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Synthesis of Alkylaminoethanethiolsulfuric Acids Substituted with Heterocyclic Moieties (I)

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Several alkylaminoethanethiolsulfuric acids substituted with heterocyclic moieties have been synthesized to determine their effectiveness as radiation protection agents. These compounds are represented by the structure $R(\text{CH}_2)_3\text{NH}(\text{CH}_2)_2\text{S}_2\text{O}_3\text{H}$, where R is 8-quinolyloxy (V), 8-quinolaldehyloxy (IX), 5-quinolyloxy (XII), 4-pyridyl (XVI), and 4-pyridylmethyl (XXIII). The diheterocyclic-substituted compound, 2-[bis-(2-phenyl-1,2,3,2*H*-triazol-4-ylmethyl)amino]ethanethiolsulfuric acid (XIV) was also synthesized.

The known radiation protection activity of 2-aminoethanethiol (3) and closely related compounds (4) has encouraged a search for other compounds of this type which might have increased activity and at the same time reduced toxicity and extended duration of action. This has been accomplished to some extent by the synthesis of related molecules, such as 2-aminoethanethiolsulfuric acid (5). Several alkylaminoethanethiolsulfuric acids substituted with heterocyclic moieties were therefore prepared to determine the effect of the heterocyclic moiety on biological activity.

Compound V was synthesized by two alternate methods A and B as shown in the accompanying flow sheet. Method A involved the interaction of the chloride (IV) with sodium thiosulfate to give V and method B involved the interaction of 2-aminoethanethiolsulfuric acid with the chloride (II) to give V. Attempts to prepare IX via method A were unsuccessful, and this method was thereafter abandoned in favor of method B, which was employed in the preparation of the remaining compounds.

Compounds V, IX, XII and XIV were insoluble in water and their purification was relatively simple. Compounds XVI and XXIII, however, were water-soluble and their purification and separation from inorganic residues required the use of anion exchange chromatography.

The infrared spectra of the alkylthiolsulfuric acids were characterized by bands and peaks at 524-538, 630, 1020 and 1190-1240 cm^{-1} . These values were in general agreement with those reported for the sulfonate ion of sodium and potassium alkylthiolsulfates (6), and were also in agreement with values reported for the thiolsulfuric acid group in 2-aminoalkylthiolsulfuric acids (7, 8).

EXPERIMENTAL

8-(3-Hydroxypropoxy)quinoline (I).

Sodium metal (9.2 g., 0.4 mole) was dissolved in 250 ml. of anhydrous methanol and to it was added a solution of 8-hydroxy-

quinoline (58.06 g., 0.4 mole) in 200 ml. of anhydrous methanol. The mixture was allowed to stand for 30 minutes and 3-bromopropanol (55.6 g., 0.4 mole) was added. The reaction mixture was refluxed 4 hours and the methanol then removed by evaporation *in vacuo* at 50°. The residue was diluted with 300 ml. of water and extracted with chloroform. The chloroform extract was washed once with aqueous 1 *N* sodium hydroxide, once with water and then dried over anhydrous magnesium sulfate. The magnesium sulfate was removed by filtration and the chloroform evaporated *in vacuo* at 50° to yield 57.3 g. (71%) of crude solid 8-(3-hydroxypropoxy)quinoline. Recrystallization from benzene gave light pink needles. Subsequent recrystallization from water yielded a pure white granular product, m.p. 126-127.5°. The reported melting point for this compound is 127-128° obtained by vacuum sublimation (9).

8-(3-Chloropropoxy)quinoline (II).

A solution of 8-(3-hydroxypropoxy)quinoline (20.71 g., 0.101 mole) and 160 ml. of chloroform was cooled in an ice bath. To this was added slowly with shaking an ice-cold solution of thionyl chloride (23.8 g., 0.2 mole) and 30 ml. of chloroform. The reaction mixture was allowed to stand at room temperature overnight. The chloroform and excess thionyl chloride were then removed *in vacuo* at 50° to yield an oily red-brown residue. The residue was made basic with dilute aqueous sodium hydroxide and extracted with chloroform. The chloroform extract dried over anhydrous magnesium sulfate, the magnesium sulfate removed by filtration and the chloroform evaporated to give 21.26 g. (95%) of 8-(3-chloropropoxy)quinoline, white needles, m.p. 72-73° from ligroin (b.p. 60-90°). A sodium fusion test was positive for chlorine.

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{ClNO}$: C, 65.01; H, 5.46; N, 6.32. Found: C, 65.18; H, 5.55; N, 6.37.

The product formed a monopierate, m.p. 157-157.5° from ethanol. *Anal.* Calcd. for $\text{C}_{18}\text{H}_{18}\text{ClN}_4\text{O}_8$: C, 47.96; H, 3.35; N, 12.43. Found: C, 47.93; H, 3.41; N, 12.57.

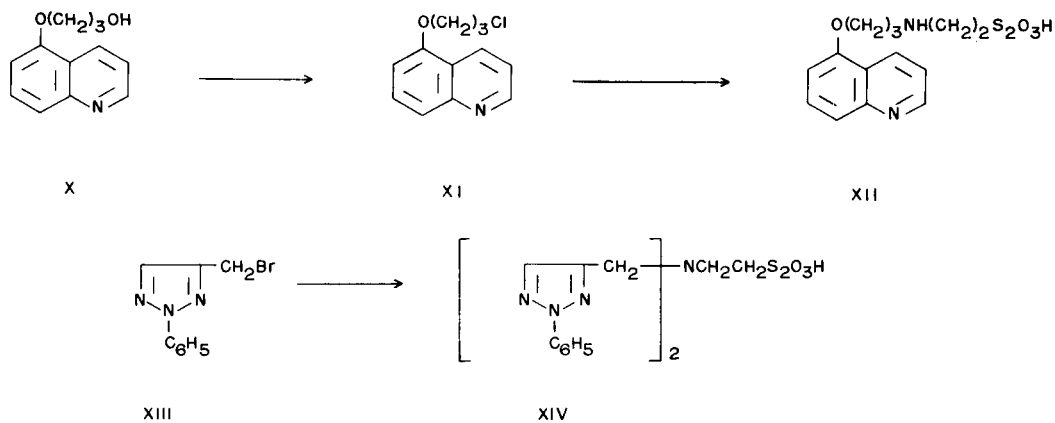
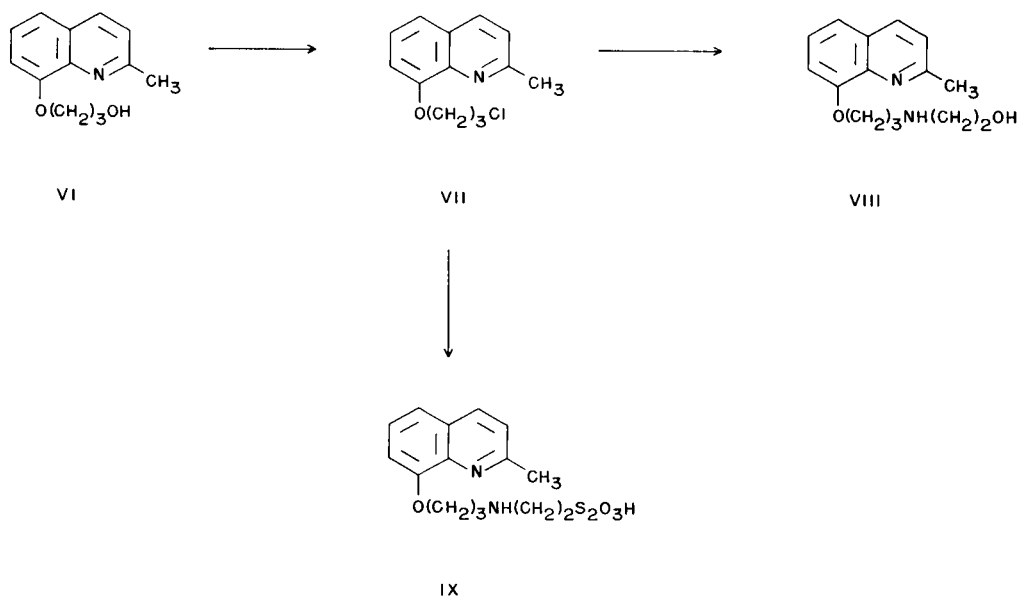
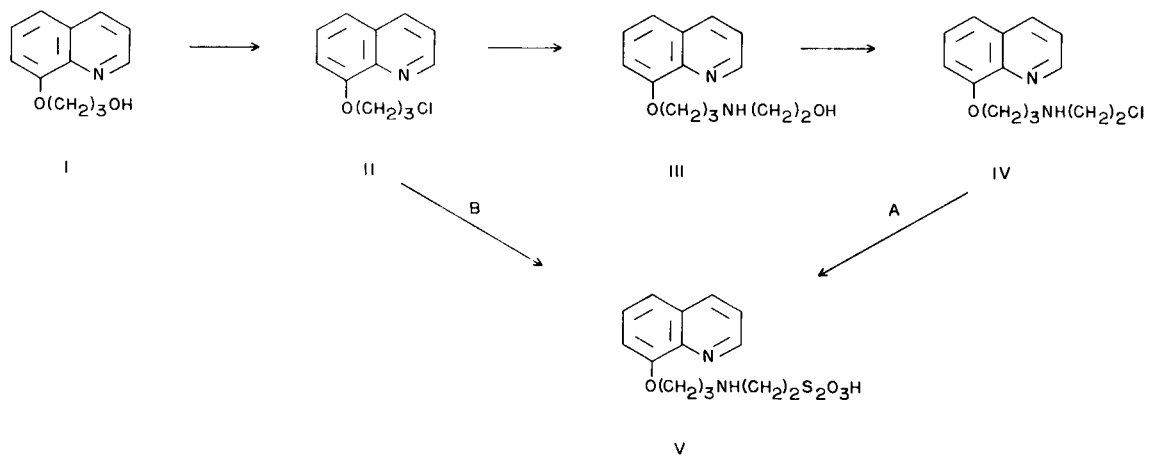
8-[3-(2-Hydroxyethylamino)propoxy]quinoline (III).

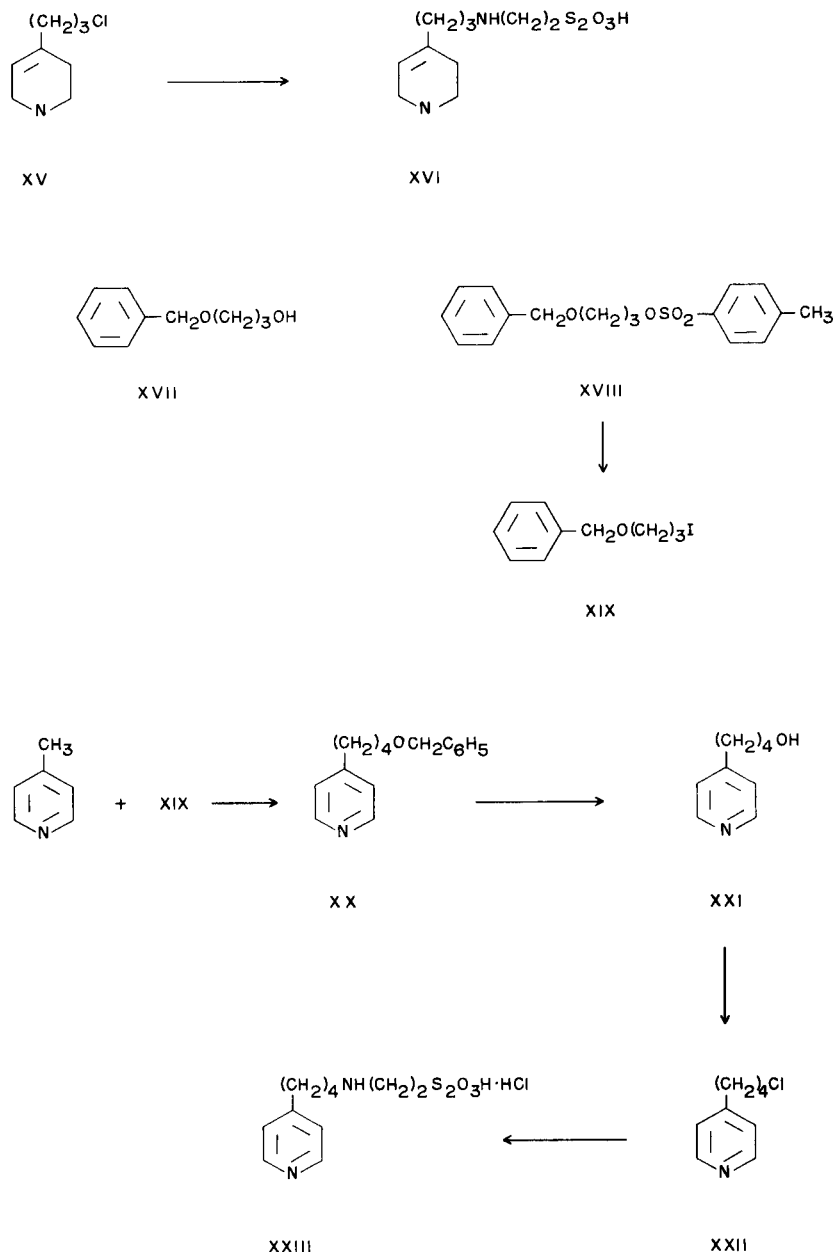
A mixture of 8-(3-chloropropoxy)quinoline (3.0 g., 0.0135 mole) and 2-aminoethanol (10.0 g., 0.164 mole) was heated for 4.5 hours on a steam bath. The reaction mixture was allowed to cool to room temperature and a solution of 5.0 g. of sodium carbonate monohydrate in 100 ml. of water was added. The mixture was then extracted with chloroform and the chloroform extract dried over anhydrous magnesium sulfate, the magnesium sulfate was removed by filtration, and the chloroform evaporated to give a yellow, viscous liquid residue. This residue was distilled under reduced pressure to give 2.4 g. (72%) of III, boiling range 173-200° at 0.2 mm. The yellow oil solidified upon standing to give white crystals, m.p. 52.5-53° from ligroin (b.p. 60-90°).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2$: C, 68.27; H, 7.37; N, 11.38. Found: C, 68.20; H, 7.45; N, 11.64.

This compound formed a monopierate, m.p. 153-154° from ethanol. *Anal.* Calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_5\text{O}_9$: C, 50.52; H, 4.45; N, 14.73. Found: C, 50.40; H, 4.56; N, 14.39.

FLOW SHEET





8-[3-(2-Chloroethylamino)propoxy]quinoline (IV).

A solution of III (2.4 g., 0.00974 mole) and 30 ml. of chloroform was cooled in an ice bath. An ice-cold solution of thionyl chloride (2.38 g., 0.02 mole) and 10 ml. of chloroform was added and the reaction mixture allowed to stand at room temperature for 4.5 hours. During this time, the reaction mixture became black. The chloroform and excess thionyl chloride were removed *in vacuo* at 50° and a solution of 5.0 g. of sodium carbonate monohydrate and 50 ml. of water was added to the residue. The mixture was then extracted with chloroform and the chloroform extract dried over anhydrous magnesium sulfate, the magnesium sulfate removed by filtration and the chloroform removed under reduced pressure to give an oily, black residue. No attempt was made to purify the product, instead the entire crude reaction product was used immediately in the preparation of V.

2-[3-(8-Quinolyloxy)propylamino]ethanethiolsulfuric acid (V).

Method A.

Crude IV (9.74 mmoles) was dissolved in 50 ml. of ethanol. To this was added a solution of sodium thiosulfate pentahydrate (2.48 g., 0.01 mole) and 20 ml. of water. The reaction mixture was stirred magnetically for 14 hours at room temperature. The ethanol was removed from the reaction mixture by evaporation *in vacuo* at 50°, and the residue, a viscous black oil, was neutralized with 0.6 g. of glacial acetic acid. This caused the separation of a black, oily

organic material from the water. The organic phase was removed from the water by decantation and the two layers treated separately.

The water was evaporated *in vacuo* from the aqueous phase to give a white, solid residue which was then treated repeatedly with boiling methanol which left a residue of inorganic salts. The methanol solutions were combined and the methanol removed, and ethanol added to the residue which caused solidification of the product V.

The black, oily organic layer was extracted repeatedly with boiling water, from which more of the product precipitated upon cooling. The combined yield was 1.08 g. (32% based on III) of white crystals, m.p. 183.5–185° from ethanol and from water. A sodium fusion test was positive for both nitrogen and sulfur.

Anal. Calcd. for $C_{14}H_{18}N_2O_4S_2$: C, 49.10; H, 5.30; N, 8.18; S, 18.73. Found: C, 48.81; H, 5.36; N, 8.29; S, 18.79.

Method B.

To a solution of sodium hydroxide (1.6 g., 0.04 mole) and 35 ml. of water was added 2-aminoethanethiolsulfuric acid (6.3 g., 0.04 mole). The resulting aqueous solution of sodium 2-aminoethanethiolsulfate was then added to a solution of 8-(3-chloropropoxy)quinoline (4.28 g., 0.0193 mole) and 75 ml. of ethanol, and the mixture refluxed for 24 hours. The ethanol was then removed from the deep red reaction mixture under reduced pressure at 50° and replaced with water. Glacial acetic acid (2.4 g., 0.04 mole) was added and the mixture allowed to stand at 0° overnight to yield an orange precipitate. The precipitate was filtered, washed once with water and once with ethanol to yield

1.66 g. (25%) of V, m.p. 183.5-185° from ethanol and from water, identical with the product from Method A.

8-(3-Hydroxypropoxy)quinoline (VI).

Sodium metal (4.6 g., 0.2 mole) was dissolved in 125 ml. of anhydrous methanol and to this was added a solution of 8-hydroxyquinoline (31.84 g., 0.2 mole) in 100 ml. of anhydrous methanol. The mixture was allowed to stand for 30 minutes and 3-bromopropanol (27.8 g., 0.2 mole) was added. The reaction mixture was refluxed for 3.5 hours and processed in the same manner as for compound I to yield 38.14 g. (88%) of VI, white crystals, m.p. 101-102° from ligroin (60-90°) and 104-105.5° after sublimation at 0.1 mm. The reported melting points for the compound are 105.5-106.5° from ligroin and 106-106.5° after sublimation (9).

8-(3-Chloropropoxy)quinoline (VII).

A solution of VI (15.88 g., 0.0731 mole) and 100 ml. of chloroform was cooled in an ice bath. To this was added an ice-cold solution of thionyl chloride (17.85 g., 0.15 mole) and 30 ml. of chloroform. The reaction mixture was allowed to stand at room temperature for 17 hours and was then processed in the same manner as for compound II to yield 16.81 g. (98%) of VII, white crystals, m.p. 59.0-60.0° from ligroin (60-90°). An analytical sample, m.p. 59.5-60.5° was obtained by sublimation at 0.1 mm.

Anal. Calcd. for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.99; N, 5.94. Found: C, 66.03; H, 6.23; N, 5.99.

The product formed a picrate, m.p. 202-203° from ethanol.

Anal. Calcd. for $C_{19}H_{17}ClN_2O_6$: C, 49.09; H, 3.69; N, 12.05. Found: C, 49.10; H, 3.97; N, 12.23.

8-[3-(2-Hydroxyethylamino)propoxy]quinoline (VIII).

A mixture of VII (8.43 g., 0.0358 mole) and 2-aminoethanol (26.27 g., 0.43 mole) was heated on a steam bath for 4.5 hours. The reaction mixture was then processed in the same manner as for compound III to give 5.94 g. (64%) of VIII, boiling range 190-210° at 0.1 mm.; white crystals, m.p. 88.0-89.0° from ligroin.

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.28; H, 7.88; N, 10.59.

The product formed a dipicrate, m.p. 169.5-170.5° from ethanol.

Anal. Calcd. for $C_{27}H_{26}N_6O_6$: C, 45.13; H, 3.65; N, 15.60. Found: C, 45.17; H, 3.96; N, 15.36.

2-[3-(8-Quinaldyloxy)propylamino]ethanethiolsulfuric acid (IX).

To a solution of VII (11.0 g., 0.047 mole) in 70 ml. of methanol was added a solution of 2-aminoethanethiolsulfuric acid (15.72 g., 0.1 mole), sodium hydroxide (4.0 g., 0.1 mole), 35 ml. of methanol and 20 ml. of water. The mixture was refluxed 46 hours on a steam bath. The methanol was then removed under reduced pressure at 50°, replaced with an equal volume of water, and glacial acetic acid (6.0 g., 0.1 mole) was added, which resulted in the separation from the clear, orange aqueous solution of a red, viscous organic material. The mixture was allowed to stand at 0° for 2 days, during which time the organic material partially solidified. The water was removed by decantation and the organic residue taken up in a minimum amount of boiling 1-propanol. The residue was redeposited from the 1-propanol as a red, viscous liquid upon cooling. After standing for 2 days this material solidified, and was removed from the 1-propanol by filtration. The separated 1-propanol was set aside and the residue was taken up in boiling water. Upon cooling, there was deposited from the aqueous solution 2.87 g. of IX. The 1-propanol, which had been set aside, was allowed to stand for one week to yield an additional 0.87 g. of IX by crystallization. The total yield of IX was 3.74 g. (22%), m.p. 192.5-194° from water and from ethanol. A sodium fusion test was positive for both nitrogen and sulfur.

Anal. Calcd. for $C_{15}H_{20}N_2O_4S_2$: C, 50.54; H, 5.66; N, 7.86; S, 17.99. Found: C, 50.45; H, 5.87; N, 8.21; S, 17.63.

5-(3-Hydroxypropoxy)quinoline (X).

Sodium metal (2.3 g., 0.1 mole) was dissolved in 100 ml. of anhydrous methanol and 5-hydroxyquinoline (14.52 g., 0.1 mole) was added. The mixture was allowed to stand for 15 minutes and 3-bromopropanol (15.29 g., 0.11 mole) was added. The reaction mixture was refluxed for 2 hours and processed in a manner similar to that for compound I to give 5.28 g. (26%) of X, violet crystals from a mixture of benzene and ligroin. The color was removed from the product by passing it through a small column of alumina, using benzene as the eluent. A white, analytically pure product, m.p. 92.0-93.0° was obtained by vacuum sublimation at 0.1 mm.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.00; H, 6.55; N, 6.73.

The product formed a picrate, m.p. 156.5-157.5° from ethanol.

Anal. Calcd. for $C_{18}H_{16}N_4O_3$: C, 50.00; H, 3.73; N, 12.96. Found: C, 50.30; H, 3.98; N, 13.18.

5-(3-Chloropropoxy)quinoline (XI).

A solution of X (4.33 g., 0.0213 mole) and 30 ml. of chloroform was cooled in an ice bath. To this was added an ice-cold solution of thionyl chloride (4.76 g., 0.04 mole) and 10 ml. of chloroform. The reaction mixture was allowed to stand at room temperature overnight and was then processed in the same manner as for compound II to give 4.57 g. (97%) of XI, which would not solidify on standing. Attempted vacuum distillation was unsuccessful, but purification was accomplished by eluting the material through a column of alumina (Woelm, neutral, activity grade I), using benzene-5% ethanol as eluent, to give the product in the form of a light yellow oil.

Anal. Calcd. for $C_{12}H_{12}ClNO$: C, 65.01; H, 5.46; N, 6.32. Found: C, 65.57; H, 5.86; N, 6.38.

The product formed a picrate, m.p. 173.5-175° from ethanol.

Anal. Calcd. for $C_{18}H_{15}ClN_2O_6$: C, 47.96; H, 3.35; N, 12.43. Found: C, 48.20; H, 3.58; N, 12.70.

2-[3-(5-Quinoloyloxy)propylamino]ethanethiolsulfuric acid (XII).

To a solution of sodium hydroxide (4.0 g., 0.1 mole) and 40 ml. of water was added 2-aminoethanethiolsulfuric acid (15.72 g., 0.1 mole). The resulting aqueous solution of sodium 2-aminoethanethiolsulfate was added to a solution of XI (4.57 g., 0.0206 mole) and 50 ml. of methanol. The reaction mixture was refluxed for 48 hours on a steam bath. The methanol was removed under reduced pressure at 50°, replaced with water, and glacial acetic acid (6.0 g., 0.1 mole) was added. This caused the separation from the aqueous phase of a red oil which did not solidify upon standing. The organic phase was separated from the aqueous phase by decantation. The aqueous phase was set aside, and a volume of absolute ethanol equal to that of the aqueous phase was added to the organic residue, which solidified after 2 days at room temperature to give 2.45 g. of XII. The aqueous phase, which had been set aside, was seeded with a small crystal of XII and allowed to stand for 4 days at room temperature to yield an additional 1.33 g. of XII. There was obtained a total of 3.78 g. (54%) of XII, white crystals, 198-199° from ethanol and from water.

Anal. Calcd. for $C_{14}H_{18}N_2O_4S_2$: C, 49.10; H, 5.30; N, 8.18; S, 18.73. Found: C, 49.03; H, 5.53; N, 8.17; S, 18.34.

2-Phenyl-1,2,3,2H-triazol-4-ylmethyl bromide (XIII).

This compound was prepared according to the procedure of Collier and Riebsomer (10).

2-[Bis-(2-phenyl-1,2,3,2H-triazol-4-ylmethyl)amino]ethanethiolsulfuric acid (XIV).

To 1.1 g. (0.0275 mole) of sodium hydroxide in 30 ml. of 95% ethanol was added with stirring 4.32 g. (0.0275 mole) of 2-aminoethanethiolsulfuric acid dissolved in 3 ml. of water. To this mixture under reflux was added 5.4 g. (0.022 mole) of the crude 2-phenyl-1,2,3,2H-triazol-4-ylmethyl bromide dissolved in 30 ml. of 95% ethanol. The bromide solution was added slowly over a period of 1.5 hours. The mixture was heated and stirred 4 hours after all the bromide had been added.

Then 25 ml. of ethanol was removed by distillation, the alcohol was replaced with 45 ml. of cold water and heated to boiling. A small portion of the product would not dissolve and it was removed by filtration. To the filtrate was added 60 ml. of water and a white solid separated and it was cooled in the refrigerator overnight. The white solid was removed by filtration and the filtrate was evaporated and found to contain 1.4 g. of unreacted 2-aminoethanethiolsulfuric acid. The weight of the white solid product was 3.5 g. To a small sample (0.5 g.) of this white solid was added 30 ml. absolute ethanol and the mixture heated to boiling several minutes. The undissolved white solid was removed by filtration and then taken up in 30 ml. of water. The mixture was boiled and the undissolved solid filtered, followed by washing with absolute ethanol. The remaining white solid was dried for an analytical sample, m.p. 208-210°.

Anal. Calcd. for $C_{20}H_{21}N_7O_3S_2$: C, 50.93; H, 4.48; N, 20.70. Found: C, 51.02; H, 4.41; N, 20.64.

Upon attempting to purify the remainder of the 3.5 g. of white solid by careful washing with hot ethanol and hot water following the procedure for the analytical sample, the washed and dried product melted at 188-189° instead of 208-210°. A sample of this material was analyzed and found to contain 19.27% nitrogen. The bis-compound as the dihydrate contains 19.32% nitrogen. Both materials (m.p. 208-210° and m.p. 188-189°) gave substantially identical infrared spectra.

3-(4-Pyridyl)-1-chloropropane (XV).

A solution of 4-(3-hydroxypropyl)pyridine (41.1 g., 0.3 mole) and

100 ml. of chloroform was cooled in an ice bath. To this was added an ice-cold solution of thionyl chloride (54.0 g., 0.45 mole) and 50 ml. of chloroform. The reaction mixture was allowed to stand at room temperature overnight and was then processed in the same manner as for compound II to give 39.0 g. (84%) of XV, colorless oil, b.p. 90-91° at 1.5 mm. This compound was used immediately in the preparation of XVI.

2-[3-(4-Pyridyl)propylamino]ethanethiolsulfuric acid (XVI).

To 18.0 g. (0.45 mole) of sodium hydroxide dissolved in 600 ml. of warm 95% ethanol was added rapidly with stirring a hot solution of 70.6 g. (0.45 mole) of 2-aminoethanethiolsulfuric acid in 50 ml. of water. To this mixture, which was then heated to reflux, there was added dropwise 31 g. (0.2 mole) of XV over 1.5 hours. Heating and stirring were continued for 16 hours. After reducing the volume, the reaction mixture was washed with ether to remove unreacted chloride. Then dilute aqueous hydrochloric acid was added until pH 5 was attained. The solution was evaporated to dryness, the residue taken up in ethanol, the insoluble material removed by filtration and the filtrate evaporated to dryness. This process was repeated with absolute methanol. Finally absolute methanol was added to the residue and heated to boiling. The insoluble residue (71.0 g.) was removed by filtration. The resulting methanol solution was purified by column chromatography. A column of Dowex 1-X4 anion exchange resin (chloride ion form) was prepared by washing 450 g. of the resin with water and separation of the wash water by decantation, followed by washing with 95% ethanol and then pouring an ethanol slurry of the resin into a glass column (4 cm x 75 cm). The wet resin bed dimensions were 4 x 50 cm. The methanol solution of the product was introduced into the column and eluted with: (1) 1000 ml. of 95% ethanol; (2) 1000 ml. of methanol; (3) 300 ml. of aqueous methanol (1:1 mixture by volume); and (4) 2000 ml. of water. In this instance the 1000 ml. of methanol eluent was concentrated to give 15.0 g. of a viscous pale yellow oil. A solution of the oil in 60 ml. of water was passed through a column [3/4 x 20 in. wet bed dimensions of 100 g. Amberlite 1R-45, anion exchange resin (hydroxyl form)]. The column was eluted with 1200 ml. of water, and the eluent concentrated to a viscous oil. A methanol solution of the oil was dried under 0.5 mm. at room temperature. This procedure left a residue of 4.8 g. (8%) of pale yellow solid (XVI).

The pale yellow solid was crystallized from methanol solution (after standing for two weeks) and white crystals were obtained, m.p. 182° (dec.).

Anal. Calcd. for $C_{10}H_{16}N_2O_3S_2$: C, 43.46; H, 5.84; N, 10.13; S, 23.20. Found: C, 43.42; H, 6.09; N, 10.04; S, 23.56.

3-Benzoyloxy-1-propanol (XVII).

This compound was prepared according to the procedure of Bennett and Hock (11).

3-Benzoyloxy-1-propyl *p*-toluenesulfonate (XVIII).

This compound was prepared in the usual manner by allowing 3-benzoyloxy-1-propanol to react with *p*-toluenesulfonyl chloride in the presence of pyridine, and was prepared previously by Butler, Renfrew, and Clapp (12).

3-Benzoyloxy-1-propyl Iodide (XIX).

A solution of 326 g. (1.02 moles) of 3-benzoyloxy-1-propyl *p*-toluenesulfonate in 1000 ml. of acetone was cooled in an ice-water bath and 173.0 g. (1.15 moles) of sodium iodide was added. The mixture was kept in a refrigerator for 3 days and there was obtained an orange solution and a precipitate of white crystals. After filtration, the solution was reduced in volume at 40° under reduced pressure, then poured into ice water and extracted with ether. The ethereal solution was washed with 5% aqueous sodium carbonate solution followed by a 1% solution of sodium thiosulfate. After drying over anhydrous sodium sulfate, the product was distilled to give 191 g. (69%) of 3-benzoyloxy-1-propyl iodide, pale yellow oil, b.p. 112-113° at 1.1 mm.

4-(4-Benzoyloxybutyl)pyridine (XX).

A solution of sodium amide (0.6 mole) and 300 ml. of liquid ammonia was prepared in the usual manner, and 27.9 g. (0.3 mole) of 4-picoline was added dropwise. After stirring 2 hours, 82.8 g. (0.3 mole) of 3-benzoyloxypropyl iodide was added and the stirring was continued for an additional 2 hours. After allowing the ammonia to evaporate, the deep blue mixture was treated with 60 ml. of water and 300 ml. of ether. After separation, the ethereal solution was dried over anhydrous sodium sulfate, filtered and the ether removed.

The residue was distilled to give 51.0 g. (70%) of 4-(4-benzoyloxybutyl)pyridine, b.p. 166-170° at 1.0 mm.

The product formed a picrate, m.p. 85-87° from ethanol.

Anal. Calcd. for $C_{22}H_{22}N_4O_8$: C, 56.17; H, 4.72; N, 11.91. Found: C, 56.18; H, 4.94; N, 11.59.

4-(4-Pyridyl)-1-butanol (XXI).

To a solution of 12.3 g. (0.051 mole) of XX in 450 ml. of acetic acid was suspended 3.5 g. of 5% Pd-charcoal. The suspension absorbed 0.05 mole of hydrogen at room temperature while being stirred for 8 hours. The catalyst was removed by filtration, the filtrate was reduced in volume, poured into water, neutralized with sodium carbonate, and extracted with ether. After drying over anhydrous sodium carbonate, the ether was removed and the product distilled to give 6.0 g. (78%) of XXI, colorless oil, b.p. 128-135° at 1.2 mm. This compound was reported previously by Zenitz (13).

This compound formed a picrate, m.p. 93-94° from ethanol.

Anal. Calcd. for $C_{15}H_{18}N_4O_8$: C, 47.37; H, 4.24; N, 14.73. Found: C, 47.75; H, 4.27; N, 14.26.

4-(4-Pyridyl)-1-chlorobutane (XXII).

A solution of XXI (25.2 g., 0.167 mole) and 100 ml. of chloroform was cooled in an ice bath. To this was added an ice-cold solution of thionyl chloride (32.0 g., 0.269 mole) and 33 ml. of chloroform. The reaction mixture was allowed to stand at room temperature overnight and was then processed in the same manner as for compound II to give 13.2 g. (47%) of XXII, b.p. 96-115° at 0.7 mm. This compound was used immediately in the preparation of XXIII.

2-[4(4-Pyridyl)butylamino]ethanethiolsulfuric acid hydrochloride (XXIII).

To 9.6 g. (0.24 mole) of sodium hydroxide dissolved in 300 ml. of warm 95% ethanol was added 37.8 g. (0.24 mole) of powdered 2-aminoethanethiolsulfuric acid. To the mixture, which was then heated under reflux, there was added dropwise 16.9 g. (0.1 mole) of XXII over a period of 2 hours. Heating and stirring were continued for an additional 24 hours. The reaction mixture was evaporated to a pasty residue, to which was added absolute methanol. After removal of the white methanol-insoluble residue, the methanol solution was reduced in volume, and to it was added water and ether. After separation, the aqueous layer was adjusted to pH 5.0 with dilute hydrochloric acid and evaporated to dryness. The residue was dissolved in absolute methanol and the methanol solution was purified by the use of column chromatography.

The methanol solution was introduced into a column of Dowex-1-X4 anion exchange resin (chloride ion form, 450 g. in 95% ethanol wet bed) and eluted with: (1) 1000 ml. of 95% ethanol; (2) 2000 ml. of absolute methanol; (3) 300 ml. of aqueous methanol (1:1 mixture by volume); and (4) 3000 ml. of water, successively. After removal of the methanol from the 2000 ml. of methanol fraction (2), there was obtained 3.5 g. (11%) of XXIII, white crystals, m.p. 194° (dec.) from 95% ethanol.

Anal. Calcd. for $C_{11}H_{18}N_2S_2O_3 \cdot HCl$: C, 40.42; H, 5.86; N, 8.58; Cl, 10.85. Found: C, 40.44; H, 5.92; N, 8.54; Cl, 10.89 (14).

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- (1) This work was supported by the Department of the Army, Walter Reed Army Institute of Research, Contract No. DA-49-193-MD-2645.
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