[Contribution from the Chemical Laboratory of Iowa State College]

γ-(6-Methoxy-8-quinolylamino)-propyl β-Diethylaminoethyl Sulfone

By Henry Gilman and Lawrence Fullhart

In extension of the preparation of some quinoline-sulfur compounds,[1] γ-(6-methoxy-8-quinolylamino)-propyl β-diethylaminoethyl sulfone (II) has been prepared. The precursory γ-bromopropyl β-diethylaminoethyl sulfone (I) was prepared by the following series of reactions incidental to the use of some of the intermediates for another study.

$$p\text{-}O_2NC_6H_4ONa + ClCH_2CH_2CH_2OH \longrightarrow$$

$$p\text{-}O_2NC_6H_4OCH_2CH_2CH_2OH \xrightarrow{SOCl_2}$$

$$p\text{-}O_2NC_6H_4OCH_2CH_2CH_2Cl \xrightarrow{NaSCH_2CH_2OH}$$

$$p\text{-}O_2NC_6H_4O(CH_2)_3SCH_2CH_2OH \xrightarrow{SOCl_2}$$

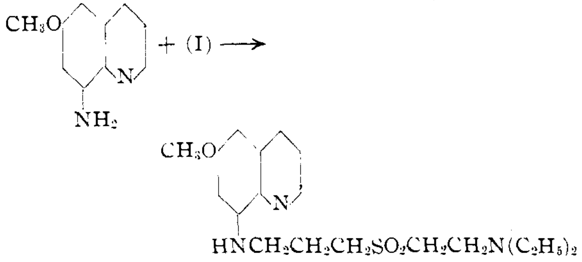
$$p\text{-}O_2NC_6H_4O(CH_2)_3SCH_2CH_2Cl \xrightarrow{H_2O_2}$$

$$p\text{-}O_2NC_6H_4O(CH_2)_3SO_2CH_2CH_2Cl \xrightarrow{(C_2H_5)_2NH}$$

$$p\text{-}O_2NC_6H_4O(CH_2)_3SO_2CH_2CH_2N(C_2H_5)_2 \xrightarrow{HBr}$$

$$Br(CH_2)_3SO_2CH_2CH_2N(C_2H_5)_2$$

(I)



(II)

In this series of reactions it was observed that the γ-(p-nitrophenoxy)-propyl β-chloroethyl sulfide had a vesicant action.

A related series of reactions was used earlier by Marvel and co-workers[2] to prepare γ-bromopropyldiethylamine and ϑ-bromobutyldiethylamine. They observed that hydrobromic acid cleaved their phenoxy compounds very satisfactorily without the use of sealed tubes. Our *p-nitro*phenoxy compound was cleaved with greater difficulty and appeared to require the use of sealed tubes.

The quinoline-sulfone (II) was also prepared from 6-methoxy-8-aminoquinoline and γ-chloropropyl β-diethylaminoethyl sulfone.[3]

Experimental

***p*-Nitrophenyl γ-Hydroxypropyl Ether.**—A mixture of 242 g. (1.5 moles) of the sodium salt of p-nitrophenol and 142 g. (1.5 moles) of trimethylene chlorohydrin in 1300 cc. of ethanol was stirred and refluxed for twenty-four hours. Then 47.3 g. (0.5 mole) of trimethylene chlorohydrin was added and refluxing was continued for an additional forty-eight hours. The hot suspension of salt was filtered; the ethanol removed under reduced pressure; the residual oil was extracted with 600 cc. of ether; the ether solution was washed with 250 cc. of 5–10% sodium hydroxide, and the resulting solution was distilled after drying over sodium sulfate. The yield of p-nitrophenyl γ-hydroxypropyl ether distilling at 162–172° at 0.08–0.8 mm. was 183.5 g. (62%). The product solidified on standing, and melted at 48–49° after recrystallization from methanol.

Anal. Calcd. for $C_9H_{11}O_4N$: N, 7.12. Found: N, 7.12.

***p*-Nitrophenyl γ-Chloropropyl Ether.**—To a stirred, cooled solution of 39.4 g. (0.2 mole) of p-nitrophenyl γ-hydroxypropyl ether in 15.8 g. (0.2 mole) of pyridine was added slowly 35.7 g. (0.3 mole) of thionyl chloride. The solution was then heated on an oil-bath for four hours in the temperature range of 80–110°. To the cooled solution was added 125 cc. of ether and then 100 cc. of water, after which the ether layer was separated and washed successively with water, dilute hydrochloric acid, and then with a saturated solution of sodium bicarbonate until neutral. The ether was removed under reduced pressure from the dried ether solution and 41 g. (95%) of p-nitrophenyl γ-chloropropyl ether melting at 41–43° was obtained. The melting point after recrystallization from ethanol was 42–43°.

Anal. Calcd. for $C_9H_{10}O_3NCl$: N, 6.51. Found: N, 6.52.

γ-(*p*-Nitrophenoxy)-propyl β-Hydroxyethyl Sulfide.—To an ethanolic solution of sodium β-hydroxyethyl mercaptide, prepared from sodium ethoxide and 62.4 g. (0.8 mole) of β-hydroxyethyl mercaptan, was slowly added with stirring 155 g. (0.72 mole) of p-nitrophenyl γ-chloropropyl ether in ethanol. The hot solution was filtered; the ethanol was removed under reduced pressure; and the red oil remaining was extracted with 600 cc. of ether, and then washed with water. After drying over sodium sulfate, the ether was removed under reduced pressure to give 160 g. (86%) of crude product. The sulfide distilled as a light yellow oil at 195–196° at 0.026 mm. On standing the product solidified, and the melting point was 48–49° after washing with petroleum ether (b. p. 60–68°).

Anal. Calcd. for $C_{11}H_{15}O_4NS$: N, 5.45. Found: N, 5.54.

γ-(*p*-Nitrophenoxy)-propyl β-Chloroethyl Sulfide.—To a solution of 90 g. (0.35 mole) of crude γ-(p-nitrophenoxy)-propyl β-hydroxyethyl sulfide in 27.6 g. (0.35 mole) of pyridine, was added slowly 62 g. (0.52 mole) of thionyl chloride. After heating the mixture for four hours in the range of 80–110°, the solution was cooled and 100 cc. of ether was added. The excess of thionyl chloride was then decomposed by the cautious addition of water, and the ether layer together with the ethereal extracts were washed with dilute hydrochloric acid, then with sodium bicarbonate solution, and finally dried over sodium sulfate. Removal of the ether gave 85 g. (87%) of crude product. An attempt was made to distill a part of this product at a pressure of 0.0012 mm., but decomposition set in when the bath temperature was in the range 150–170°.

γ-(*p*-Nitrophenoxy)-propyl β-Chloroethyl Sulfone.—To a stirred solution of 85 g. (0.31 mole) of crude γ-(p-nitrophenoxy)-propyl β-chloroethyl sulfide in 200 cc. of glacial acetic acid was added 35.2 g. (0.31 mole) of 30% hydrogen peroxide and the temperature was kept below 60°. Then, after adding 70.4 g. (0.62 mole) of 30% hydrogen peroxide with the same precautions, the mixture was heated on a steam cone until the hydrogen peroxide started to decompose. The heat was removed immediately and the

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[1] Gilman and Woods, This Journal, **67**, Oct. (1945).

[2] Marvel, Zartman and Bluthardt, *ibid.*, **49**, 2299 (1927).

[3] The preparation of this sulfone was described recently by Clinton, Suter, Laskowski, Jackman and Huber, *ibid.*, **67**, 594 (1945).

refluxing controlled by a cooling bath. When the refluxing had subsided the mixture was heated on the steam cone for two hours. After removal of the water and acetic acid under reduced pressure, the residue was crystallized from 95% ethanol to give 85 g. (89%) of crude sulfone melting over the range 74–81°, with sintering. Recrystallization raised the melting point to 81–82°.

Anal. Calcd. for $C_{11}H_{14}O_5NClS$: N, 4.57. Found: N, 4.59.

γ-(*p*-Nitrophenoxy)-propyl β-Diethylaminoethyl Sulfone Hydrochloride.—On the addition of 4.4 g. (0.06 mole) of diethylamine to a stirred mixture of 15 g. (0.049 mole) of γ-(*p*-nitrophenoxy)-propyl β-chloroethyl sulfone, 3.9 g. (0.049 mole) of anhydrous potassium carbonate and 100 cc. of absolute ethanol there was an exothermic reaction accompanied by a darkening of the mixture. After refluxing for five hours on a water-bath, the hot mixture was filtered and the residue washed with hot ethanol. The ethanolic solutions were combined, and concentrated under reduced pressure to a gum, to which was added an absolute ethanolic solution of hydrogen chloride. Recrystallization of the solid from absolute ethanol gave 14 g. (75%) of γ-(*p*-nitrophenoxy)-propyl β-diethylaminoethyl sulfone hydrochloride melting at 156–157°.

Anal. Calcd. for $C_{15}H_{25}O_5N_2ClS$: N, 7.35. Found: N, 7.54.

The **hydrobromide of γ-(*p*-nitrophenoxy)-propyl β-diethylaminoethyl sulfone** melted at 147–148°.

Anal. Calcd. for $C_{15}H_{25}O_5N_2BrS$: N, 6.52. Found: N, 6.57.

γ-Bromopropyl β-Diethylaminoethyl Sulfone Hydrobromide.—A mixture of 25 g. (0.066 mole) of γ-(*p*-nitrophenoxy)-propyl β-diethylaminoethyl sulfone hydrochloride and 55.5 g. (0.33 mole) of constant boiling hydrobromic acid was heated in a sealed tube for eighteen hours at 150°. After cooling, the solid reaction product was dissolved in water and extracted with ether. The aqueous layer was evaporated to dryness; taken up in absolute ethanol; and clarified with charcoal. Crystallization from ethanol gave 10 g. (41%) of crude product, which melted after purification at 106.5–108°. The compound is hygroscopic.

Anal. Calcd. for $C_9H_{21}O_2NBr_2S$: N, 3.82. Found: N, 3.97.

Several other attempts were made to cleave the *p*-nitrophenoxy compound. There was apparently no significant cleavage after refluxing in glacial acetic acid with constant boiling hydrobromic acid for seven hours. Also, the open-container hydrobromic procedure[2] used with some phenoxy compounds was ineffective. Refluxing in hydriodic acid did not yield any isolable crystalline material.

γ-(6-Methoxy-8-quinolylamino)-propyl β-Diethylaminoethyl Sulfone Hydrochloride.—A mixture of 10 g. (0.036 mole) of γ-bromopropyl β-diethylaminoethyl sulfone hydrobromide, 6.44 g. (0.037 mole) of 6-methoxy-8-aminoquinoline and 6 cc. of absolute ethanol was heated on a water-bath for forty-five minutes. Then the yellow solid mixture was heated in an oil-bath for six hours at 110–120°. The solid was dissolved in 50 cc. of hot water; the cooled solution was extracted with ether; and after covering the aqueous layer with 250 cc. of ether, the solution was neutralized with 20% sodium hydroxide. The ether layer was separated; the aqueous layer was extracted with three 50-cc. portions of ether; and the ether extracts were combined and dried over sodium sulfate. Addition of ethereal hydrogen chloride to the ether solution precipitated a red gum which later solidified. Recrystallization from 95% ethanol gave 12 g. (80%) of quinoline sulfone melting at 236–237°.

Anal. Calcd. for $C_{19}H_{30}O_3N_3ClS$: N, 9.30. Found: N, 9.20.

The γ-(6-methoxy-8-quinolylamino)-propyl β-diethylaminoethyl sulfone hydrochloride was also prepared from 6-methoxy-8-aminoquinoline and γ-chloropropyl β-diethylaminoethyl sulfone,[3] and was shown by the method of mixed melting points to be identical with the product prepared from γ-bromopropyl β-diethylaminoethyl sulfone hydrobromide. The γ-chloropropyl β-diethylaminoethyl sulfone was prepared[4] by adding 30 cc. of 30% hydrogen peroxide to 22.9 g. (0.11 mole) of γ-chloropropyl β-diethylaminoethyl sulfide[1,3] in 50 cc. of acetic acid, keeping the temperature below 0°. The solution was allowed to stand at room temperature for three days; then cooled and neutralized with ammonium hydroxide; and the ether extract was dried over sodium sulfate. Removal of the ether gave 18.5 g. (70%) of crude product, the picrate of which melted at 113–113.5°. This agrees with the reported[3] melting point (112–113°) of the picrate.

The γ-chloropropyl β-diethylaminoethyl sulfide was prepared[1,3] in 87% yield (b. p., 102–104° at 1 mm.; $n^{20}D$ 1.4899) by the action of thionyl chloride on a chloroform solution of γ-hydroxypropyl β-diethylaminoethyl sulfide. This hydroxy-sulfide was prepared[1,3] in turn from sodium γ-hydroxypropyl mercaptide and β-diethylaminoethyl chloride; the yield was 83% of product distilling at 121° at 1.5 mm.; $n^{20}D$ 1.4949.

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Summary

The preparation of γ-(6-methoxy-8-quinolylamino)-propyl β-diethylaminoethyl sulfone is described.

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(4) See Pomerantz and Connor, THIS JOURNAL, **61**, 3386 (1939), for a general procedure for oxidizing sulfides to sulfones.