1,5-NAPHTHYRIDINES AND THEIR N-OXIDES. III. SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME MONO- AND DISUBSTITUTED 1,5-NAPHTHYRIDINES AND THEIR N-OXIDES

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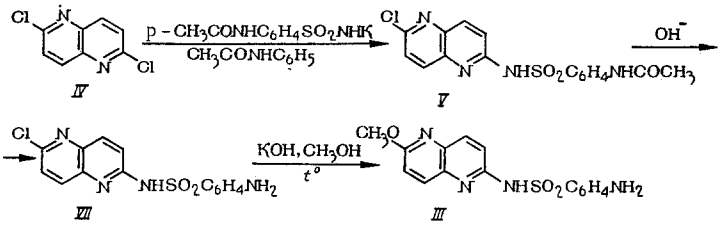
In order to search for biologically active compounds in the 1,5-naphthyridine series, we synthesized 2-mercapto- and 2-(4'-aminobenzenesulfonamido)-1,5-naphthyridines and some of their 6-substituted derivatives. 2-(4'-Aminobenzenesulfonamido)-1,5-naphthyridine (I) was obtained by reaction of 2-amino-1,5-naphthyridine with 4-carbomethoxyaminobenzenesulfonyl chloride in pyridine with subsequent saponification of the carbomethoxy group in the resulting 2-(4'-carbomethoxyaminobenzenesulfonamido)-1,5-naphthyridine (II).

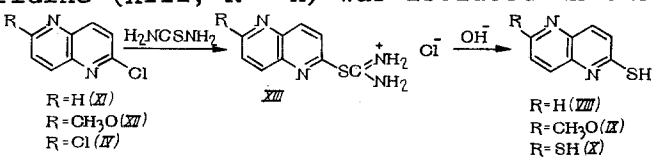
It is known that the introduction of a methoxy group into the ring of a heterocycle, as a rule, increases the antibacterial activity of sulfamide preparations and prolongs their action. In this connection we synthesized 2-(4'-aminobenzenesulfonamido)-6-methoxy-1,5-naphthyridine (III) via the following scheme:



Replacement of the chlorine atoms by a sulfamide group in the pyrimidine series is usually carried out in dimethylformamide (DMF). 2-Chloro-6-dimethylamino-1,5-naphthyridine (VI) was isolated along with 2-(4'-acetamidobenzenesulfonamido)-6-chloro-1,5-naphthyridine (V) from the reaction mixture when 2,6-dichloro-1,5-naphthyridine (IV) was heated with the potassium salt of acetamidobenzenesulfonamide in DMF. Compound VI was also formed by prolonged heating of IV in DMF. No side products were isolated when the reaction was carried out in acetanilide.

Compound III was obtained by reaction of 2-(4'-aminobenzenesulfonamide)-6-chloro-1,5-naphthyridine (VII) with a solution of potassium hydroxide in methanol at 125-135°C.

Mercapto derivatives of 1,5-naphthyridine (VIII, IX, and X) were obtained by reaction of the corresponding chloro derivatives of 1,5-naphthyridine (XI, XII, and IV) with thiourea. The thiuronium salts (XIII) are readily decomposed to give the corresponding mercapto derivatives. Only the thiuronium salt of 2-mercapto-1,5-naphthyridine (XIII, R = H) was isolated in the individual state.



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hydrochloric acid. The resulting precipitate was treated with 2% ammonium hydroxide, and the precipitated p-aminobenzenesulfonamide was removed by filtration. The filtrate was acidified to pH 6.0 with hydrochloric acid to give 1.8 g (62%) of VII with mp 157.5-158.5° (from alcohol) and R_f 0.9 (dark spot with a luminophore). Found (%): Cl 10.25; N 16.98; S 9.3. $C_{14}H_{11}ClN_4O_2S$. Calculated (%): Cl 10.59; N 16.74; S 9.53.

B) A mixture of 0.5 g of IV and 1.26 g of the potassium salt of acetamidobenzenesulfonamide in 10 ml of DMF was stirred at 120-125° for 30 h. The DMF was removed by vacuum distillation, and the residue was treated with 10% sodium hydroxide solution. The insoluble material was removed by filtration to give 0.18 g (34%) of VI with R_f 0.82 (bright-blue spot) with mp 123-125°. Found (%): C 57.9; H 4.8; Cl 16.8; N 20.35. $C_{10}H_{10}ClN_3$. Calculated (%): C 57.84; H 4.85; Cl 17.07; N 20.23.

Acidification of the aqueous alkaline mother liquor gave 0.25 g (26.6%) of V with mp 140-148°.

2-Chloro-6-dimethylamino-1,5-maphthyridine (VI). A 0.5 g sample of IV was heated at 100-110° in 10 ml of DMF for 30 h, after which the mixture was evaporated to dryness. The residue was treated with 3 ml of 2.5 N hydrochloric acid, and the mixture was filtered. The filtrate was made alkaline to pH 10.0 with 10% sodium hydroxide solution, and the resulting precipitate was removed by filtration to give 0.25 g (48%) of VI with mp 123-125° (from alcohol) and R_f 0.82 (bright-blue spot). No melting-point depression was observed for a mixture of this product with the VI isolated in the preceding experiment.

2-(4'-Aminobenzenesulfonamido)-6-methoxy-1,5-naphthyridine (III). A mixture of 0.26 g of VII and 0.2 g of potassium hydroxide in 5 ml of methanol was heated in an autoclave at 125-135° for 7 h. The resulting solution was vacuum evaporated to dryness, and the residue was treated with 5 ml of water. The mixture was acidified to pH 5.0 with hydrochloric acid to give 0.18 g (72%) of III with mp 212-214° (from alcohol) and R_f 0.8 (blue spot). Found (%): C 54.8; H 4.5; N 16.65; S 9.2. $C_{15}H_{14}N_4O_3S$. Calculated (%): C 54.54; H 4.27; N 16.9; S 9.7.

2-Mercapto-1,5-naphthyridine (VIII). A mixture of 0.83 g of XI and 0.38 g of thiourea in 15 ml of anhydrous alcohol was refluxed for 1 h, after which it was cooled to 10° and filtered to give 0.86 g (71.5%) of the thiuronium salt (XIII, R = H) with mp 236-237°. Found (%): Cl 14.86; N 23.2. $C_9H_9ClN_4S$. Calculated (%): Cl 14.72; N 23.2.

A mixture of 0.94 g of XIII (R = H) and 0.65 g of anhydrous sodium carbonate in 10 ml of water was stirred at 20-22° for 2 h, after which 10% sodium hydroxide solution was added until the solid had dissolved. The solution was filtered, and the filtrate was acidified to pH 5.0 with acetic acid to give 0.6 g (94.5%) of VIII with mp 269-270° (from alcohol). Found (%): C 59.08; H 3.95; N 17.6; S 19.88. $C_8H_6N_2S$. Calculated (%): C 59.24; H 3.73; N 17.27; S 19.77.

2-Chloro-6-methoxy-1,5-naphthyridine (XII). A 1.75 g sample of IV was refluxed for 40 h in sodium methoxide solution (0.2 g of sodium metal in 10 ml of methanol), after which the mixture was cooled and filtered to give 1.5 g (88.4%) of XII with mp 126° (from alcohol). Found (%): C 55.78; H 3.80; Cl 17.96; N 14.08. $C_9H_7ClN_2O$. Calculated (%): C 55; H 3.6; Cl 18.2; N 14.4.

2-Mercapto-6-methoxy-1,5-naphthyridine (IX). A mixture of 0.39 g of XII and 0.16 g of thiourea was refluxed in 5 ml of anhydrous alcohol, after which it was vacuum evaporated to dryness. The residue was treated with 5 ml of 10% sodium hydroxide solution, and the mixture was filtered. The filtrate was acidified to pH 5.0 with acetic acid to give 0.2 g (52%) of IX with mp 235-237° (from alcohol). Found (%): C 55.94; H 4.4; H 14.35; S 16.6. $C_9H_8N_2OS$. Calculated (%): C 56.2; H 4.2; N 14.57; S 16.67.

2,6-Dimercapto-1,5-naphthyridine (X). A mixture of 0.3 g of IV and 0.24 g of thiourea in 5 ml of anhydrous alcohol was refluxed for 2 h, after which it was vacuum evaporated to dryness. The residue was treated with 6 ml of 10%

sodium hydroxide solution, and the mixture was filtered. The filtrate was acidified to pH 5.0 with acetic acid to give 0.2 g (68.7%) of X with mp 310°. Found (%): N 14.2; S 32.5. $C_8H_6N_2S_2$. Calculated (%): N 14.4; S 33.0

2-Chloro-1,5-naphthyridine 5-N-Oxide (XIV). A mixture of 3.29 g of XI, 15 ml of 30% hydrogen peroxide, and 0.33 g of sodium vanadate was stirred at room temperature for 6 days, after which the precipitate was removed by filtration and washed with water to give 3.6 g (91.3%) of hydrate of XIV with mp 165.5° (from heptane) and R_f 0.84 (dark spot with a luminophore). Found (%): C 48.42; H 3.28; Cl 17.44; N 14.38. $C_8H_6ClN_2O \cdot H_2O$. Calculated (%): C 48.38; H 3.55; Cl 17.8; N 14.1.

2-Hydroxy-1,5-naphthyridine 5-N-Oxide (XV). A mixture of 0.1 g of XIV and 1 ml of 10% sodium hydroxide solution was heated at 80° for 5 min, after which it was cooled and acidified to pH 5.0 with hydrochloric acid to give 0.07 g (85%) of XV with mp 306° and R_f 0.27 (blue spot). No melting-point depression was observed for a mixture of this product with the previously obtained XV [4].

2-Mercapto-1,5-naphthyridine 5-N-Oxide (XVI). A mixture of 0.91 g of XIV, 0.38 g of thiourea, and 30 ml of anhydrous alcohol was refluxed for 1 h and 20 min, after which it was vacuum evaporated to dryness. The residue was treated with 5 ml of 10% sodium hydroxide solution and filtered. The filtrate was acidified with acetic acid to give 0.8 g (89.8%) of bright-orange crystals of XVI with mp 210-211° (after reprecipitation with 10% sodium hydroxide solution). Found (%): N 15.66; S 17.56. $C_8H_6N_2OS$. Calculated (%): N 15.72; S 17.99.

Ethyl 1,5-Naphthyridyl-2-cyanoacetate (XVII). A 5 g sample of 1,5-naphthyridine N-oxide was dissolved in 22 ml of acetic anhydride, and 4.32 ml of cyanoacetic ester was added in such a way that the temperature of the reaction mixture did not rise above 20°. The mixture was stirred at 20-22° for 7 h, after which it was cooled to 0° and filtered to give 3.9 g (47.4%) of XVIII with mp 180-181.5° (from heptane) and R_f 0.78 (bright-yellow spot). Found (%): C 64.75; H 4.4; N 17.16. $C_{13}H_{11}N_3O_2$. Calculated (%): C 64.72; H 4.6; N 17.4. IR spectrum: 2200 cm^{-1} (CN). PMR spectrum (in parts per million): δ -.32(CH_3, triplet), 4.26 (CH_2, quartet), 7.46 (7-H, quartet), 7.50 (4-H, quartet), 7.76 (8-H, quartet), 7.96 (3-H, doublet), 8.61 (6-H, quartet), 13.4 (NH).

2-Methyl-1,5-naphthyridine. A solution of 1.2 g of XVIII in 4 ml of 60% sulfuric acid was stirred at 103-105° for 8.5 h, after which it was neutralized to pH 3.0 with 10% sodium hydroxide solution and extracted with chloroform. The solvent was removed by distillation to give 0.7 g (97.8%) of 2-methyl-1,5-naphthyridine with mp 61-62°. No melting-point depression was observed for a mixture of this product with a sample of 2-methyl-1,5-naphthyridine obtained by a known method [9].

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