[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some 6-Methoxy-8-quinolylamino Sulfides

BY HENRY GILMAN AND LAUREN A. WOODS[1]

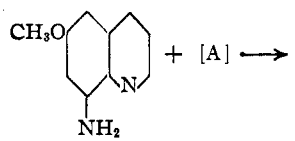
γ-(6-Methoxy-8-quinolylamino)-propyl β'-diethylaminoethyl sulfide (I) was prepared by the sequence of reactions

$$(C_2H_5)_2NCH_2CH_2SH + Na \longrightarrow (C_2H_5)_2NCH_2CH_2SNa$$

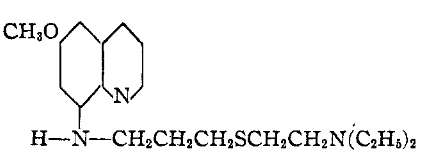
$$(C_2H_5)_2NCH_2CH_2SNa + ClCH_2CH_2CH_2OH \longrightarrow$$

$$(C_2H_5)_2NCH_2CH_2SCH_2CH_2CH_2OH \xrightarrow{[SOCl_2]}$$

$$\underset{[A]}{(C_2H_5)_2NCH_2CH_2SCH_2CH_2CH_2Cl}$$



[B]



[I]

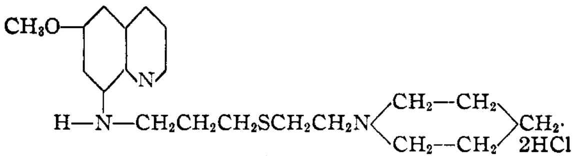
Other related types in which the diethylamino group has been replaced by a piperidino, morpholino and thiomorpholino group were prepared by the following procedure used for the piperidyl analog:

$$(CH_2)_5NCH_2CH_2OH \xrightarrow{(SOCl_2)}$$

$$(CH_2)_5NCH_2CH_2Cl \xrightarrow{(NaSCH_2CH_2CH_2OH)}$$

$$(CH_2)_5NCH_2CH_2SCH_2CH_2CH_2OH \xrightarrow{(SOCl_2)}$$

$$(CH_2)_5NCH_2CH_2SCH_2CH_2CH_2Cl \xrightarrow{(B)}$$



[II]

It should be stated that a homolog, β-(6-methoxy-8-quinolylamino)-ethyl β'-diethylaminoethyl sulfide, is mentioned in a patent.[2]

Experimental

γ-(6-Methoxy-8-quinolylamino)-propyl β'-Diethylaminoethyl Sulfide Dihydrochloride.—A mixture of 17.4 g. (0.1 mole) of 6-methoxy-8-aminoquinoline, 28.1 g. (0.115 mole) of γ-chloropropyl β'-diethylaminoethyl sulfide hydrochloride and 15 cc. of absolute ethanol was first heated on a boiling water-bath for three-fourths of an hour. The resulting solution was then heated at about 130° for six and one-half hours. On cooling slowly to room temperature, the mixture set to a yellow crystalline material which was dissolved in 100 cc. of water. To the cooled solution was added 500 cc. of ether and then a 20% solution of sodium hydroxide to an excess. After separation and extraction of the aqueous layer with 300 cc. of ether, the ether extracts were dried over sodium sulfate. The ether was removed and the residue was distilled at 1.3 mm. to give 25.2 g. (72%) of product boiling at 230–233°. The compound also boiled at 208° (0.05 mm.).

Anal. Calcd. for $C_{19}H_{29}ON_3S$: N, 12.09. Found: N, 12.17.

The dihydrochloride was formed by dissolving the base in 160 cc. of absolute ethanol and adding 0.21 mole of hydrogen chloride in 35 cc. of ether. On cooling in a refrigerator, there separated 28.4 g. (90% from the base) of product melting at 154–156.5°.

Anal. Calcd. for $C_{19}H_{31}ON_3Cl_2S$: N, 10.01. Found: N, 10.06, 9.94.

In general, the condensation of 6-methoxy-8-aminoquinoline with the chloroalkyl sulfides proceeds better when the hydrochloride of the chloroalkyl sulfide is used.

Table I lists other 6-methoxy-8-quinolylamino sulfides prepared in a related manner.

γ-Chloropropyl β'-Diethylaminoethyl Sulfide.—A clear red solution formed when 47.6 g. (0.4 mole) of thionyl chloride in 125 cc. of benzene was added during one and one-fourth hours to a stirred solution of 38.3 g. (0.2 mole) of γ-hydroxypropyl β'-diethylaminoethyl sulfide in 65 cc. of benzene at 25–30°. The benzene was removed, the residue was evaporated down with 25 cc. of ethanol, and then the oily residue was poured into 50 cc. of water and 475 cc. of ether. To this mixture, cooled on ice, was added 200 cc. of 10% potassium hydroxide, and from the dried, red ether layer was obtained 33.2 g. (79%) of colorless oil which distilled at 100–102° (2 mm.). A precipitate slowly formed on standing.

Anal. Calcd. for $C_9H_{20}NClS$: N, 6.68. Found: N, 6.97.

The hydrochloride is readily prepared by adding hydrogen chloride in ether, under anhydrous conditions, to an ether solution of the amino-sulfide.

Table II lists other γ-chloropropyl aminoethyl sulfides prepared in a related manner.

γ-Hydroxypropyl β'-Diethylaminoethyl Sulfide.[2]—To a suspension of sodium β-diethylaminoethyl mercaptide in toluene (prepared from 0.45 mole of β-diethylaminoethyl mercaptan and 0.45-g. atom of sodium in toluene) was added 43 g. (0.46 mole) of trimethylene chlorohydrin and the mixture was then refluxed for four hours. After hydrolysis there was obtained 67 g. (78%) of the pale-yellow sulfide which distilled at 124–126° (1-2 mm.).

Anal. Calcd. for $C_9H_{21}ONS$: N, 7.32. Found: N, 7.14.

Mr. L. Fullhart has examined four other procedures[2] for the preparation in an inert atmosphere, of the related β-hydroxyethyl β'-diethylamino sulfide from β'-hydroxyethyl mercaptan and β-diethylaminoethyl chloride. First, from an experiment in which a slurry of sodium hydroxide solution was added to a refluxing aqueous solution of the mercaptan and chloride, followed by four minutes of heating and then stirring for ten minutes, the yield of sulfide was 69%. Second, the chloride was added to a hot solution of the mercaptan in 95% ethanol (vigorous reaction), and then the calculated quantity of sodium hydroxide was added and the reaction was allowed to run for ten minutes. The yield was 59%, and the appreciable forerun indicated that the reaction was not completed. Third, the alkyl chloride in absolute ethanol was added as rapidly as

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[2] I. G. Farbenindustrie, British Patent 286,087 (1926) [*C. A.*, **23**, 241 (1929)]. In a paper by Clinton and co-workers, THIS JOURNAL, **67**, 594 (1945), which just appeared, but which was submitted after this paper, a preparation (by a different procedure) is described for γ-hydroxypropyl β'-diethylaminoethyl sulfide. The corresponding chloride was prepared in both laboratories by means of thionyl chloride.

TABLE I

6-METHOXY-8-QUINOLYLAMINO SULFIDES

Product, sulfide dihydrochloride	Exptl. conditions	Yield, %	M. p., °C.	Analyses, % N Calcd.	Analyses, % N Found
γ-(6-Methoxy-8-quinolylamino)-propyl β'-(N-piperidyl)-ethyl	135–145°, 18 hr.	59	208–211 (dec.) (yellow crystals from abs. C_2H_5OH)	9.72	9.62 9.57
γ-(6-Methoxy-8-quinolylamino)-propyl β'-(N-morpholino)-ethyl	140–145°, 18 hr.	50	205–210 (from 95% C_2H_5OH)	9.67	9.42
γ-(6-Methoxy-8-quinolylamino)-propyl β'-(N-thiomorpholino)-ethyl	120–150°, 22 hr.	60	224–228 (yellow crystals from 87% C_2H_5OH)	9.33	9.52

TABLE II

γ-CHLOROPROPYL AMINOETHYL SULFIDES

Product	Yield, %	B. p. or m. p., °C.	Analyses, % N Calcd.	Analyses, % N Found
γ-Chloropropyl β'-(N-piperidyl)-ethyl sulfide	54	110–112 (0.5 mm.)	6.32	6.52
γ-Chloropropyl β'-(N-morpholino)-ethyl sulfide hydrochloride[a]	85	128–128.5	5.38	5.58
γ-Chloropropyl β'-(N-thiomorpholino)-ethyl sulfide hydrochloride[a]	80	158–160	5.07	5.21 5.15

[a] These compounds were prepared in a chloroform medium using the hydrochlorides of the respective γ-hydroxypropyl sulfides.

possible to the mercaptide (prepared in absolute ethanol from the mercaptan and sodium ethoxide), and the reaction was allowed to run for five minutes. The yield was 89% and, inasmuch as similar unreported types have given yields in the range of 87–92%, this appears to be a procedure of choice. Fourth, a 40% yield of sulfide was obtained by refluxing the chloride and mercaptan in absolute ethanol for one hour without the addition of sodium hydroxide.

β-Diethylaminoethyl Mercaptan.—To a solution of $(C_2H_5)_2NLi$, prepared from 88 g. (1.2 moles) of diethylamine and 1.2 moles of methyllithium in ether, cooled to −15°, was added a solution of 78 g. (1.3 moles) of ethylene sulfide in 200 cc. of ether during two hours. The mixture was maintained below −5° for two hours, and color test IV[3a] was negative. Then the mixture was cooled to −15° and 1.4 moles of hydrogen chloride in 485 cc. of anhydrous ether was added during one hour, and this was followed by the addition of 100 cc. of water. From the dried ether layer was obtained 76.9 g. (48%) of the mercaptan which distilled at 64–66° (20 mm.). In another preparation the yield was 70.2 g. (44%).

The β-diethylaminoethyl mercaptan was also prepared in 20.5% yield by refluxing for nine hours a mixture of 139.5 g. (0.81 mole) of β-chlorethyl-diethylamine hydrochloride and 64.7 g. (0.85 mole) of thiourea in 200 cc. of *n*-propanol. The reaction was somewhat vigorous. Treatment with potassium hydroxide preceded the ether extraction and distillation.[3b]

From an experiment in which diethylamine and ethylene sulfide were heated in phenol, the mercaptan was also formed, but was isolated as the bis-(β-diethylaminoethyl) disulfide.

γ-Hydroxypropyl β'-(N-Piperidyl)-ethyl Sulfide.—A solution of 20.3 g. (0.22 mole) of γ-hydroxypropyl mercaptan[4] in 50 cc. of toluene was added to a stirred and gently refluxed suspension of sodium ethoxide (from 0.22 g. atom of sodium) in toluene. After refluxing for twenty minutes, there was added to the sodium mercaptide a solution of 32.4 g. (0.22 mole) of N-β-chloroethylpiperidine in 30 cc. of toluene, and the resulting mixture was refluxed for five hours. There was obtained 36.5 g. (81%) of colorless product distilling at 134–136° (0.5 mm.).

Anal. Calcd. for $C_{10}H_{21}ONS$: N, 6.89. Found: N, 6.66, 6.68.

The N-β-chloroethylpiperidine[5] was obtained in a 62.7% yield (b. p., 36–38° (0.5 mm.)) from β-hydroxyethylpiperidine and thionyl chloride in chloroform; and the N-β-hydroxyethylpiperidine[6] was prepared in a 61% yield (b. p., 96–98° (19 mm.)) from reaction of piperidine with ethylene chlorohydrin in acetone.

γ-Hydroxypropyl β'-(N-Morpholino)-ethyl Sulfide.—To a toluene suspension of sodium ethoxide (prepared from 4.5 g. of sodium) was added 18 g. (0.195 mole) of γ-hydroxypropyl mercaptan in 50 cc. of toluene. After refluxing for twenty minutes, 29 g. (0.195 mole) of N-β-chloroethylmorpholine in 25 cc. of toluene was added and the mixture refluxed for four hours. Subsequent to cooling, hydrolysis, and separation, the residue was distilled to yield 4 g. (10%) of product distilling at 154–157° (1 mm.).

Anal. Calcd. for $C_9H_{19}O_2NS$: N, 6.82. Found: N, 7.04.

From another preparation, 27.6 g. (0.3 mole) of γ-hydroxypropyl mercaptan in 40 cc. of absolute ethanol was added to sodium ethoxide prepared from 0.3-g. atom of sodium. Then, 30 g. (0.2 mole) of N-β-chloroethylmorpholine in absolute ethanol was added and the mixture refluxed for five hours. After removal of the ethanol, the residue was treated with a mixture of 200 cc. of ether and 25 cc. of water. The ether layer was separated, dried and treated with hydrogen chloride; the ether was then removed and 50 cc. of absolute ethanol added to the oil. The crystals which separated on standing, after the addition of dry ether, weighed 16.2 g. (33%) and this hydrochloride of γ-hydroxypropyl β'-(N-morpholino)-ethyl sulfide melted at 101–102°.

Anal. Calcd. for $C_9H_{20}O_2NClS$: N, 5.79. Found: N, 5.87.

The N-β-chlorethylmorpholine was prepared in 32% yield (b. p., 83–86° (6–8 mm.)) from N-β-hydroxyethylmorpholine and thionyl chloride in chloroform.[7] The precursory N-β-hydroxyethylmorpholine was prepared by two procedures. One of these was from triethanolamine hydrochloride,[8] and the yield in a 3 mole run was 33% of compound distilling at 118–120° (23–24 mm.). The other procedure was to add 106 g. (1.25 moles) of ethylene chlorohydrin in acetone to a solution of 235 g. (2.5 moles) of morpholine in acetone. This solution was heated, with stirring, by a water-bath to 75° (bath temp.). An exothermic reaction set in. Crystals started to form in the mixture which was stirred and heated at 70° for two hours, and then allowed to stand overnight. The crystals of morpholine hydrochloride were filtered and washed with acetone. After removal of the acetone from the filtrate by distillation, the product came over at 116–119° (21–23 mm.) and the yield was 104 g. (66%).

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(3) (a) Gilman and Woods, THIS JOURNAL, **65**, 33 (1943). (b) In general accordance with directions by Renshaw and co-workers, *ibid.*, **60**, 1765 (1938). An improved procedure has just been described by Albertson and Clinton, *ibid.*, **67**, 1222 (1945). These authors isolated the isothiouronium salt.

(4) Rajahn and Lemme, *Arch. Pharm.*, **263**, 612 (1925).

(5) I. G. Farbenindustrie, French Patent 802,416 (1936) [*Chem. Zentr.*, **107**, II, 4255 (1936)].

(6) v. Braun, Brainsdorf and Räth, *Ber.*, **55**, 1666 (1922).

(7) Mason and Block, THIS JOURNAL, **62**, 1443 (1940).

(8) Gardner and Haenni, *ibid.*, **53**, 2763 (1931).

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

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

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

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β-Diethylaminoethyl Mercaptan and γ-Diethylaminopropyl Mercaptan

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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

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[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).