[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF MINNESOTA]

Heterocyclic Derivatives Related to Sulfanilamide. I. The Quinoline Analog of Sulfanilamide and Derivatives[1]

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The successful use of sulfanilamide and its derivatives in chemotherapy made it desirable to prepare quinoline analogs of two basic types, namely, 5-aminoquinoline-8-sulfonamide (I) and 8-aminoquinoline-5-sulfonamide (II).

The following methods for the preparation of these analogs were tried without success: (1) the sulfonation of 8-aminoquinoline, 8-hydroxyquinoline and their derivatives with sulfuric acid[2] and chlorosulfonic acid[3] and the preparation of (II) from the corresponding sulfonic acid[4]; (2) the preparation of 8-aminoquinoline-5-sulfonic acid by the Piria reaction[5]; (3) the replacement of the halogen atom in 8-bromo-5-nitroquinoline by the use of sodium sulfite and sodium bisulfite[6]; (4) the preparation of 5-nitro-8-quinolyl mercaptan[7]; (5) the preparation of 5-nitro-8-quinolinesulfonic acid by the Skraup reaction.[8]

From all of the preceding failures, it was decided that the aminoquinolinesulfonic acid could not be used and the nitroquinolinesulfonic acid appeared more promising; the nitro group could be reduced after the sulfonamide group was in the molecule.

(I) was successfully prepared by the following reactions. The Skraup reaction on *o*-chloroaniline produced 8-chloroquinoline, which was nitrated to yield 8-chloro-5-nitroqunoline. The latter compound was treated with sodium disulfide to produce 5,5′-dinitro-8,8′-diquinolyl disulfide. This was oxidized with nitric acid to 5-nitroquinoline-8-sulfonic acid and the sodium salt of this was prepared. The reaction of sodium 5-nitroquinoline-8-sulfonate and phosphorus pentachloride produced 5-nitroquinoline-8-sulfonyl chloride which on treatment with ammonium hydroxide yielded 5-nitroquinoline-8-sulfonamide.

Much difficulty was encountered in the reduction of the nitro group. Most of the ordinary methods of reduction were tried with little or no success. Finally it was found that powdered iron and 50% acetic acid gave the best results. An unusual experience occurred in the reduction; it was found that if crude 5-nitroquinoline-8-sulfonamide was used, the reduction occurred, but if the purified product was used little or no reduction took place. Efforts to determine the nature of the impurity giving this result have been unsuccessful.

Derivatives were synthesized by treating equal moles of α-aminopyridine and α-aminothiazole dissolved in anhydrous pyridine with purified 5-nitroquinoline-8-sulfonyl chloride. In both cases the reduction of the nitro group was unsuccessful.

Experimental

All melting points were taken by a standard immersion thermometer.

8-Chloroquinoline and 8-Chloro-5-nitroquinoline.—The procedures used were essentially those of Fourneau, *et al.*[8]

5,5′-Dinitro-8,8′-diquinolyl Disulfide.—The procedure was essentially as described for the preparation of di-*o*-nitrophenyl disulfide in "Organic Syntheses."[9] A 90% yield was obtained. A small amount decolorized with norite and recrystallized from toluene melted at 250–252° (with decomposition). This product has been recently synthesized by Winter and Reinhart.[10]

5-Nitroquinoline-8-sulfonic Acid.—In a 3-liter three-necked, round-bottomed flask fitted with a mechanical stirrer through a mercury seal, a reflux condenser connected to a gas trap and a dropping funnel, was placed 100 g. of the organic disulfide prepared in the preceding experiment, and 400 cc. of concentrated nitric acid was added slowly with constant stirring. The flask was then heated with continuous stirring for one hour on a steam-bath. The resulting solution was diluted with an equal volume of water and allowed to remain in the cold for several hours and yielded 90 g. (75%) of orange-red crystals. A small portion decolorized with norite and recrystallized from water melted above 211° (with decomposition).

Anal. Calcd. for $C_9H_6O_5N_2S$: S, 12.60. Found: S, 12.65.

Benzylisothiourea Salt of 5-Nitroquinoline-8-sulfonate.—This derivative was prepared essentially as described by,

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(2) Cybulski, *et al.*, *Roczniki Chem.*, **14**, 1172–1181 (1934); *C. A.*, **29**, 6235 (1935).

(3) Smiles and Steward, "Organic Syntheses," Coll. Vol. I, 1932, p. 8.

(4) Woroshtzow and Kogan, *Ber.*, **65**, 145 (1932).

(5) Hunter and Sprung, THIS JOURNAL, **53**, 1434 (1931).

(6) Besthorn and Geisselbrecht, *Ber.*, **53**, 1021–1023 (1920).

(7) Hodgson and Rosenberg, *J. Chem. Soc.*, 180–181 (1930).

(8) Fourneau, *et al.*, *Bull. soc. chim.*, (4) **47**, 738–741 (1930).

(9) Bogert and Stull, "Organic Syntheses," Coll. Vol. I, 1932, p. 215.

(10) Winter and Reinhart, THIS JOURNAL, **62**, 3510 (1940).

Veibel and Lillelund.[11] Greenish yellow platelets were obtained; m. p. 216.5–217.5°.

Anal. Calcd. for $C_{17}H_{16}O_5N_4S_2$: S, 15.30. Found: S, 15.14.

Sodium 5-Nitroquinoline-8-sulfonate.—To a hot suspension of 90 g. of 5-nitroquinoline-8-sulfonic acid in water, sufficient sodium carbonate was added to make the solution alkaline and the precipitate thus obtained was placed in the cold. The sodium salt was collected and recrystallized from water; yellow platelets were obtained; yield 80 g. (94%).

Anal. Calcd. for $C_9H_5O_5N_2SNa$: Na, 8.33. Found: Na, 8.23.

5-Nitroquinoline-8-sulfonyl Chloride.—The procedure used was essentially the method of Edinger.[12] An 80% yield of the crude product was obtained. A small portion was decolorized with norite and recrystallized from a petroleum ether–acetone mixture; light yellow platelets were obtained; m. p. 104–106°.

5-Nitroquinoline-8-sulfonamide.—The dried product just described was dissolved in 100 cc. of acetone, filtered and added drop by drop with stirring to 75 cc. of concentrated ammonium hydroxide. The stirring was then continued for thirty minutes longer. The precipitate which resulted was placed in the cold for several hours and collected without washing; yield, 20 g. (practically quantitative). A small amount decolorized with norite was recrystallized by suspending the substance in boiling water and adding sufficient alcohol to dissolve the crystals; yellowish-brown crystals were obtained; m. p. 186–187°.

Anal. Calcd. for $C_9H_7O_4N_3S$: S, 12.65. Found: S, 12.92.

Special precautions to be noted in this experiment are: (1) the reaction should be run soon after the 5-nitroquinoline-8-sulfonyl chloride is prepared or hydrolysis will occur. (2) The product obtained should not be washed with water or little or no reduction will take place in the next synthesis.

5-Aminoquinoline-8-sulfonamide.—The reduction method was that of Dikshoorn[13] with several modifications. To 4 g. of crude 5-nitroquinoline-8-sulfonamide suspended in 40 cc. of 50% acetic acid was added 4 g. of powdered iron over a period of three hours. The suspension was kept at 90° and stirring was continuous. The stirring and heating were continued for one hour longer and then the mixture was diluted with water and placed in the cold for several hours. The product which precipitated was collected and warmed with 5% sodium hydroxide and filtered. To the filtrate was added enough acetic acid so that the desired product precipitated, but the solution was still on the basic side. The precipitate was collected and recrystallized as in the preceding preparation; orange yellow needles were obtained; m. p. 261–265.5° (with decomposition); yield, 1 g. (28.6%).

Anal. Calcd. for $C_9H_9O_2N_3S$: S, 14.30. Found: S, 14.16.

5-Nitro-N⁸-(2-pyridyl)-8-quinolinesulfonamide.—To 0.946 g. of α-aminopyridine[14] dissolved in 10 cc. of anhydrous pyridine and kept in an ice-bath, was added 2.72 g. of purified 5-nitroquinoline-8-sulfonyl chloride slowly with shaking. The reaction mixture was placed in the cold overnight and then diluted with water and allowed to remain in the cold again. The product was recrystallized as in the previous preparations from dilute alcohol; greenish yellow needles were obtained; m. p. 249–250° (with decomposition); yield, 2.1 g. (63.6%).

Anal. Calcd. for $C_{15}H_{11}O_4N_3S$: S, 9.66. Found: S, 9.73.

5-Nitro-N⁸-(2-thiazyl)-8-quinolinesulfonamide.—The method is the same as described in the preceding synthesis. To 0.5 g. of α-aminothiazole[15] dissolved in 10 cc. of anhydrous pyridine, was added 1.36 g. of 5-nitroquinoline-8-sulfonyl chloride. Difficulty was encountered in recrystallizing the product. For analytical purposes the product was purified by dissolving in 50% sulfuric acid and precipitating with water and repeating this process several times. A yellow product was obtained; m. p. 260–261° (with decomposition).

Anal. Calcd. for $C_{12}H_8O_4N_4S_2$: S, 19.04. Found: S, 18.13.

Summary

1. The quinoline analog of sulfanilamide, 5-aminoquinoline-8-sulfonamide, and several intermediates were prepared.

2. Two other related compounds were prepared: 5-nitro-N⁸-(2-pyridyl)-8-quinolinesulfonamide and 5-nitro-N⁸-(2-thiazyl)-8-quinolinesulfonamide.

3. The compounds are being tested pharmacologically and bacteriologically.

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(11) Veibel and Lillelund, *Bull. soc. chim.*, **5**, 1153–1158 (1938).

(12) A. Edinger, *Ber.*, **41**, 937–938 (1908).

(13) R. P. Dikshoorn, *Rec. trav. chim.*, **48**, 153–154 (1929).

(14) Gattermann-Wieland, "Laboratory Methods of Organic Chemistry," English edition, The Macmillan Company, New York, N. Y., 1937, p. 365.

(15) Synthesis: E. Wertheim, "Organic Syntheses," Vol. XV, 1915, p. 55; description: V. Traumann, *Ann.*, **249**, 36 (1888).