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Synthesis of Some Sulfur-Containing Derivatives of Pyridine 1-Oxide and Quinoline 1-Oxide[1]

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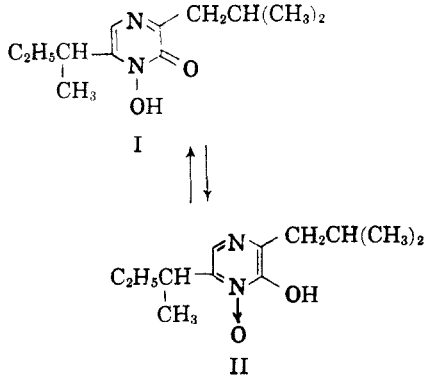
Several sulfur-containing derivatives of pyridine 1-oxide and quinoline 1-oxide were prepared for evaluation as antibacterial and antifungal agents. Both 2-thiocyano- and 4-nitro-2-thiocyano-pyridine 1-oxide were obtained by displacement reactions on the appropriate bromide 1-oxides. Anomalous reaction behaviour was encountered in all attempts to convert 3- or 4-bromopyridine 1-oxides and 3-bromoquinoline 1-oxide to the corresponding thiocyanates. 3-Bromopyridine 1-oxide and 3-bromoquinoline 1-oxide were found to add in the normal fashion to thiourea with the formation of the corresponding thiuronium bromides. 4-Thiocyanopyridine 1-oxide but not 3-thiocyanopyridine 1-oxide was obtained in very low yield by a Sandmeyer reaction. Treatment of picolinonitrile 1-oxide with ammonia and hydrogen sulfide gave thiopicolinamide 1-oxide. Only those of our compounds which bore a sulfur-containing group at position 2 of the pyridine 1-oxide ring system, wherein the sulfur atom was contiguous to the pyridine ring, showed outstanding antimicrobic activity.

The antibiotic, aspergillic acid,[3] 1-hydroxy-3-isobutyl-6-*sec*-butyl-1,2-dihydro-2-pyrazinone (I) has served as the model compound for the synthesis of a considerable number of cyclic hydroxamic acids.[4-12] On the other hand, in spite of the tautomeric relationship which exists between cyclic hydroxamic acids (*i.e.*, I) and 2-hydroxy aromatic N-oxides (*i.e.*, II) no attention has been given to the possibility that superior antimicrobic agents might



I ⇅ II

be obtained by replacement of the hydroxyl group in structures such as II by bacteriotoxophores and fungitoxophores which *cannot undergo tautomeric equilibration with a cyclic hydroxamic acid.*

A number of N-oxides[13-18] have been prepared. Some have demonstrated significant *in vitro* antibacterial and antifungal activity. It should be noted however, that none of the previously described aromatic N-oxides were substituted on the carbon *alpha* to the N-oxide moiety with microbial toxophores. It was the purpose of the present investigation therefore to provide for antibacterial and antifungal screening, a number of pyridine and quinoline 1-oxides substituted *alpha* to the N-oxide function with sulfur-containing bacterio- and fungitoxophores. An additional objective of this investigation was the synthesis of positional isomers of at least one of our 2-substituted N-oxides. Details only of the chemical effort which resulted in the synthesis of hitherto undescribed compounds are described in this communication.

Interaction of 2-bromopyridine 1-oxide with potassium thiocyanate proceeded smoothly in refluxing ethanol to yield 2-thiocyanopyridine 1-oxide. 4-Nitro-2-thiocyanopyridine 1-oxide was similarly prepared although in lower yield from 2-bromo-4-nitropyridine 1-oxide. 2-Chloro-4-nitropyridine 1-oxide on the other hand failed to react with potassium thiocyanate under these conditions and could be recovered unchanged in good yield.

The 2-halo-4-nitropyridine 1-oxides used in this study were prepared by nitration of the appropriate 2-halopyridine 1-oxides with a mixture of concentrated nitric and sulfuric acids and the nitro derivatives were isolated in the usual way. This pro-

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(3) Dutcher and Wintersteiner, *J. Biol. Chem.*, **155**, 359 (1944); Newbold, Sharp, and Spring, *J. Chem. Soc.*, 2679 (1951).

(4) Newbold and Spring, *J. Chem. Soc.*, 519, 1864 (1948).

(5) Cunningham, Newbold, Spring, and Stark, *J. Chem. Soc.*, 2091 (1949).

(6) Shaw, *J. Am. Chem. Soc.*, **71**, 67 (1949).

(7) Lott and Shaw, *J. Am. Chem. Soc.*, **71**, 70 (1949).

(8) Shaw and McDowell, *J. Am. Chem. Soc.*, **71**, 1691 (1949).

(9) Shaw, Bernstein, Losee, and Lott, *J. Am. Chem. Soc.*, **72**, 4362 (1950).

(10) Colonna and Runte, *Gazz. chim. ital.*, **82**, 513 (1952) [*Chem. Abstr.*, **48**, 680 (1954)].

(11) Wright and Smith, *J. Am. Chem. Soc.*, **77**, 3927 (1955).

(12) Wright and Collins, *J. Am. Chem. Soc.*, **78**, 221 (1956).

(13) McIlwain, *J. Chem. Soc.*, 322 (1943).

(14) King, Clark and Davis, *J. Chem. Soc.*, 3012 (1949).

(15) Mamalis and Petrow, *J. Chem. Soc.*, 703 (1950).

(16) Shchukina and Savitskaya, *Zhur. Obschchei Khim.*, **22**, 1224 (1952) [*Chem. Abstr.*, **47**, 7506 (1953)].

(17) Clemo and McIlwain, *J. Chem. Soc.*, 479 (1938); Clemo and Dagleish, *J. Chem. Soc.*, 1481 (1950).

(18) Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

cedure is considerably simpler than that employed by Den Hertog and co-workers[19] who nitrated 2-bromopyridine 1-oxide in unspecified yield with a mixture of sulfuric and fuming nitric acids and isolated 2-bromo-4-nitropyridine 1-oxide by continuous ether extraction.

It was of interest to prepare a pyridine 1-oxide, substituted in the 2-position with a sulfur-containing group wherein the sulfur atom, unlike the sulfur atom in the thiocyanates, was not linked directly to the pyridine ring. Thiopicolinamide 1-oxide satisfied these spatial requirements and was therefore prepared by oxidation of picolinonitrile to picolinonitrile 1-oxide followed by treatment of the nitrile 1-oxide with a mixture of ammonia and hydrogen sulfide.

The synthesis of the isomeric thiocyanopyridine 1-oxides offered unanticipated difficulty. 4-Thiocyanopyridine 1-oxide was ultimately synthesized in very low yield by a Sandmeyer reaction on 4-pyridinediazonium sulfate 1-oxide. When 4-aminopyridine 1-oxide was diazotized in the usual way at 0° in the presence of four equivalents of hydrochloric acid, the diazonium salt which formed decomposed energetically during the entire course of the addition of sodium nitrite solution and thus precluded diazonium group displacement. It was found, however, that a stable diazonium salt solution could be obtained by diazotization of 4-aminopyridine 1-oxide at −10°, in the presence of a very large excess (17 equivalents) of *ca.* 10 *N* sulfuric acid.[20] Cobalt chloride-catalyzed displacement[20] of the diazonium group yielded after workup and repeated recrystallization enough material for analysis. The analytical data showed that the product so obtained was 4-thiocyanopyridine 1-oxide contaminated by inorganic matter.

After the completion of this work Berson and Cohen[21] reported that diazotization of an "ice-cooled solution of 4-amino-2-methyl-5-ethylpyridine 1-oxide" in approximately six equivalents of 10 *N* sulfuric acid gave a diazonium salt which was sufficiently stable to be neutralized. 4-Pyridinediazonium sulfate, however, 1-oxide decomposed very rapidly under these conditions. At lower temperatures (−15 to −10°), it crystallized from solution and could be redissolved only after the addition of another six to eight equivalents of 10 *N* sulfuric acid. At this temperature and acid excess the diazonium salt evolved nitrogen slowly and gave when added to a solution of cobalt chloride and potassium thiocyanate the same substance which was obtained when 4-aminopyridine 1-oxide was diazotized with the larger excess of sulfuric acid.

Prior to undertaking the study of the Sandmeyer reaction on 4-aminopyridine 1-oxide as a means of preparing 4-thiocyanopyridine 1-oxide, metathetical reactions were attempted with 4-chloro- and 4-bromo-pyridine 1-oxide and potassium thiocyanate. It was expected that 4-bromopyridine 1-oxide would be less reactive than 2-bromopyridine 1-oxide. Ochiai, however, reported that 4-chloropyridine 1-oxide undergoes nucleophilic displacement with alkoxides, phenoxides, thiophenoxides, and amines.[18] It was hoped that the thiocyanate ion possesses a high enough order of nucleophilicity to likewise participate in displacement reactions with the 4-halopyridine 1-oxides. When 4-chloropyridine 1-oxide was refluxed with an alcoholic solution of potassium thiocyanate, for periods up to eight hours, it was recovered unchanged. Under these conditions 4-bromopyridine 1-oxide reacted to form products which appeared homogeneous but did not give analytical data for the desired thiocyanate or for the corresponding 4-ethoxypyridine 1-oxide (possible metathesis of 4-bromopyridine 1-oxide with the reaction solvent).

Den Hertog and Combe[22] prepared 4-bromopyridine 1-oxide hydrobromide by heating 4-nitropyridine 1-oxide with a 30% solution of hydrogen bromide in glacial acetic acid in a sealed tube at 120°. When 45% aqueous hydrobromic acid was used instead of 30% hydrobromic acid but the reaction otherwise was run in the same way, they reported the formation of 3,5-dibromo-4-pyridinol. This result is in agreement with that observed by Ochiai, Ito, and Okuda[23] who reported the formation not only of 3,5-dibromo-4-pyridinol but also of 3-bromo-4-pyridinol and 4-pyridinol 1-oxide when 4-nitropyridine 1-oxide is heated at 160° with 48% aqueous hydrobromic acid and a trace of urea in a sealed tube. Both of the published procedures were useless for scaled up preparative purposes. We therefore attempted and found that 4-bromopyridine 1-oxide hydrobromide can be obtained in good yield simply by refluxing 4-nitropyridine 1-oxide with 48% aqueous hydrobromic acid for about 16 hours.

All attempts to prepare 3-thiocyanopyridine 1-oxide by the Sandmeyer reaction on 3-aminopyridine 1-oxide were unsuccessful. 3-Aminopyridine 1-oxide hydrochloride was obtained stepwise by peroxidation of 3-acetamidopyridine followed by hydrolysis with hydrochloric acid. Diazotization of 3-aminopyridine 1-oxide at 0° in excess 6 *N* hydrochloric acid appeared to proceed normally but none of our attempts to displace the diazonium group by thiocyanate gave the desired 3-thiocyanopyridine 1-oxide. When diazonium group displacement was attempted using thiocyanate alone the only product

(19) Den Hertog, Kolder, and Combe, *Rec. trav. chim.*, **70**, 591 (1951).

(20) Procedure employed by Wagner-Jauregg and Helmert, *Ber.*, **75**, 935 (1942), for the diazotization of *o*-nitroaniline and subsequent diazonium group displacement by thiocyanate.

(21) Berson and Cohen, *J. Org. Chem.*, **20**, 1461 (1955).

(22) Den Hertog and Combe, *Rec. trav. chim.*, **70**, 581 (1951).

(23) Ochiai, Ito, and Okuda, *J. Pharm. Soc. Japan*, **71**, 591 (1951) [*Chem. Abstr.*, **46**, 980 (1952)].

we could isolate was a small amount of urea which evidently had been added in excess to destroy nitrous acid. Cobalt chloride-catalyzed displacement of the 3-diazonium group by the same method which gave 4-thiocyanopyridine 1-oxide (see below) yielded a dark green gum which had such unfavorable solution properties that it could neither be purified by recrystallization or chromatographic procedures.

Metathetical reactions of 3-bromopyridine 1-oxide and potassium thiocyanate in alcohol under reflux gave like 4-bromopyridine 1-oxide reaction products which appeared homogeneous but which did not give correct analytical data for the desired thiocyanate or any readily understandable product.

In contrast to the anomalous reaction behavior of 3-bromopyridine 1-oxide with potassium thiocyanate, we found that this oxide adds normally to thiourea to yield S-(3-pyridyl) thiuronium bromide 1-oxide. Itai[24] likewise noted the normal addition of 4-chloropyridine 1-oxide to thiourea with the formation of S-(4-pyridyl) thiuronium chloride 1-oxide.

3-Bromoquinoline 1-oxide, like 3- and 4-bromopyridine 1-oxide, reacted anomalously with potassium thiocyanate but added in the usual way to thiourea to yield S-(3-quinolinyl) thiuronium bromide 1-oxide.

Naito[25a] prepared 3-bromoquinoline 1-oxide by bromination of 4-aminoquinoline 1-oxide, diazotization of the 4-amino-3-bromoquinoline 1-oxide so-obtained, and treatment of the diazonium salt with sodium dihydrogen phosphate to displace the diazonium group. Naito's product melted at 120–103° and gave a picrate which melted at 132–134°. Murray and Hauser[25b] obtained the same substance, m.p. 96–101°, as that reported by Naito by peroxidation of 3-bromoquinoline with a mixture of hydrogen peroxide and glacial acetic acid. We synthesized 3-bromoquinoline 1-oxide hydrochloride by peroxidation of 3-bromoquinoline with 40% peracetic acid. Our material gave a picrate which melted at 218–219°. This discrepancy in picrate melting data may possibly be due to polymorphism or to an error in abstracting.

All of our intermediates and "target" compounds were submitted to microbiological screening against a representative group of bacteria and fungi. Detailed activity data on our compounds have been published elsewhere.[26] The findings show that substitution of the 2-carbon in the pyridine 1-oxide series by selected toxophores can yield antibacterial and antifungal agents with a very high order of activity. The most active compounds prepared in this study bear a sulfur-containing group at position 2 of the pyridine 1-oxide system wherein the sulfur atom is contiguous to the pyridine ring. 2-Thiocyanopyridine 1-oxide and 4-nitro-2-thiocyanopyridine 1-oxide possess broad spectrum activity at very low concentrations. Thiopicolinamide 1-oxide, a compound wherein the sulfur atom is not adjacent to the pyridine ring, is inactive.

EXPERIMENTAL[27]

2-Thiocyanopyridine 1-oxide. 2-Bromopyridine 1-oxide hydrochloride[9] (9 g., 0.05 mole) was dissolved in 200 ml. of absolute ethanol and neutralized with a solution of 2 g. of potassium hydroxide in 50 ml. of alcohol. Potassium bromide which precipitated was removed and the filtrate was combined with a solution of 5 g. of potassium thiocyanate in 50 ml. of ethanol. The mixture was stirred and refluxed for three hours, and filtered hot. On cooling, 2-thiocyanopyridine 1-oxide separated; yield 4.5 g., m.p. 155–157°. Recrystallization gave material which melted at 158–160°.

Anal. Calc'd for $C_6H_4N_2OS$: N, 18.42. Found: N, 18.60.

2-Chloro-4-nitropyridine 1-oxide. A solution of 23 g. (0.2 mole) of 2-chloropyridine was peroxidized and worked up according to the procedure described by Ochiai for the preparation of pyridine 1-oxide.[18] The crude reaction product crystallized after five days storage in the refrigerator; yield, 15 g., m.p. 65–70°. 2-Chloropyridine 1-oxide (10 g.) was nitrated in the same manner as pyridine 1-oxide[18] to yield 2-chloro-4-nitropyridine 1-oxide, m.p. 135–140°. Recrystallization from acetone gave pale yellow crystals, m.p. 140–143°; yield, 7 g.

Anal. Calc'd for $C_5H_3ClN_2O_3$: N, 16.08. Found: N, 16.07.

2-Bromo-4-nitropyridine 1-oxide. A mixture of 50 g. of 2-bromopyridine 1-oxide hydrochloride, 150 ml. of concentrated sulfuric acid, and 60 g. of concentrated nitric acid was heated for 3½ hrs. at 128–130°. The reaction mixture was cooled, poured onto cracked ice, and neutralized with solid sodium carbonate. The yellow precipitate, a mixture of crude 2-bromo-4-nitropyridine 1-oxide and sodium sulfate, was filtered off by suction and washed well with water, m.p. 60°. After two recrystallizations from acetone, the precipitate melted at 143–144° (yield 40 g.).

Den Hertog, *et al.*[19] prepared this compound by nitrating 2-bromopyridine 1-oxide with a mixture of sulfuric and *fuming* nitric acids. They maintained the reaction mixture at 90° for 1½ hours, cooled, poured onto ice, made slightly basic, and extracted the mixture in a continuous extractor to obtain yellow crystals, m.p. 145.5–146° (yield not specified).

4-Nitro-2-thiocyanopyridine 1-oxide. A solution of 4.85 g. of potassium thiocyanate in 30 ml. of ethanol was mixed with a solution of 10.8 g. of 2-bromo-4-nitropyridine 1-oxide in 150 ml. of ethanol and the mixture was stirred and refluxed for four hours. The reaction mixture was filtered while hot to remove precipitated potassium bromide and the filtrate was set aside to cool. The crystal mass which separated, a mixture of potassium bromide and 4-nitro-2-thiocyanopyridine 1-oxide, was removed by filtration, washed with water, and dried; m.p. 165–167°. Three recrystallizations from ethanol elevated the melting point to 180–181°; yield 3.5 g.

Anal. Calc'd for $C_6H_3N_3O_3S$: C, 36.54; H, 1.53; N, 21.31; S, 16.27. Found: C, 36.90; H, 1.77; N, 20.70; S, 15.87.

Picolinonitrile 1-oxide. Picolinonitrile (10 g.) was converted

(24) Itai, *J. Pharm. Soc. Japan*, **69**, 542 (1949) [*Chem. Abstr.*, **44**, 4473 (1950)].

(25a) Naito, *J. Pharm. Soc. Japan*, **67**, 246 (1947) [*Chem. Abstr.*, **45**, 9541 (1951)]. (b) Murray and Hauser, *J. Org. Chem.*, **19**, 2008 (1954).

(26) Leonard, Barkley, Brown, Anderson, and Green, *Antiobiotics and Chemotherapy*, **6**, 261 (1956).

(27) Nitrogen analyses were performed by Miss R. Becker of these laboratories. Carbon-hydrogen determinations were carried out by the Schwarzkopf Microanalytical Laboratory, Woodside 77, New York. Melting points and boiling points are uncorrected.

to the corresponding N-oxide using the procedure described by Ochiai[18] for the N-oxidation of pyridine. A white crystalline solid was obtained which melted at 112–115°, crude, and at 117–118° after recrystallization from chloroform; yield, 4 g.

Anal. Calc'd for $C_6H_4N_2O$: N, 23.32. Found: N, 22.80.

Thiopicolinamide 1-oxide. Picolinonitrile 1-oxide (2 g.) was dissolved in a mixture of 40 ml. of half saturated methanolic ammonia and 8 ml. of chloroform and the resulting solution was saturated with hydrogen sulfide with external ice-bath cooling. A crystalline substance separated from the mixture during the hydrogen sulfide treatment. The mixture was stored overnight at room temperature and filtered. The crude precipitate melted at 143–145°. Two recrystallizations from ethanol gave constant melting material (145–146°); yield after recrystallization, 1.5 g.

Anal. Calc'd for $C_6H_6N_2OS$: C, 46.73; H, 3.92; N, 18.22. Found: C, 46.46; H, 3.80; N, 18.01.

4-Thiocyanopyridine 1-oxide. Catalytic reduction at 50 p.s.i. initial hydrogen pressure in the presence of a 10% palladium-on-carbon catalyst of 14 g. (0.1 mole) of 4-nitropyridine 1-oxide[18] in 250 ml. of warm ethanol yielded 5 g. of 4-aminopyridine 1-oxide (picrate, m.p. 191–192°; Ochiai[18] reported m.p. 198–199°). The amine oxide was dissolved with cooling in a solution of 83 g. of concentrated sulfuric acid in 140 ml. of water and diazotized by slow addition at −10° of a solution of 7.5 g. of sodium nitrite in 20 ml. of water. The diazonium salt solution was kept at −10° and added portionwise during 30 min. to a solution maintained at −5° of 25 g. of cobalt chloride hexahydrate and 29 g. of potassium thiocyanate in 180 ml. of water. The mixture was stored for 24 hours at room temperature, the aqueous phase decanted, and the residual dark green gummy solid recrystallized twice from methanol and twice from a water-methanol mixture; m.p. 190° (decompn.): Yield, *ca.* 30 mg.

Anal. Calc'd for $C_6H_4N_2OS$: C, 47.36; H, 2.63; N, 18.42. Found: C, 46.02; H, 2.61; N, 17.81.

When diazonium group displacement was attempted under copper catalysis[28] a black tarry product was obtained which could not be purified.

4-Bromopyridine 1-oxide hydrobromide. 4-Nitropyridine 1-oxide (15 g.) was suspended in 50 ml. of 48% aqueous hydrobromic acid and the mixture was refluxed overnight (17 hours). The reaction mixture was concentrated *in vacuo* and the residual syrup was triturated with acetone. The white crystalline solid (17 g.) melted at 143–144° and gave a picrate which melted at 142–143°; lit.[22] m.p. — hydrobromide, 142–143°; picrate, 142–142.5°.

Attempted preparation of 4-thiocyanopyridine 1-oxide by metathesis of 4-bromopyridine 1-oxide with potassium thiocyanate. 4-Bromopyridine 1-oxide hydrobromide (2 g.) was dissolved in 50 ml. of absolute ethanol and neutralized with alcoholic potassium hydroxide. The precipitated potassium bromide was removed and the filtrate was combined with a saturated alcoholic potassium thiocyanate solution. The mixture was refluxed for 2½ hours and filtered. Concentration of the filtrate *in vacuo* gave a crystalline solid, m.p. 125–128°. Two recrystallizations from acetone elevated the melting point to 136–138°.

Anal. Calc'd for $C_6H_4N_2OS$: N, 18.42. Found: N, 9.47.

When this reaction was repeated, with an 8-hour reflux period, a crystalline product was obtained which melted at 155–157°. One recrystallization elevated the melting point to 160–161°.

Anal. Calc'd for $C_6H_4N_2OS$: N, 18.42. Found: N, 9.25.

3-Acetamidopyridine 1-oxide. 3-Aminopyridine (120 g., 1.28 moles) was dissolved in 160 ml. of acetic anhydride with cooling and the resulting solution was heated on a steam-bath for 15 minutes. Water (10 ml.) was added to the reaction mixture to destroy excess acetic anhydride and the mixture was concentrated to dryness. Recrystallization from ethyl acetate gave 145 g. (83.5%) of 3-acetamidopyridine, m.p. 133°; lit.[29] m.p., 131°.

3-Acetamidopyridine (110 g., 0.81 mole) was added portionwise (stirring and cooling to maintain a reaction temperature no higher than 40°) to 200 ml. of 40% peracetic acid. The mixture thereafter was warmed at 45° for 24 hours and concentrated to dryness *in vacuo*. The residual crude 3-acetamidopyridine 1-oxide, after one recrystallization from ethanol, melted at 205–207°; yield 60 g. (39.5%). A second recrystallization from ethanol elevated the melting point to 208–210°.

Anal. Calc'd for $C_7H_8N_2O_2$: C, 55.25; H, 5.23. Found: C, 55.52; H, 5.41.

3-Aminopyridine 1-oxide hydrochloride. 3-Acetamidopyridine 1-oxide (54.6 g., 0.36 mole) was dissolved in 360 ml. of 3 *N* hydrochloric acid and the solution was refluxed for 4 hours. The reaction mixture was concentrated to dryness and the crude amine oxide hydrochloride was recrystallized twice from ethanol; yield 22 g. (42%); m.p. 149–150°.

Anal. Calc'd for $C_5H_7ClN_2O$: C, 41.10; H, 4.70. Found: C, 41.41; H, 4.75.

Attempted preparations of 3-thiocyanopyridine 1-oxide by metathesis of 3-bromopyridine 1-oxide with potassium thiocyanate. 3-Bromopyridine was N-oxidized by the procedure of Shaw, *et al.*[9] to yield 3-bromopyridine 1-oxide hydrochloride, m.p. 179–182°. (Den Hertog and Overhoff[30] reported m.p. 181–182°.) The oxide hydrochloride (9 g., 0.05 mole) was dissolved in 200 ml. of absolute ethanol and neutralized with an alcoholic solution of potassium hydroxide. Potassium bromide was removed and the filtrate was combined with a solution of 5 g. of potassium thiocyanate in ethanol (50 ml.). The mixture was stirred and refluxed for 4 hours, filtered hot to remove potassium bromide, and the filtrate was evaporated *in vacuo*. The crystalline residue melted at 145–150°. Two recrystallizations from ethanol elevated the melting point to 157–160°. A fusion mixture of the compound gave positive tests for nitrogen and sulfur.

Anal. Calc'd for $C_6H_4N_2OS$: N, 18.42. Found: 13.10.

The reaction was repeated with stirring and heating for 18 hours. A product was obtained which after recrystallization from ethanol melted at 170–172°.

Anal. Calc'd for $C_6H_4N_2OS$: N, 18.42. Found: 14.10.

S-(3-Pyridyl)thiuronium bromide 1-oxide. 3-Bromopyridine 1-oxide hydrochloride (4.85 g.) was dissolved in 100 ml. of ethanol and was neutralized with alcoholic potassium hydroxide. The precipitated potassium bromide was removed, 2.43 g. of thiourea was added to the filtrate, and the resulting solution was refluxed for three hours. The reaction mixture was cooled and treated with ether and the white precipitate was collected, m.p. 165–166°. It gave a negative test for bromine, and a trace of sulfur. S-(3-Pyridyl)thiuronium bromide 1-oxide separated from the filtrate after 24 hours of refrigeration; m.p. 129–131°, crude, and 140–142° after recrystallization from isopropyl alcohol; yield, 3.1 g. (51%).

Anal. Calc'd for $C_6H_8BrN_3OS$: N, 16.8. Found: N, 16.87.

3-Bromoquinoline 1-oxide hydrochloride. 3-Bromoquinoline[31] (20.5 g., 0.1 mole) was oxidized with 25 g. of 40% peracetic acid and worked up using the procedure described by Shaw, *et al.*[9] for the N-oxidation of 2-bromopyridine. Upon workup of the reaction mixture a residue was obtained which melted at 190–192°. Recrystallization from a mixture of ethanol and acetone gave 3-bromoquinoline 1-oxide hydrochloride, m.p. 194–196°; *picrate*, m.p. 218–220°.

Anal. Calc'd for $C_9H_7ClBrNO$: N, 5.27. Found: N, 5.26.

(28) Cuprous thiocyanate was generated *in situ* by the procedure of Brand and Leyerzapf, *Ber.*, **70**, 284 (1937).

(29) Pictet and Crepieux, *Ber.*, **28**, 1908 (1895).

(30) Den Hertog and Overhoff, *Rec. trav. chim.*, **69**, 468 (1950).

(31) Shirley, *Preparation of Organic Intermediates*, John Wiley and Sons, New York, N. Y., 1951, p. 59.

Naito[25a] reported m.p. for picrate, 132–134°; for oxide base, 102–103°. Murray and Hauser[25b] gave for oxide base, m.p. 96–101°.

S-(3-Quinolinyl)thiouronium bromide 1-oxide. Interaction of 5.5 g. of 3-bromoquinoline 1-oxide hydrochloride and 2.43 g. of thiourea by the general procedure described above for S-(3-pyridyl)thiuronium bromide 1-oxide gave S-(3-quinolinyl)thiuronium bromide 1-oxide. The reaction mixture was concentrated to yield the crude thiuronium bromide, m.p. 163–165° which after two recrystallizations from ethanol melted without change at 175–178°.

Anal. Calc'd for $C_{10}H_{10}BrN_3OS$: N, 14.05. Found: N, 14.15.

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