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

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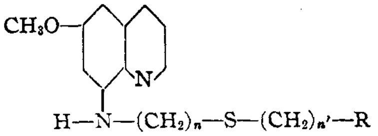
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

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 ($n = 3$; $n' = 3$).

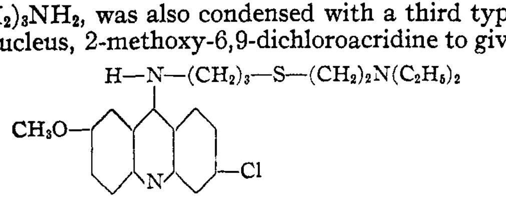
The compounds were prepared, in accordance with the general procedure described earlier,[1] by condensing 6-methoxy-8-aminoquinoline with the appropriate diethylaminoalkyl chloroalkyl sulfides. These sulfides were prepared, in turn, by the reactions

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

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

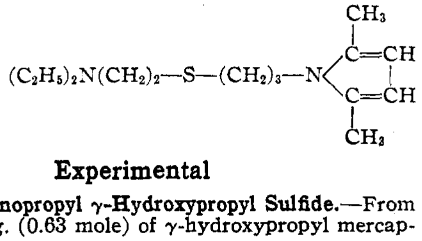
One of the sulfur side-chains ($n = 3$; $n' = 3$) was also condensed with *m*-trifluoromethylaniline.

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

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[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).

110°. The bath temperature was held at 110° for six hours and then at 110–115° for an additional five hours. Heating at higher temperatures gave significantly reduced yields. After working up in the manner previously described for the homologous compound, there was obtained 7 g. (41%) of sulfide distilling at 205–210° (0.1 mm.).

Anal. Calcd. for $C_{19}H_{29}ON_3S$: N, 12.10. Found: N, 12.08.

The **dihydrochloride of β-(6-methoxy-8-quinolylamino)-ethyl γ-diethylaminopropyl sulfide** melted at 164–165° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{19}H_{31}ON_3Cl_2S$: N, 10.00. Found: N, 9.75.

γ-Diethylaminopropyl γ-(*m*-Trifluoromethylanilino)-propyl Sulfide.—After heating a mixture of 7.9 g. (0.05 mole) of *m*-trifluoromethylaniline and 11.3 g. (0.05 mole) of γ-diethylaminopropyl γ-chloropropyl sulfide slowly in an oil-bath to 110°, then at 110–125° for eight hours, and finally at 120° for twenty-four hours, there was obtained 7 g. (40%) of the sulfide distilling at 173–175° (0.1 mm.).

Anal. Calcd. for $C_{17}H_{27}N_2F_3S$: N, 8.09. Found: N, 8.22.

The **dihydrochloride** melted at 123–124° after crystallization from ether–absolute ethanol.

Anal. Calcd. for $C_{17}H_{29}N_2Cl_2F_3S$: Cl, 16.90. Found: Cl, 17.00.

γ-(2-Methoxy-6-chloro-9-acridylamino)-propyl β-Diethylaminoethyl Sulfide.—A solution of 13.9 g. (0.05 mole) of 6,9-dichloro-2-methoxyacridine and 11 g. (0.057 mole) of β-diethylaminoethyl γ-aminopropyl sulfide in 60 cc. of phenol was heated in a boiling water-bath for two hours. After pouring into dilute sodium hydroxide solution, the oil was extracted with ether, and from the ether extract there was obtained (subsequent to removal of unchanged β-diethylaminoethyl γ-aminopropyl sulfide by steam distillation) a solid crystalline mass. A small part of this was recrystallized from benzene–petroleum ether (b. p., 80–110°) to give the sulfide melting at 62–64°.

Anal. Calcd. for $C_{23}H_{30}ON_3ClS$: N, 9.73. Found: N, 9.85.

The main portion of the crystalline mass was dissolved in absolute ethanol, and the dihydrochloride which precipitated on the addition of ethereal hydrogen chloride weighed 20 g. (80%) and melted at 247–249°. One crystallization from 95% ethanol gave 13.5 g. of **dihydrochloride** melting at 252–254°.

Anal. Calcd. for $C_{23}H_{32}ON_3Cl_3S$: N, 8.35. Found: N, 8.25.

The β-diethylaminoethyl γ-aminopropyl sulfide was prepared in 39% yield by 48% hydrobromic acid cleavage of the condensation product of sodium β-diethylaminoethyl mercaptide with γ-bromopropylphthalimide. This compound is mentioned in the patent literature[4a] and has been prepared recently by Clinton and co-workers.[4b]

β-Diethylaminoethyl γ-(2,5-Dimethyl-1-pyrryl)-propyl Sulfide.—From the mixture resulting after refluxing for three hours a solution of 9 g. (0.047 mole) β-diethylaminoethyl γ-aminopropyl sulfide, 5.7 g. (0.05 mole) of acetonylacetone, 1 cc. of glacial acetic acid in 30 cc. of absolute ethanol, there was obtained 5.5 g. (41%) of sulfide distilling at 143–145° (0.1 mm.).

Anal. Calcd. for $C_{15}H_{28}N_2S$: N, 10.43. Found: N, 10.42.

β-Hydroxyethyl γ-Chloropropyl Sulfide.—A solution of 173 g. (1.1 moles) γ-chloropropyl bromide in 50 cc. of absolute ethanol was added over a one-hour period (with vigorous stirring and at 20°) to sodium β-hydroxyethyl mercaptide, prepared from 78 g. (1 mole) of β-hydroxyethyl mercaptan and one equivalent of sodium ethoxide in 400 cc. of absolute ethanol. The ethanol was removed by distillation; the residue was dissolved in ether; and after filtration and distillation there was obtained 130 g. (85%) of sulfide which distilled at 93–96° (0.1 mm.); n^{20}_{D} 1.5140; d^{20}_{4} 1.1766; MR calcd., 40.29; found, 39.75.

Anal. Calcd. for $C_5H_{11}OClS$: Cl, 22.97. Found: Cl, 22.90.

β-Acetoxyethyl γ-Chloropropyl Sulfide.—From 30.8 g. (0.2 mole) of β-hydroxyethyl γ-chloropropyl sulfide and 22.4 g. (0.22 mole) of acetic anhydride was obtained 37 g. (94%) of sulfide distilling over the range 85–95° (0.1 mm.). Redistillation gave 35 g. which distilled at 86–87° (0.1 mm.); n^{20}_{D} 1.4879; d^{20}_{4} 1.1531; MR calcd., 48.96; found, 49.28.

Anal. Calcd. for $C_7H_{13}O_2ClS$: S, 16.28. Found: S, 16.03.

β-Diethylaminoethyl γ-Hydroxypropyl Sulfide.—To a solution of sodium γ-hydroxypropyl mercaptide, prepared by adding 92 g. (1 mole) of γ-hydroxypropyl mercaptan to one equivalent of sodium ethoxide in 300 cc. of absolute ethanol, was added, dropwise and at the reflux temperature, 136 g. (1 mole) of β-diethylaminoethyl chloride. Subsequent to the completion of addition, the mixture was refluxed for one hour. The yield of sulfide distilling at 105–106° (0.1 mm.) was 143 g. (75%). This sulfide was prepared previously from β-diethylaminoethyl mercaptan and γ-chloropropanol,[1] and from the isothiouronium chloride and γ-chloropropanol.[4b]

The yield of β-diethylaminoethyl γ-chloropropyl sulfide,[1,4b] from an experiment starting with 110 g. (0.58 mole) of β-diethylaminoethyl γ-chloropropyl sulfide, was 72%; and the compound distilled at 92–93° (0.1 mm.).

Summary

Syntheses are described for γ-(6-methoxy-8-quinolylamino)-propyl γ-diethylaminopropyl sulfide, β-(6-methoxy-8-quinolylamino)-ethyl γ-diethylaminopropyl sulfide, γ-diethylaminopropyl γ-(*m*-trifluoromethylanilino)-propyl sulfide, γ-(2-methoxy-6-chloro-9-acridylamino)-propyl β-diethylaminoethyl sulfide and β-diethylaminoethyl γ-(2,5-dimethyl-1-pyrryl)-propyl sulfide.

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[4] (a) German Patent 450,254 (1935) [*Chem. Zentr.*, **108**, I, 384 (1937)]; (b) Clinton and co-workers, THIS JOURNAL, **67**, 594 (1945).