The Ring Opening of *N*-(1-Phthalazyl)- and *N*-(4-Quinazolyl)aziridines (1)

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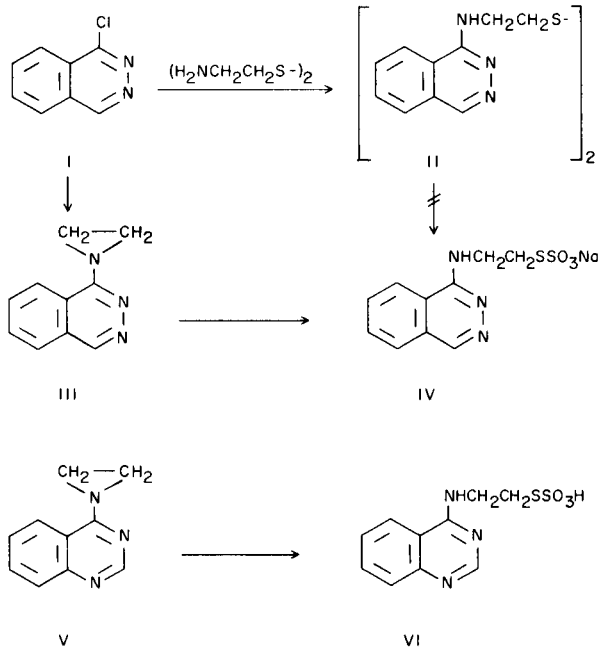
The radiation protection activity of 2-aminoethanethiosulfuric acid (4) and 2-*N*-substituted amidinoethylthiosulfuric acids (5) provided the stimulus for the synthesis of 2-(1-phthalazylamino)ethyl- (IV) and 2-(4-quinazolylamino)ethylthiosulfuric acids and/or their sodium salts.

Attempts to prepare IV by the cleavage of 2,2′-bis-(1-phthalazylamino)diethyl disulfide (II) with potassium bisulfite which was successful in the case of substituted diphenyl disulfides (6) failed.

It has been reported (7) that aziridines substituted on the nitrogen atom by a heterocyclic moiety such as the *s*-triazinyl group could be quantitatively analyzed by acid titration in the presence of sodium thiosulfate. It was suggested that the aziridinyl group was converted into the sodium *N*-substituted 2-aminoethylthiosulfate. This ring opening reaction has now been successfully applied to the synthesis of IV and VI.

1-Chlorophthalazine (8) was allowed to react with aziridine in the presence of triethylamine. 1-(1-Aziridinyl)-phthalazine (III) was obtained in a yield of 10% after purification through an alumina column. The structure of III was confirmed by the infrared spectrum which had an absorption band at 845 cm^{-1} characteristic of the aziridinyl group. The reaction of aziridine with 4-chloroquinazoline (9) at 0° in the presence of triethylamine gave 4-(1-aziridinyl)quinazoline (V) in 63% yield. An absorption band at 830 cm^{-1} in the infrared indicated the presence of the aziridinyl group.



The 1-aziridinyl heterocycles (III or V) in an aqueous solution of sodium thiosulfate (1 molar equivalent) gave the heterocyclic substituted aminoethylthiosulfate (IV) or the corresponding acid (VI) when a 1% hydrochloric acid solution was added dropwise while maintaining the *p*H of the reaction mixture at 5.

Compounds IV and VI have been screened for radiation protection activity via the Walter Reed Army Institute screening protocol. At dosages ranges of 51-150 mg./kg. both compounds were inactive.

EXPERIMENTAL (10)

2,2′-Diaminodiethyl Disulfide.

This compound was prepared in good yield by a modification of the method reported in the literature (11). To a cold solution of 0.1 g. of iodine and 18.4 g. (0.16 mole) of 2-mercaptoethylamine hydrochloride in 60 ml. of methanol was added carefully 9.2 g. (0.84 moles) of 30% hydrogen peroxide with stirring. The reaction mixture was evaporated to dryness under reduced pressure at 50°. The resultant mass was recrystallized from ethanol to give 16.25 g. of 2,2′-diaminodiethyl disulfide dihydrochloride as colorless prisms, m.p. 212°. This dihydrochloride was decomposed with a 1 molar equivalent of sodium methoxide in methanol. After removal of the resultant sodium chloride and the methanol, the residue was extracted with an ethanol-dioxane mixture. Removal of the solvent gave 9.5 g. of the free base, 2,2′-diaminodiethyl disulfide, as a brown oil.

2,2′-bis-(1-Phthalazylamino)diethyl Disulfide (II).

A mixture of 15.2 g. (0.1 mole) of the above 2,2′-diaminodiethyl disulfide and 16.2 g. (0.1 mole) of 1-chlorophthalazine (I) (8) in 50 ml. of toluene was heated at 100° with stirring for 15 hours. The resultant yellow mass, which was almost insoluble in toluene, benzene, chloroform or acetone, was filtered off, washed with water and recrystallized from hot ethanol to give 8.4 g. of yellow needles, m.p. 225-226°, dec.

Anal. Calcd. for $C_{20}H_{20}N_6S_2$: C, 58.79; H, 4.93. Found: C, 58.65; H, 4.81.

An Unsuccessful Attempt to Cleave the *S-S* Bond of II.

A mixture of 0.76 g. (0.002 mole) of finely powdered II and 0.89 g. (0.004 mole) of potassium bisulfite in 75 ml. of methanol containing 5 ml. of water was refluxed for 5 hours. After the addition of 0.23 g. of potassium hydroxide in 2 ml. of

methanol, the precipitated potassium sulfite was filtered off while hot. The filtrate was reduced in volume at 50° and the resultant precipitate was collected, washed with methanol and dried. This was identical with the starting material (II), yield 0.45 g.

1-(1-Aziridinyl)phthalazine (III).

To a solution of 12.3 g. of 4-chlorophthalazine in 245 ml. of anhydrous benzene was added 18 g. of triethylamine and then 6.8 g. of aziridine. The mixture was heated at 53° for 3 days with stirring in an atmosphere of nitrogen.

Although a large amount of brown resinous substance covered the inside of the flask, the pale yellow benzene solution was decanted and evaporated to dryness at a temperature below 45° *in vacuo* with repeated addition of dry benzene. The resultant yellow mass was purified through an alumina column (Length; 250 mm; diameter 25 mm). The successive elutions with benzene (1800 ml.), ether (500 ml.), chloroform:benzene (1:1, 900 ml.) and evaporation of the solvent gave a yellow mass which gave a positive Beilstein test (chlorine). Additional elution with ethyl acetate (1000 ml.) and evaporation of the solvent gave a crystalline mass which gave a negative Beilstein test and was recrystallized from anhydrous ether to give 0.95 g. of colorless needles, m.p. 115°. The infrared spectrum determined in a nujol mull absorbed at 845 cm^{-1} indicative of the aziridinyl group.

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.17; H, 5.23; N, 24.55. Found: C, 70.01; H, 5.10; N, 24.48.

This substance formed a picrate from ethanol, m.p. 148°.

Anal. Calcd. for $C_{16}H_{12}N_6O_7$: C, 48.00; H, 3.02. Found: C, 48.07; H, 3.00.

Sodium 2-(1-Phthalazylamino)ethylthiosulfate (IV).

To a mixture of 0.143 g. of 1-(1-aziridinyl)phthalazine and 0.21 g. (1 molar equivalent) of sodium thiosulfate pentahydrate in 30 ml. of water was added dropwise 4.5 ml. of 1% hydrochloric acid through a very fine capillary burette tip with vigorous stirring, during which time the acidity of the reaction mixture was maintained at *p*H 5. To the reaction mixture was then added 1% sodium hydroxide to adjust the *p*H to 7.6. The filtrate was evaporated to dryness *in vacuo* with repeated addition of ethanol and benzene. The white residue was digested with 120 ml. of hot ethanol and the resultant sodium chloride was removed by filtration.

The filtrate was reduced in volume to 50 ml. and treated with activated charcoal and filtered. Addition of anhydrous ether to the filtrate gave a white precipitate which was filtered and washed with anhydrous ether. Recrystallization of the product from a small amount of an ethanol-ether mixture until a negative halogen test was observed by the sodium fusion technique, gave 0.12 g. of a white powder, d.p. 72° (swelling), 210° (darking).

Anal. Calcd. for $C_{10}H_{10}N_3O_3S_2Na\cdot\frac{1}{2}H_2O$: C, 37.96; H, 3.50. N, 13.28. Found: C, 38.09; H, 3.51; H, 12.94.

4-(1-Aziridinyl)quinazoline (V).

To a solution containing 6.45 g. (0.04 mole) of 4-chloroquinazoline (9), 5.15 g. (0.06 mole) of triethylamine and 80 ml. of anhydrous benzene was added dropwise at 0°, 2.5 g. (0.075 mole) of aziridine in 20 ml. of anhydrous benzene with stirring. The reaction mixture was then allowed to stand at room temperature for 3 hours and filtered. The filtrate was evaporated to dryness under reduced pressure at a temperature below 40° with repeated addition of dry benzene. The resultant yellow mass was purified on an alumina column with benzene as the eluant. Removal of benzene from the eluate gave a pale yellow mass which was recrystallized from petroleum ether to give 4.3 g. (63%) of almost colorless long needles, m.p. 38°. This substance gave a negative Beilstein test and the characteristic infrared absorption of the aziridinyl group at 830 cm^{-1}. The product was soluble in water, ether and benzene.

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.17; H, 5.30; N, 24.55. Found: C, 70.09; H, 4.91; N, 24.48.

2-(4-Quinazolylamino)ethylthiosulfuric Acid (VI).

To a vigorously stirred mixture containing 6.84 g. (0.04 mole) of 4-(1-aziridinyl)quinazoline and 9.92 g. of sodium thiosulfate pentahydrate in 150 ml. of water was added dropwise over a period of 4 hours 1% aqueous hydrochloric acid at such a rate that the *p*h of the reaction mixture was maintained at 5 ± 0.5. The resultant white precipitate was filtered, washed with cold water and dried. Recrystallization from hot water gave 10.4 g. (91%) of 2-(4-quinazolylamino)ethylthiosulfuric acid as colorless needles, m.p. 232° dec.

Anal. Calcd. for $C_{10}H_{11}N_3O_3S_2\cdot\frac{1}{2}H_2O$: C, 40.80; H, 4.11; N, 14.28. Found: C, 40.49; H, 4.06; N, 13.94.

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