1-(2-Mercaptoethyl)phthalazines and Related Compounds (1)

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1-(2-Mercaptoethyl)phthalazine (VII) and its analogs such as *S*-2-(1-phthalazyl)ethylisothiuronium bromide (VI), sodium *S*-2-(1-phthalazyl)ethylthiosulfate (VIII), 1,3-bis-acetylthio-2-(1-phthalazyl)propane (XII), 2-(1-phthalazyl)-1,3-propanedithiol (XIII), disodium 2-(1-phthalazyl)-1,3-propanedithiosulfate (XIV), 3-dimethylamino-2-(1-phthalazyl)-1-propanethiol (XVII) and 3-(4-methyl-1-piperazinyl)-2-(1-phthalazyl)-1-propanethiol (XIX) have been prepared as potential radiation protection agents.

An interest in the radiation protection activity of several aminothiol derivatives such as 2-aminoethanethiol (4), *S*-2-aminoethyl- and *S*-3-aminopropylisothiuronium bromide (5) led us to investigate the preparation of 1-(2-mercaptoethyl)phthalazine and some of its analogs.

One of the key intermediates, 1-(2-hydroxyethyl)-phthalazine (V), was prepared by allowing 1-methylphthalazine (6) to react with a 1 molar equivalent of formalin. Earlier attempts to prepare the alcohol (V) by lithium aluminum hydride reduction of ethyl 1-phthalazylacetate (III) failed. Likewise another procedure consisting of the successive reaction of phenyllithium and dry formaldehyde vapor with 1-methylphthalazine, which had been successful in the case of picoline (7), gave only a 14% yield of 1-(2-hydroxyethyl)phthalazine together with a by-product of unknown structure, m.p. 160-163°.

The method for preparing alkylisothiuronium bromides from the corresponding alcohols (8) was successfully applied to 1-(2-hydroxyethyl)phthalazines (V). This method afforded *S*-2-(1-phthalazyl)ethylisothiuronium bromide (VI) in good yield.

Hydrolysis of the isothiuronium bromide (VI) to 1-(2-mercaptoethyl)phthalazine (VII) was achieved by heating with ammonium hydroxide in a nitrogen atmosphere for a short time. During this reaction bis-2-(1-phthalazyl)ethyl sulfide was formed as a by-product. 1-(2-Mercaptoethyl)phthalazine (VII) rapidly decolorized iodine in ethanol showing the presence of a thiol group. Compound VII was also characterized as the crystalline hydrochloride, m.p. 205° and as 2,4-dinitrophenyl-2-(1-phthalazyl)ethyl sulfide, prepared according to the procedure reported by Bost, *et al.* (9).

In order to prepare sodium *S*-2-(1-phthalazyl)ethylthiosulfate (VIII), 1-(2-hydroxyethyl)phthalazine (V) was

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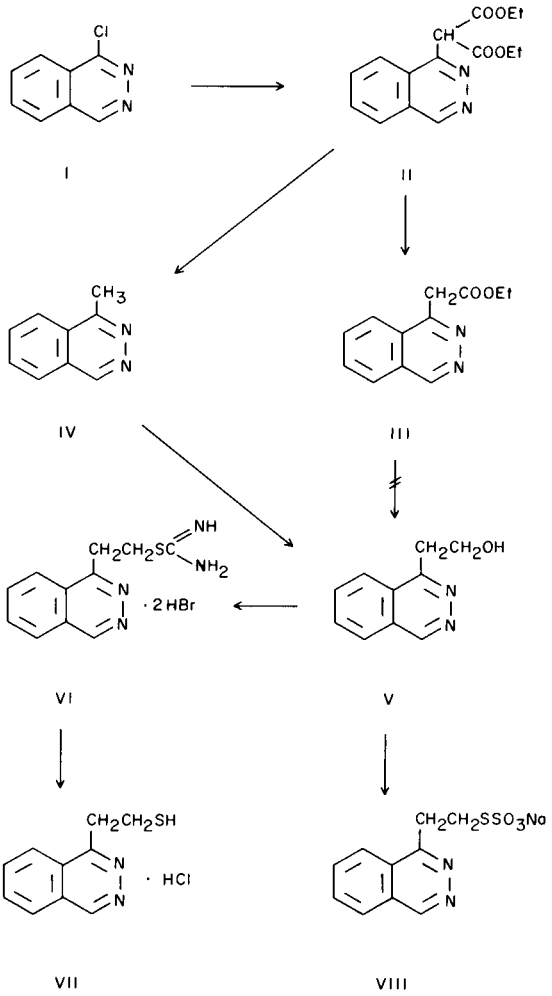

I II IV III VI V VII VIII

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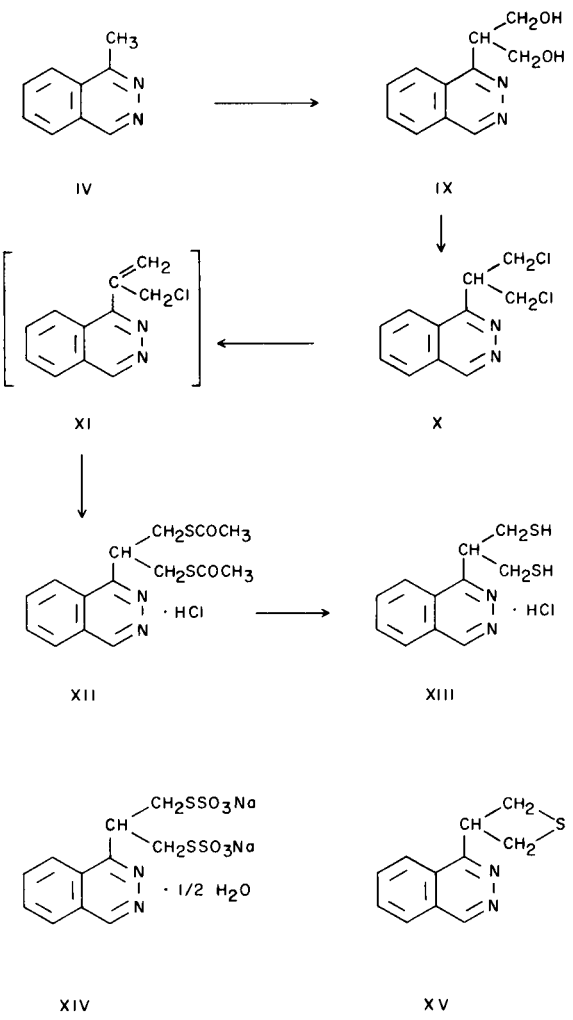

converted into the hydrochloride of 1-(2-chloroethyl)-phthalazine with thionyl chloride in chloroform solution and this was allowed to react with 1 molar equivalent of sodium thiosulfate in water at *p*H 4.5.

The second key intermediate, 2-(1-phthalazyl)-1,3-propanediol (IX) was prepared in good yield by refluxing a mixture of 1-methylphthalazine (IV) and excess formalin. Treatment of 2-(1-phthalazyl)-1,3-propanediol with excess thionyl chloride at room temperature gave 1,3-dichloro-2-(1-phthalazyl)propane (X) which was converted into 2-(1-phthalazyl)-3-chloropropene (XI) with potassium hydroxide in methanol. 2-(1-Phthalazyl)-3-chloropropene was so unstable that it was allowed to react immediately with thioacetic acid in toluene to give the hydrochloride of 1,3-bis-acetylthio-2-(1-phthalazyl)propane (XII). Removal of the acetyl group from 1,3-bis-acetylthio-2-(1-phthalazyl)propane (XII) with methanolic hydrogen chloride afforded the hydrochloride of 2-(1-phthalazyl)-1,3-propanedithiol (XIII).

Attempts to prepare the same dithiol (XIII) by the action of sodium hydrosulfide on 1,3-dichloro-2-(1-phthalazyl)propane (X) failed, however a small amount of 3-(1-phthalazyl)thietane (XV) was obtained as a by-product.

A Bunte salt (XIV) was also obtained by treatment of the 1,3-dichloropropane derivative (X) with sodium thiosulfate.

Dimethylamine and 4-methylpiperazine were easily alkylated by the highly reactive allyl chloride moiety of XI to give the corresponding 3-dialkylamino-2-(1-phthalazyl)-propene (XVI and XVIII), although the free bases could not be isolated.

Treatment of the crude 3-dialkylamino-2-(1-phthalazyl)-propene (XVI and XVIII) with thioacetic acid, followed by methanolysis of the resulting thioacetates with methanolic hydrogen chloride as described in the case of XII gave the hydrochlorides of 3-dimethylamino-2-(1-phthalazyl)propane-1-thiol (XVII) and 3-(4-methylpiperazinyl)-

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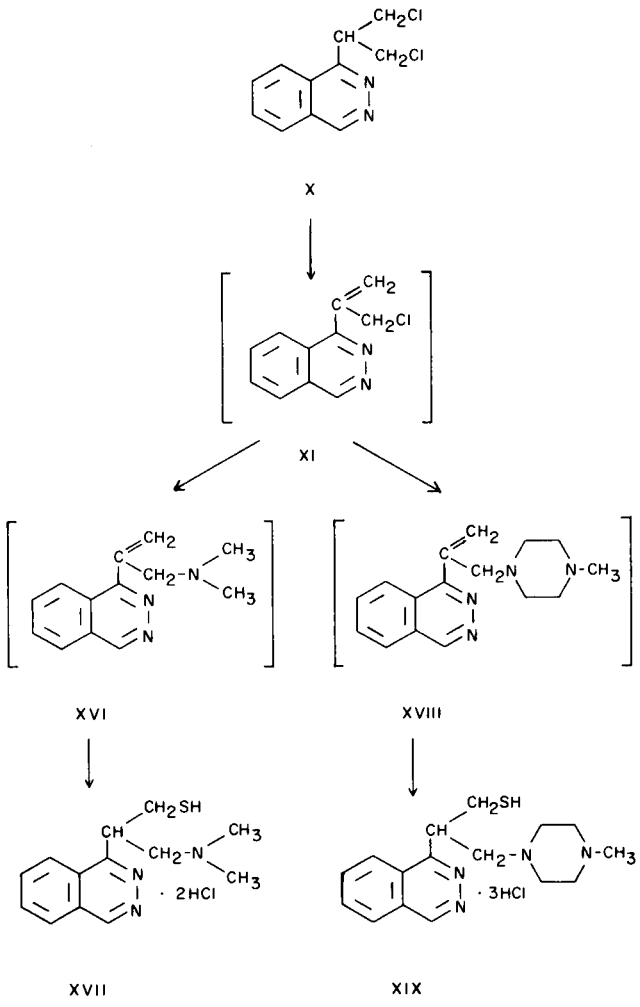

2-(1-phthalazyl)propane-1-thiol (XIX). Both rapidly decolorize an ethanolic solution of iodine, indicative of the presence of the thiol group. The infrared spectra of both free bases (XVII and XIX) showed absorption bands at 2550 and 2510 cm^{-1} respectively confirming the presence of thiol groups.

Compounds VII, XIII, XIV and XIX have been screened for radiation protection activity via the Walter Reed Army Institute screening protocol. All were inactive except XIII. Compound XIII at dose levels of 50 mg./kg. or less provided some measure of protection in that 5-25% of the test animals were protected while 100% of the controls died.

EXPERIMENTAL (10)

1-Chlorophthalazine (1).

This compound was prepared from 1-(2*H*)-phthalazinone (Eastman Kodak No. 7264) and phosphorus oxychloride, yield 99%, m.p. 121-123° (II).

Diethyl 2-(1-Phthalazyl)malonate (II).

This compound was prepared by the method of Mizuno, *et al.* (6).

Ethyl 1-Phthalazylacetate (III).

To a solution of sodium ethoxide, prepared from 0.23 g. (0.01 gram atom) of finely cut sodium and 35 ml. of anhydrous ethanol, was added a solution of 2.9 g. (0.01 mole) of diethyl 2-(1-phthalazyl)malonate in 5 ml. of anhydrous ethanol. After being well stirred the mixture was refluxed for 2 hours. After removal of the ethanol the residue was dissolved in 50 ml. of water and then poured into 50 ml. of ice water containing 10 ml. of 3 *N* hydrochloric acid. This aqueous solution was adjusted to *p*H 6.4 and extracted with benzene. The benzene extract was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The dried benzene solution was purified through an alumina column using benzene as the eluant. Removal of the benzene gave a pale yellow mass which was recrystallized from ligroin-benzene. There was obtained 1.6 g. of pale yellow needles, m.p. 80-83°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.28; H, 5.58; N, 13.15.

1-Methylphthalazine (IV).

This compound was prepared by the method of Mizuno *et al.* (6).

4-(2-Hydroxyethyl)phthalazine (V).

Method A.

A mixture of 7.2 g. (0.05 mole) of 1-methylphthalazine and 6 g. of 37% formalin (0.15 mole) was heated at 63-65° for 4 hours. Removal of the water and the formaldehyde under reduced pressure with repeated addition of anhydrous ethanol and benzene, gave a brown viscous oil which was chromatographed on an alumina column (12 x 2.5 cm.). Elution with benzene (600 ml.) and subsequent recrystallization of the product from ligroin gave 3.5 g. of recovered 1-methylphthalazine. Successive elution with chloroform (1300 ml.) and evaporation of the solvent gave a yellow mass which was recrystallized from benzene to give 3.7 g. of colorless needles, m.p. 90-91°; U.V. λ max (95% ethanol); 218, 265 mμ.

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.96; H, 5.79. Found: C, 68.88; H, 5.67.

Method B.

A 500 ml. three necked flask was equipped with a reflux condenser with calcium chloride drying tube, mechanical stirrer and a gas inlet tube for dry nitrogen. Freshly cut lithium (1.4 g.) was suspended in 140 ml. of anhydrous ether under a dry nitrogen atmosphere. To this suspension was then added 14.5 g. of bromobenzene at such a rate that the ether was maintained at a gentle reflux. Stirring was continued for 1 hour and then 13 g. of 4-methylphthalazine in 30 ml. of anhydrous benzene was added. After 45 minutes the flask was immersed in a freezing mixture and the dropping funnel was replaced by the side-arm of a distilling flask which contained 4.6 g. of paraformaldehyde dried over phosphorus pentoxide. The side-arm of the flask reached just to the surface of the reaction mixture. The paraformaldehyde was heated at 180-190° until it had been completely depolymerized and the gaseous formaldehyde was driven over into the reaction flask with a slow stream of dry nitrogen. A pinkish white precipitate separated from the reaction mixture. After the mixture stood overnight 10 ml. of water and then 20 ml. of hydrochloric acid (1:1) was added with stirring. The aqueous layer was separated, made alkaline with potassium hydroxide and salted out with potassium carbonate. The aqueous layer was extracted with five 100 ml. portions of chloroform. The chloroform extract was dried over potassium carbonate. Removal of the potassium carbonate and the solvent gave 2.3 g. of a brown mass. Recrystallization from benzene gave colorless needles, m.p. 90° which were identical with 2-hydroxyethylphthalazine as shown by a mixture melting point and by infrared spectroscopy. On the other hand, removal of the solvent from the ether-benzene layer gave 12.6 g. of a dark brown oil from which a small amount of crystalline substance separated after standing in the refrigerator for two days.

This crystalline substance was collected and recrystallized from ether to give 5.2 g. of pale yellow hexagonal plates, m.p. 160-163°. This substance of unknown constitution readily decolorized permangenate in acetic acid and gave analytical data as follows: found: C, 81.05; H, 5.78.

S-2-(1-Phthalazyl)ethylisothiuronium Bromide (VI).

A mixture of 1 g. (0.0058 mole) of 1-(2-hydroxyethyl)-phthalazine, 0.44 g. (0.0058 mole) of thiourea and 4 ml. of 48% hydrobromic acid was refluxed for 15 hours. The clear yellow reaction mixture was diluted to three times its volume with water and evaporated to dryness *in vacuo*.

The residue was dissolved in 30 ml. of anhydrous methanol, treated with activated charcoal and filtered. Removal of the solvent gave a white mass which was recrystallized from ethanol to give 1.36 g. of colorless needles, m.p. 184-185° dec.

Anal. Calcd. for $C_{11}H_{12}N_4S \cdot 2HBr$: C, 33.52; H, 3.58; N, 14.21. Found: C, 33.30; H, 3.21; N, 14.04.

1-(2-Mercaptoethyl)phthalazine (VII).

A mixture of 27.1 g. of 2-(1-phthalazyl)ethylisothiuronium bromide (VI) in 60 ml. of water and 250 ml. of 28% ammonium hydroxide was heated on a steam bath in an atmosphere of nitrogen for 2 hours. On cooling white mirco needles separated. The mixture was diluted with water and extracted with chloroform. The chloroform extract was washed with saturated sodium chloride solution and dried over sodium sulfate. Removal of the sodium sulfate and the solvent gave a viscous oil which was digested with a small amount of anhydrous ethanol and the

resultant white mass (a) was removed by filtration.

To the ethanol filtrate was added 35 ml. of ethanol containing 4.3 g. of dry hydrogen chloride. Removal of the ethanol and excess hydrogen chloride gave 8 g. of a yellow viscous oil which was dissolved in a mixture of 50 ml. of methanol and 20 ml. of 2-propanol. The solution was treated with activated charcoal and filtered. The filtrate was reduced in volume to about 15 ml. by evaporation *in vacuo* and allowed to stand in the refrigerator to form 6 g. of the hydrochloride of 1-(2-mercaptoethyl)phthalazine, m.p. 205° dec.

Anal. Calcd. for $C_{10}H_{10}N_2S$·HCl: C, 52.98; H, 4.89; N, 12.36. Found: C, 53.28; H, 4.87; N, 12.28.

The structure of VII was further confirmed by the formation of 2,4-dinitrophenyl-2-(1-phthalazyl)ethyl sulfide (9).

Anal. Calcd. for $C_{16}H_{12}N_4O_4S$: C, 53.91; H, 3.39. Found: C, 53.73; H, 3.24.

The ethanol insoluble mass (a) described above, was recrystallized from hot benzene to give 5.7 g. of cream colored needles, m.p. 138-139°. This substance did not decolorize iodine in ethanol at room temperature. The product was bis-2-(1-phthalazyl)ethyl sulfide.

Anal. Calcd. for $C_{20}H_{18}N_4S$: C, 69.33; H, 5.24; N, 16.17. Found: C, 69.03; H, 4.99; N, 16.55.

Sodium *S*-2-(1-Phthalazyl)ethylthiosulfate (VIII).

A solution of 1.74 g. (0.01 mole) of 1-(2-hydroxyethyl)-phthalazine in 4.5 ml. of chloroform was added dropwise to 4.5 ml. of cold thionyl chloride with stirring. The reaction mixture was then stirred at room temperature for an additional 2 hours during which time a white crystalline precipitate separated.

Removal of the chloroform and excess thionyl chloride gave 2.2 g. of the crude hydrochloride of 1-(2-chloroethyl)phthalazine, m.p. 140°, swelling. Attempts to isolate the free base [1-(2-chloroethyl)phthalazine] were unsuccessful because benzene insoluble polymers were easily formed. To a solution of 2.2 g. (0.01 mole) of the above hydrochloride of 1-(2-chloroethyl)phthalazine in 10 ml. of water was added a solution of 2.48 g. (0.01 mole) of sodium thiosulfate pentahydrate in 10 ml. of water.

The reaction mixture was adjusted to *p*H 4.5 with sodium bicarbonate and heated at 60° with stirring for 40 hours. This was diluted to twice its volume with ethanol and treated with activated charcoal and then the volume was reduced to 20 ml. To this solution was added anhydrous ether to form a white precipitate which was collected, washed with anhydrous ether and dried. Repeated purification from hot ethanol gave 0.6 g. of sodium *S*-2-(1-phthalazyl)ethylthiosulfate as a white powder, d.p. 261°, darkening.

Anal. Calcd. for $C_{10}H_9N_2O_3S_2Na$: C, 41.10; H, 3.10. Found: C, 40.93; H, 3.63.

2-(1-Phthalazyl)-1,3-propandiol (X).

A mixture of 100 g. of 1-methylphthalazine, 215 g. of 37% formalin and 7 ml. of pyridine was refluxed for 16 hours. The reaction mixture was evaporated *in vacuo* with repeated addition of anhydrous ethanol to remove the formaldehyde, water and pyridine. The solid residue was recrystallized from ethanol to give 67.4 g. of colorless pillars, m.p. 161-162°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.71; H, 5.91. Found: C, 64.40; H, 5.81.

1,3-Dichloro-2-(1-phthalazyl)propane (X).

Thirteen g. of finely powdered 2-(1-phthalazyl)-1,3-propandiol (IX) was added with stirring to 71.4 g. of thionyl chloride previously cooled in an ice bath in thirteen equal portions during 15 minutes. The clear yellow reaction mixture was stirred for 2 hours at room temperature, and then evaporated to dryness under reduced pressure at a temperature below 38° with addition of 3 x 30 ml. of chloroform.

The resultant yellow mass was dissolved into 50 ml. of chloroform and poured onto ice (50 g.) and the mixture was made alkaline with 28% ammonium hydroxide and extracted with 3 x 100 ml. portions of chloroform. The chloroform extract was washed with saturated sodium chloride solution and dried over magnesium sulfate. Filtration of the magnesium sulfate and evaporation of the solvent gave an oil which was purified by chromatography on alumina. Elution with benzene and subsequent recrystallization of the product from a small amount of benzene gave 6.0 g. of pale yellow plates, m.p. 70.5°.

Anal. Calcd. for $C_{11}H_{10}Cl_2N_2$: C, 54.79; H, 4.18; N, 11.62; Cl, 29.40; Found: C, 55.11; H, 3.82; N, 11.96; Cl, 29.40.

1,3-bis-Acetylthio-2-(1-phthalazyl)propane (XII).

To a cold solution of 1,3-dichloro-2-(1-phthalazyl)propane in 20 ml. of anhydrous methanol was added a solution containing 4.3 g. of potassium hydroxide (1 molar equivalent) in 30 ml. of anhydrous methanol.

The mixture was shaken at room temperature in the dark for 2 hours. After removal of the methanol at a temperature below 30°, the residue was extracted with benzene and 3.7 g. of the resultant potassium chloride was removed by filtration. To prevent polymerization of the resultant 3-chloro-2-(1-phthalazyl)propene, the benzene filtrate was reduced in volume only to 10 ml. at a temperature below 30°, and then diluted with 40 ml. of anhydrous toluene. To this solution was added dropwise a solution of 6.5 g. (0.082 mole) of thioacetic acid in 50 ml. of toluene at −15° with vigorous stirring. After standing overnight, the resultant white precipitate was removed by filtration, washed with dry benzene and dried. Recrystallization from chloroform-acetone gave 7.75 g. of colorless pillars, m.p. 145-146° dec.

Anal. Calcd. for $C_{15}H_{16}N_2O_2S_2$·HCl: C, 50.49; H, 4.80; N, 7.83. Found: C, 50.13; H, 4.51; N, 8.05.

2-(1-Phthalazyl)-1,3-propanedithiol Hydrochloride (XIII).

To a cold solution of XII in 40 ml. of methanol was added 15 ml. of anhydrous methanol containing 4 g. of dry hydrogen chloride. The mixture was allowed to stand in the dark for two days. The resultant colorless crystals (4 g.) were filtered off and the filtrate was evaporated to dryness. The residue was crystallized from ethanol to give an additional 1.7 g. of product. The combined crystals were recrystallized from ethanol to form 5.2 g. of colorless pillars, m.p. 178° dec. This substance immediately decolorized 2 equivalents of iodine in ethanol at room temperature. Although the free base of XIII was a viscous oil, it showed a sharp absorption band for the thiol group at 2560 cm^{-1} in the infrared.

Anal. Calcd. for $C_{11}H_{12}N_2S_2$·HCl: C, 48.42; H, 4.80; N, 10.29. Found: C, 48.60; H, 5.04; N, 10.33.

The Formation of 3-(1-Phthalazyl)thietane (XV).

To a solution of sodium hydrosulfide, freshly prepared by bubbling 0.5 mole of hydrogen sulfide through a mixture of 20 g. (0.5 mole) of sodium hydroxide in 40 ml. of water and 200 ml. of ethanol with cooling, was added 6 g. of 1,3-dichloro-2-(1-phthalazyl)propane in 20 ml. of ethanol while cooling in an ice bath. The mixture was stirred for 20 hours at room temperature and then heated on a steam bath for 1 hour. After removal of the ethanol under reduced pressure the residue was dissolved in 100 ml. of water and the solution was treated with ammonium chloride to adjust the *p*H of the solution to 8, and then extracted with 3 x 100 ml. portions of chloroform. The chloroform extract was washed with saturated sodium chloride solution and dried over

magnesium sulfate. Filtration of the magnesium sulfate and evaporation of the solvent gave a brown viscous oil which was purified by chromatography on alumina. Elution with chloroform:benzene (1:1) and subsequent recrystallization of the product from benzene and ligroin gave 0.4 g. of colorless plates, m.p. 131-135°. This substance did not decolorize iodine in ethanol at room temperature and also showed no absorption characteristic of the thiol group in the infrared spectrum.

Anal. Calcd. for $C_{11}H_{10}N_2S$: C, 65.28; H, 4.98; N, 13.85. Found: C, 65.36; H, 4.97; N, 13.87. Molecular weight: Calcd: 204.3. Found: 197.4 (Rast method).

Disodium 2-(1-Phthalazyl)-1,3-propanedithiosulfate (XIV).

A mixture of 7.64 g. of 1,3-dichloro-2-(1-phthalazyl)propane in 40 ml. of ethanol and 17.4 g. of sodium thiosulfate pentahydrate in 40 ml. of water was stirred at 39° for 24 hours, at 56° for the next 24 hours and at 61° for an additional 48 hours. The reaction mixture was evaporated to dryness *in vacuo* with repeated addition of anhydrous ethanol. The resultant mass was digested with 500 ml. of anhydrous ethanol:methanol (1:1) at 45°. After removal of the insoluble sodium chloride by filtration, the filtrate was reduced in volume to 150 ml., treated with activated charcoal and filtered. The almost colorless filtrate was evaporated to dryness and the white residue was recrystallized repeatedly from hot ethanol until no more chlorine was observed in sodium fusion tests, 9.44 g. of white powder, d.p. 103°, swelling; 203°, darkening. This substance is the hemihydrate and very hygroscopic.

Anal. Calcd. for $C_{11}H_{10}N_2O_6S_4Na_2 \cdot 0.5H_2O$: C, 29.40; H, 2.47; N, 6.23. Found: C, 29.42; H, 3.11; N, 6.51.

3-Dimethylamino-2-(1-phthalazyl)-1-propanethiol (XVII).

To a cold solution of 4.8 g. (0.02 mole) of 1,3-dichloro-2-(1-phthalazyl)propane in 6 ml. of methanol was added a solution of 1.12 g. (0.02 mole) of potassium hydroxide in 8 ml. of methanol. The mixture was shaken at room temperature in the dark for 2 hours and then 1.8 g. (0.04 mole) of dimethylamine in 18 ml. of anhydrous ethanol was added.

The mixture was heated at 50° for 30 minutes, at 70° for the next 30 minutes and then refluxed for an additional 30 minutes. The resultant potassium chloride was filtered off and the filtrate was reduced in volume to about 7 ml. under reduced pressure at a temperature below 30°, with repeated addition of dry benzene. This benzene solution was diluted with three times its volume of dry benzene, washed with saturated sodium chloride solution and dried over potassium carbonate. To avoid polymerization of the product, the solution was concentrated only to 7 ml. at 30°. To this benzene solution was added 30 ml. of dry toluene and then the solution was added to a cold solution of 4.6 g. (0.06 mole) of thioacetic acid in 25 ml. of dry toluene at −15° with vigorous stirring. The clear yellow reaction mixture was exposed to the light from a 200 watt light bulb for 2 hours and then allowed to stand overnight at room temperature. After removal of the solvent and the excess thioacetic acid, the residue was dissolved in benzene and purified by passage through an alumina column (100 ml. of alumina, diameter; 2 mm.) with 1200 ml. of benzene:ethyl acetate (1:1) as the eluant. Removal of the solvent from the eluate gave 2.52 g. of a pale yellow viscous oil which was subjected to methanolysis with 15 ml. of methanol containing 1 g. of dry hydrogen chloride in an atmosphere of nitrogen for 16 hours. After removal of the solvent the resultant mass was recrystallized from a small amount of anhydrous ethanol to give 2.1 g. of colorless needles, m.p. 116°, swelling, 153° dec., in a sealed tube. This substance is the hemihydrate dihydrochloride and decolorized iodine in ethanol at room temperature.

Anal. Calcd. for $C_{13}H_{17}N_3S \cdot 2HCl \cdot 0.5H_2O$: C, 47.41; H, 6.12; N, 12.76. Found: C, 47.15; H, 6.15; N, 12.70.

3-(4-Methyl-1-piperazinyl)-2-(1-phthalazyl)-1-propanethiol (XIX).

To a cold solution of 7.0 g. (0.029 mole) of 1,3-dichloro-2-(1-phthalazyl)propane in 10 ml. of methanol was added a solution of 1.63 g. (0.029 mole) of potassium hydroxide in 20 ml. of methanol. The mixture was shaken at room temperature in the dark for 2 hours. To this reaction mixture was added 5.8 g. (0.058 mole) of 4-methylpiperazine. After standing for 30 minutes at room temperature the reaction mixture was heated at 50° for the next 30 minutes and then refluxed for an additional 30 minutes. After removal of the solvent at 30° the residue was dissolved in benzene, washed with saturated sodium chloride solution and dried over potassium carbonate. To avoid polymerization of the product (XVIII) the benzene solution was reduced in volume to 15 ml. at 30° and then diluted with three times its volume of dry toluene. This solution was added to a cold solution of 6.6 g. (0.087 mole) of thioacetic acid in 30 ml. of dry toluene at −15° with vigorous stirring. The reaction mixture was exposed to the light from a 200 watt light bulb for 2 hours and then allowed to stand overnight at room temperature.

After removal of the solvent and the excess thioacetic acid the residue was treated with 30 ml. of methanol containing 2 g. of dry hydrogen chloride in an atmosphere of nitrogen for 16 hours. After removal of the solvent, the residue was dissolved in ethanol, treated with activated charcoal and filtered. Addition of a large amount of dry ether gave a white precipitate, which was filtered in a dry box and washed with dry ether.

Anal. Calcd. for $C_{16}H_{22}N_4S \cdot 3HCl \cdot H_2O$: C, 44.70; H, 6.33; N, 13.03; S, 7.46. Found: C, 44.37; H, 6.03; N, 12.67; S, 7.58.

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