and hydrogen sulfide. We prepared the sulfide dihydrochloride by treating β-diethylaminoethyl mercaptan (prepared from the ethylene sulfide procedure[1]) with β-diethylaminoethyl chloride.

$$(C_2H_5)_2NCH_2CH_2SH + ClCH_2CH_2N(C_2H_5)_2 \longrightarrow [(C_2H_5)_2NCH_2CH_2]_2S$$

This reaction is probably responsible for the formation of some of the sulfide which is the principal by-product in the preparation of the mercaptan. In this connection we have shown that the solid which sometimes separates from the distilled mercaptan is the sulfide dihydrochloride, which may owe its formation to reaction of the mercaptan with some initially unreacted β-diethylaminoethyl chloride carried over in the distillation.

In one preparation of the mercaptan, bis-(β-diethylaminoethyl) disulfide was formed when the

---

[1] Gilman and Woods, THIS JOURNAL, 67, 1843 (1945). See, also, Albertson and Clinton, *ibid.*, 67, 1222 (1945).

[2] Cook and Kreke, *ibid.*, 61, 2971 (1939).

mercaptan was exposed to the air for some time in the presence of sodium hydroxide solution. The dihydrobromide of this disulfide had been obtained previously by Lischer and Jordan[3] in an attempt to prepare the mercaptan from β-diethylaminoethyl bromide hydrobromide and sodium hydrosulfide in ethanol solution. We prepared the disulfide by treating the sodium salt of β-diethylaminoethyl mercaptan with iodine.

$$2(C_2H_5)_2NCH_2CH_2SNa + I_2 \longrightarrow [(C_2H_5)_2NCH_2CH_2S—]_2 + 2NaI$$

The disulfide was also obtained as a product of the reaction of 2-chloroquinoline and β-diethylaminoethyl mercaptan in an ethanolic solution containing sodium ethoxide.

γ-Diethylaminopropyl mercaptan was prepared in a 55% yield from γ-diethylaminopropyl chloride and sodium hydrosulfide. The corresponding disulfide was obtained by reaction of the sodium salt of the mercaptan with iodine.

Experimental

β-Diethylaminoethyl Mercaptan.—Hydrogen sulfide was bubbled through 340 g. (1.4 moles) of melted sodium sulfide nonahydrate for several hours until it was saturated. To the resulting solution was added 90 g. (0.67 mole) of freshly distilled β-diethylaminoethyl chloride,[4] and the mixture was refluxed with *vigorous* stirring for one hour, preferably under an inert atmosphere. After cooling, the solution was extracted with ether; the ethereal extract was dried over sodium sulfate; and then distillation was effected with a minimum exposure to the air. The yield of mercaptan distilling at 62–65° (21 mm.) was 51 g. (57%); n^{20}_D 1.4680; d^{20}_4 0.8751. The range of yields extended from 25 to 57%. The difficulty of checking some yields may have been due to variations in the quality of sodium hydrosulfide. It is probable that more consistent and also higher yields might have been realized by carrying out the reaction with sodium hydrosulfide in a closed container with an excess of hydrogen sulfide under pressure.

Under essentially corresponding conditions in which sodium hydrosulfide was allowed to react with β-diethylaminoethyl chloride *hydrochloride*, the products isolated were β-diethylaminoethyl mercaptan (20%) and bis-(β-diethylaminoethyl) sulfide (57%). In another experiment involving a longer period of heating, the yield of mercaptan was 18%, and the yield of sulfide was 70%. A repetition of the experiment using absolute ethanolic solutions instead of aqueous gave a 17% yield of mercaptan.

The **hydrochloride of β-diethylaminoethyl mercaptan,** prepared by the addition of ethanolic hydrogen chloride to a solution of the mercaptan in absolute ethanol, melted at 170–172° after crystallization from absolute ethanol.

Anal. Calcd. for $C_6H_{16}NClS$: N, 8.29. Found: N, 8.12.

β-Diethylaminoethyl 2,4-dinitrophenyl sulfide hydrochloride, prepared from the mercaptan and 2,4-dinitrochlorobenzene, melted at 187–188° after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{12}H_{18}O_4N_3ClS$: N, 12.51. Found: N, 12.78.

Bis-(β-diethylaminoethyl) Sulfide.—This sulfide, obtained as the chief product from the residue after distilling off the mercaptan, boiled at 105–106° (0.3 mm.); d^{20}_4 0.8947; n^{20}_D 1.4470. Its dihydrochloride melted at 246–248° after crystallization from absolute ethanol-ethyl acetate. The melting point reported earlier[3] was 245.5–247.5°.

The dihydrochloride was also prepared in about 50% yields by warming a mixture of the mercaptan and β-diethylaminoethyl chloride, and it was shown to be identical (mixed m. p.) with the dihydrochloride of the compound obtained as a by-product in the preparation of the mercaptan. From the dihydrochloride prepared in this manner was obtained by the action of ammonium hydroxide, the free base of the sulfide: b. p. 105–106° (0.3 mm.); d^{20}_4 0.8950; n^{20}_D 1.4482. Then the free base was reconverted to the dihydrochloride (m. p. 246–248°).

Anal. Calcd. for $C_{12}H_{30}N_2Cl_2S$: Cl, 23.23; S, 10.53. Found: Cl, 23.20; S, 10.65.

Bis-(β-diethylaminoethyl) Disulfide.—This disulfide was obtained in a 25% yield by adding 3.78 g. (0.03 mole) of iodine in ethanol to the sodium mercaptide solution prepared in absolute ethanol from 8 g. (0.06 mole) of β-diethylaminoethyl mercaptan and 0.06 g. atom of sodium. The sulfide, which distilled over at 155–160° (20 mm.), was converted to the dihydrochloride by adding ethereal hydrogen chloride. Recrystallization from absolute ethanol gave a product melting at 216–217° which showed no depression in a mixed m. p. determination with the disulfide obtained from the reaction of 2-chloroquinoline with sodium β-diethylaminoethyl mercaptide.

Anal. Calcd. for $C_{12}H_{30}N_2Cl_2S_2$: N, 8.3; Cl, 20.8. Found: N, 7.9, 8.0, and 8.1; Cl, 20.8, and 20.6.

The dihydrobromide of bis-(β-diethylaminoethyl) disulfide, prepared from the free base and hydrogen bromide in ether, melted at 222–223°. The melting point reported previously[3] was 223°.

The disulfide was obtained earlier[1] from a reaction between ethylene sulfide and diethylamine.

γ-Diethylaminopropyl Mercaptan.—This mercaptan, prepared in 55% yield by reaction of γ-diethylaminopropyl chloride[5] with sodium hydrosulfide, using essentially the same procedure as that reported for its next lower homolog distilled at 76–77.5° (26 mm.); n^{20}_D 1.4668; d^{20}_4 0.8908. Calcd. M_D 46.16; found, 46.0.

Anal. Calcd. for $C_7H_{17}NS$: S, 21.76. Found: S, 21.74 and 21.52. The *hydrochloride of γ-diethylaminopropyl mercaptan* melts at 74–76°, and is very hygroscopic and quite soluble in absolute ethanol.

Anal. Calcd. for $C_7H_{18}NClS$: N, 7.65. Found: N, 7.78.

γ-Diethylaminopropyl 2,4-dinitrophenyl sulfide hydrochloride, prepared like its homolog from the mercaptan and 2,4-dinitrochlorobenzene, melted at 143–145° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{13}H_{20}O_4N_3ClS$: N, 12.02. Found: N, 11.95.

Some samples of freshly distilled mercaptan deposit a white solid which may be the sulfide hydrochloride formed by reaction of some original γ-diethylaminopropyl chloride carried over with the mercaptan on distillation.

Bis-(γ-diethylaminopropyl) Disulfide.—This disulfide, prepared like the ethyl derivative from the mercaptide and iodine, distilled at 175–177° (25 mm.). The dihydrochloride of the disulfide melted at 220–221°.

Anal. Calcd. for $C_{14}H_{34}N_2Cl_2S_2$: N, 7.69; Cl, 19.2. Found: N, 8.0 and 7.9; Cl, 19.3 and 19.3.

A mixed m. p. determination showed this dihydrochloride of the disulfide to be identical with a hydrochloride of the product of the reaction of 2-chloroquinoline with the sodium γ-diethylaminopropyl mercaptide.

Acknowledgment.—The authors are grateful to R. A. Benkeser and R. H. Kyle for assistance.

Summary

β-Diethylaminoethyl mercaptan and γ-diethylaminopropyl mercaptan have been prepared from

---

[3] Lischer and Jordan, THIS JOURNAL, **59**, 1623 (1937).

[4] Prepared in accordance with the directions of Gough and King, *J. Chem. Soc.*, 2437 (1928).

[5] Prepared in accordance with directions described in a paper by Gilman and Shirley, THIS JOURNAL, **66**, 888 (1944).

the corresponding chlorides and sodium hydrosulfide. Some secondary products have been isolated and identified.

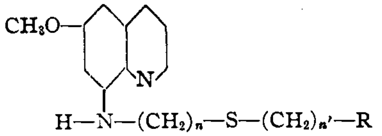
AMES, IOWA RECEIVED JUNE 30, 1945

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Compounds with Some Sulfur-containing Side-chains

BY HENRY GILMAN AND LEO TOLMAN

In connection with some studies on pharmacological action and chemical constitution there has been reported[1] the synthesis of compounds of this general type



in which R is the diethylamino, piperidino, morpholino, and thiomorpholino group; and where $n = 3$, and $n' = 2$. It seemed of interest to examine some related types where $R = -N(C_2H_5)_2$, and where ($n = 2$; $n' = 3$), and ($n = 3$; $n' = 3$).

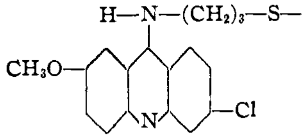
The compounds were prepared, in accordance with the general procedure described earlier,[1] by condensing 6-methoxy-8-aminoquinoline with the appropriate diethylaminoalkyl chloroalkyl sulfides. These sulfides were prepared, in turn, by the reactions

$$(C_2H_5)_2N(CH_2)_3Cl + NaS(CH_2)_nOH \longrightarrow$$

$$(C_2H_5)_2N(CH_2)_3{-}S{-}(CH_2)_nOH \xrightarrow{SOCl_2} (C_2H_5)_2N(CH_2)_3{-}S{-}(CH_2)_nCl$$

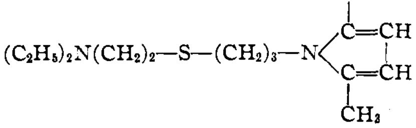
One of the sulfur side-chains ($n = 3$; $n' = 3$) was also condensed with *m*-trifluoromethylaniline.

A sulfur side-chain, $(C_2H_5)_2N(CH_2)_2{-}S{-}(CH_2)_3NH_2$, was also condensed with a third type of nucleus, 2-methoxy-6,9-dichloroacridine to give



This side-chain was also condensed with acetonylacetone to give β-diethylaminoethyl γ-(2,5-dimethyl-1-pyrryl)-propyl sulfide

$$(C_2H_5)_2N(CH_2)_2{-}S{-}(CH_2)_3NH_2 + CH_3COCH_2CH_2COCH_3 \longrightarrow$$



Experimental

γ-Diethylaminopropyl γ-Hydroxypropyl Sulfide.—From reaction of 58 g. (0.63 mole) of γ-hydroxypropyl mercaptan, 14.5 g. (0.63 g. atom) of sodium and 94 g. (0.63 mole) of γ-diethylaminopropyl chloride[2] in 300 cc. of ethanol, there was obtained 89 g. (69%) of sulfide distilling at 126-129° (0.1 mm.).

Anal. Calcd. for $C_{10}H_{23}ONS$: N, 7.18. Found: N, 6.90.

The γ-hydroxypropyl mercaptan was prepared in accordance with the procedure of Rojahn and Lemme[3] in yields which varied from 40 to 60%.

γ-Diethylaminopropyl γ-Chloropropyl Sulfide.—From 89 g. (0.43 mole) of γ-diethylaminopropyl γ-hydroxypropyl sulfide and 102 g. (0.86 mole) of thionyl chloride in chloroform there was obtained 70 g. (74%) of sulfide distilling at 95-97° (0.1 mm.): n^{20}_{D} 1.4890; d^{20}_{4} 0.9980: MR: calcd., 64.87: found, 64.45.

Anal. Calcd. for $C_{10}H_{22}NClS$: N, 6.28. Found: N, 6.00.

γ-Diethylaminopropyl β-Hydroxyethyl Sulfide.—From 85 g. (0.57 mole) of γ-diethylaminopropyl chloride, 44.5 g. (0.57 mole) of β-hydroxyethyl mercaptan, and 13.1 g. (0.57 g. atom) of sodium in 300 cc. of absolute ethanol was obtained 85 g. (77%) of sulfide distilling at 100-102° (0.1 mm.).

Anal. Calcd. for $C_9H_{21}ONS$: N, 7.73. Found: N, 7.55.

γ-Diethylaminopropyl β-Chloroethyl Sulfide.—From 85 g. (0.445 mole) of γ-diethylaminopropyl β-hydroxyethyl sulfide and 107 g. (0.9 mole) of thionyl chloride in 200 cc. of chloroform at 0° there was obtained 50 g. (54%) of sulfide distilling at 71-75° (0.1 mm.).

Anal. Calcd. for $C_9H_{20}NClS$: N, 6.70. Found: N, 6.56.

γ-(6-Methoxy-8-quinolylamino)-propyl γ-Diethylaminopropyl Sulfide.—A mixture of 22.3 g. (0.1 mole) of γ-diethylaminopropyl γ-chloropropyl sulfide and 17.4 g. (0.1 mole) of 6-methoxy-8-aminoquinoline was heated on a boiling water-bath for one hour. The melt was then heated in an oil-bath at 100-110° for an additional three hours. The reaction product was dissolved in water and made strongly basic with ammonium hydroxide while maintaining the temperature below 15°. The oil was extracted with ether, and fractionation of the dried ether extract gave 10 g. of forerun which was largely 6-methoxy-8-aminoquinoline, and 17 g. (44%) of a yellow viscous oil distilling at 215-220° (0.1 mm.).

Anal. Calcd. for $C_{20}H_{31}ON_3S$: N, 11.63. Found: N, 11.60.

The dihydrochloride of γ-(6-methoxy-8-quinolylamino)-propyl γ-diethylaminopropyl sulfide, obtained as an orange compound by addition of hydrogen chloride to an absolute ethanol-ether solution of the base, melted at 128-130° after crystallization from absolute ethanol.

Anal. Calcd. for $C_{20}H_{33}ON_3Cl_2S$: N, 9.70. Found: N, 9.74.

β-(6-Methoxy-8-quinolylamino)-ethyl γ-Diethylaminopropyl Sulfide.—A mixture of 15 g. (0.066 mole) of γ-diethylaminopropyl β-chloroethyl sulfide hydrochloride, 8.7 g (0.05 mole) of 6-methoxy-8-aminoquinoline and 5 cc. of absolute ethanol was slowly heated in an oil-bath to

---

(1) Gilman and Woods, THIS JOURNAL, **67**, **1843** (1945).

(2) See Gilman and Shirley, *ibid.*, **66**, 888 (1944).

(3) Rojahn and Lemme, *Arch. Pharm.*, **263**, 612 (1925).