Synthesis of *p*-[*N*′,*N*′-Bis(2-chloroethyl)amino]-*N*-sulfinylaniline.

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ABSTRACT

The title compound, an analog of antitumor compounds related to nitrogen mustard, has been synthesized by reaction of *N*,*N*-bis(2-hydroxyethyl)aniline with phosphorus oxychloride followed by nitrosation of the product with nitrous acid; then reduction of the *N*,*N*-bis(2-chloroethyl)-*p*-nitrosoaniline to the corresponding amine hydrochloride, and subsequent reaction of the dichloroamine hydrochloride with thionyl chloride to give *p*-[*N*′,*N*′-bis(2-chloroethyl)amino]-*N*-sulfinylaniline.

INTRODUCTION

In previous work we have synthesized sulfinylamino derivatives (Ib) of nitrogen mustard (Ia).

$(ClCH_2CH_2)_2N\text{-}R$

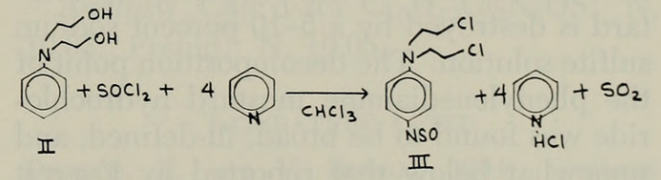
a,R = CH_3 b,R = NSO

I

These compounds showed varying degrees of antitumor activity. Of special interest was *N*′,*N*′-bis(2-chloroethyl)-*N*-sulfinylhydrazine (Ib), which is active against Walker carcinosarcoma 256 at the 1.6 mg/kg level and in cell culture cytotoxicity tests had an ED_{50} of 6.6 mg/ml (Smith and Chen 1968). As part of a program to modify this active structure, we have synthesized *p*-[*N*′,*N*′-bis(2-chloroethyl)amino]-*N*-sulfinylaniline. This structure may be thought of as compound Ib in which a benzene ring has been inserted between the nitrogens of the hydrazine moiety.

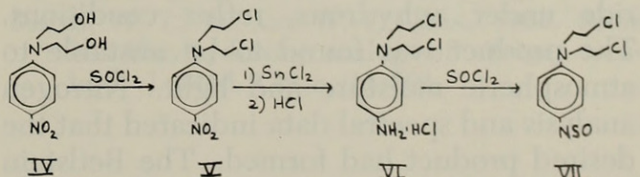
METHODS

The initial approach to the synthesis of this compound was designed to keep the number of synthetic steps to a minimum. *N*,*N*-Bis(2-hydroxyethyl)-*p*-nitroaniline was prepared by reaction of 1-chloro-4-nitrobenzene with 2,2′-iminodiethanol. The somewhat low yield obtained in this step was offset by the commercial availability of the reagents. Catalytic reduction of the nitro group readily converted the nitro group to an amino group but considerable difficulty was encountered in obtaining the amino compound in a pure state, due to its very rapid oxidation in air. This problem was eventually overcome by keeping the product as free from oxygen as possible. This entailed the bubbling of nitrogen through the ethanolic solution of the compound during any pauses in the isolation procedure. It was found that *N*,*N*-bis(2-hydroxyethyl)-*p*-phenylenediamine was relatively more stable in ethereal solution and in dry crystalline form than when dissolved in ethanol. The crystalline product is preferably stored in the dark under dry nitrogen. Several attempts were made to convert the above diamine to the desired product in one step. This conversion should be possible since both the conversion of alcohols to alkyl chlorides and of aromatic amines to *N*-sulfinylamines have been accomplished by the action of thionyl chloride.



II III

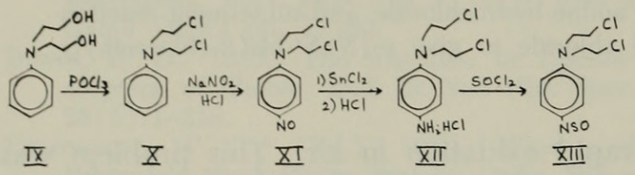
After a number of reaction conditions were found unsatisfactory for conversion of II to III in one step, it was concluded a more feasible method would be conversion first of IV to VI, then reaction of the latter with thionyl chloride to convert it to the desired *N*-sulfinyl compound (VII) as shown below.



IV V VI VII

This synthetic route was discontinued after

preparation of V using the procedure that Degutis and Bieksa (1964) used to prepare the *meta* isomer. The yield for this conversion was low and made a multistep synthetic route involving the *p*-nitro mustard (V) less desirable. It was then decided that *N*,*N*-bis(2-hydroxyethyl)aniline (IX) could provide a more efficient route to the desired product.



IX X XI XII XIII

The *N*,*N*-bis(2-chloroethyl)aniline (X) was prepared in reasonable yield by the method of Ross (1949). The light lavender product was reasonably stable except on long exposure to light. This aromatic mustard was then nitrosated in good yield by the method of Everett and Ross (1949). The nitroso mustard [*N*,*N*-bis(2-chloroethyl)-*p*-nitrosoaniline] (XI) was unstable on exposure to air and light for a period of several hours. The nitroso mustard was then reduced by the method of Everett and Ross (1949). The resulting phenylenediamine mustard [*N*,*N*-bis(2-chloroethyl)-*p*-phenylenediamine] (XII), was stored as the hydrochloride which is stable to both air and light, but exerted powerfully vesicant action on skin. The vesicant action of the mustard is destroyed by a 5–10 percent sodium sulfite solution. The decomposition point of the phenylenediamine mustard hydrochloride was found to be broad, ill-defined, and somewhat below that reported by Everett and Ross (1949). Evidence that the structure was correct, however, was provided by elemental analysis, nmr, and ir data.

The final, desired product, *p*-[*N*′,*N*′-bis(2-chloroethyl)amino]-*N*-sulfinylaniline, (XIII) was prepared by the action of a large excess of purified thionyl chloride on the phenylenediamine mustard hydrochloride under anhydrous, reflux conditions. The product was found to be unstable to atmospheric moisture and light. Nitrogen analysis and spectral data indicated that the desired product had formed. The Beilstein test showed the presence of chlorine, and a sodium fusion followed by lead acetate treatment indicated the presence of sulfur.

In view of the exceedingly poor stability of the compound to moisture and light, no attempt has been made to submit the compound for biological testing and efforts to synthesize closely related analogs have been dropped.

Experimental Section

N,N-*Bis(2-chloroethyl)*-p-*nitroaniline.*—An adaptation of the procedure used by Degutis and Bieksa (1964) in preparation of the corresponding *meta* isomer was employed.

To 5.0 g (0.022 mole) of *N*,*N*-bis(hydroxyethyl)-*p*-nitroaniline in a 250-ml single-necked flask fitted with reflux condenser, magnetic stirrer, and oil bath was added 75 ml of dry, distilled 1,2-dichloroethane and 4.5 ml (0.062 mole) of purified thionyl chloride. The mixture was refluxed with stirring 2 hours. The excess thionyl chloride and solvent were removed by evaporation under reduced pressure. The residue was treated with 100 ml of chloroform, the resulting solution was filtered, and the filtrate evaporated to dryness yielding 3.1 g (52%) of unpurified product. The crude crystals were slurried with hot absolute ethanol and removed by filtration. The resulting solid (1.2 g, 21%) melted at 192–195° C. From an analogous procedure a melting point of 198–199° corr. was obtained on recrystallization from acetone.

N,N-*Bis(2-chloroethyl)aniline.*—The procedure employed was a modification of the procedure used by Ross (1949).

N,N-*Bis(2-chloroethyl)*-p-*nitrosoaniline.*—A modification of the procedure used by Everett and Ross (1949) was employed.

N,N-*Bis(2-chloroethyl)*-p-*phenylenediamine hydrochloride.*—A larger-scaled modification of the basic procedure of Everett and Ross (1949) was used.

To 22.4 g (0.091 mole) of *N*,*N*-bis(2-chloroethyl)-*p*-nitrosoaniline dissolved in 200 ml of concentrated hydrochloric acid in a 500-ml Erlenmeyer flask equipped with stirring and cooling, 40.8 g (0.18 mole)

of stannous chloride dihydrate was added. The amine stannichloride formed as a salmon colored precipitate during the addition. The solid was removed by filtration, dissolved in water, and the solution was made slightly basic with 1*N* sodium hydroxide (ca. 1 l was required). The aqueous soln was extracted several times with ether and the combined ether layers (ca. 750 ml total) dried over sodium hydroxide pellets. Then hydrogen chloride gas was bubbled through the unstirred ether solution until lustrous silver crystals separated. The crystals were collected by filtration, and hydrogen chloride gas was then bubbled through the filtrate using caution that the brownish dihydrochloride did not separate as well. The crystalline product was dissolved in a small amount of anhydrous methanol and reprecipitated with ether and cooling to yield 12.7 g (52%). A small portion of crystals sublimed for analysis had an approximate decomposition range of 232–242 C (lit mp 250–260 C, decomp); ir (KBr) bands at 2880, 2950, 1610, 1510, 820, and 745 cm^{-1}; nmr (DMSO-d_6) 10.25 (s, broad), 7.03 (m), 3.75 ppm (*s*). It was noted that dissolution of the *N,N*-bis(2-chloroethyl)-*p*-phenylenediamine hydrochloride in tap water produced a red coloration in the water solution. Distilled water gave no noticeable coloration with the above compound. It was further observed that dilute solutions of ferric nitrate in distilled water did produce a red coloration with the above compound.

Analysis Calc'd for $C_{10}H_{15}Cl_3N_2$: C, 44.55; H, 5.61; N, 10.39. Found: C, 44.44; H, 5.68; N, 10.20.

p-*[N′,N′-Bis(2-chloroethyl)amino]-N-sulfinylaniline.*—To 1.0 ml (0.014 mole) of purified thionyl chloride dissolved in 50 ml of dry benzene in a 100-ml round-bottomed flask was slowly added 2.0 g (0.0074 mole) of *N′,N′*bis(2-chloroethyl)-*p*-phenylenediamine hydrochloride. The reaction mixture was refluxed for 2 hours on a steam bath until the solid starting material was dissolved and the solution was clear dark brown. The excess thionyl chloride and benzene were removed by evaporation to dryness under vacuum to yield 1.8 g (87%) of crude brown solid product. The product was purified by a vacuum distillation carried out in a vacuum sublimation apparatus in oil bath at 105 C bath temperature. A large amount of product is lost during the purification procedure. The purified crystalline product was yellow–orange and was found to be unstable to light and atmospheric moisture. The instability of the product required that the chemical analysis be performed on a freshly prepared and purified product obtained by procedures analogous to the above preparation. The best melting point range obtained was 78–79 C corrected; ir (KBr) bands at 2966 (very weak), 1597 (aromatic ring), 1505, 1400, 1366, 1290 (NSO), 1260, 1197, 1135 (NSO), 1018, 817, and 742 cm^{-1} (C-Cl); nmr (DMSO-d_6) 7.35 (m) and 3.82 ppm (s). On a sample obtained using 1.5 g (0.0055 mole) of the phenylenediamine mustard hydrochloride and 1.0 ml (0.014 mole) of thionyl chloride, the Beilstein test showed the presence of chlorine (green flame), and a sodium fusion with subsequent lead acetate treatment gave a brown–black precipitate of lead sulfide.

Analysis Calc'd for $C_{10}H_{12}Cl_2N_2OS$: N, 10.03. Found: N, 10.05.

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