over a 3-hour period of the above benzene solution to a chilled and stirred solution of 521 g. (2 moles) of anhydrous stannic chloride dissolved in 300 ml. of benzene and stirring for 15 minutes. The solid tin complex was changed to a liquid complex by adding 300 ml. of ordinary ether. The reaction mixture was poured into a mixture of 4 l. of 6 *N* NaOH and 2 to 3 liters of chopped ice and stirred for 15 minutes. The benzene layer was separated, and the hydrindone suspended in the alkaline solution allowed to stand overnight. It was then filtered, washed with water, thoroughly air-dried, dissolved in 5 l. of boiling benzene to remove inorganic salts and filtered hot. The benzene solutions were combined and steam distilled to remove the benzene, and the resulting insoluble hydrindone filtered and washed with water. A light yellow material (148 g., 83% of theory) m.p. 159–164° was obtained which was pure enough for the next step. A pure white product was obtained by crystallizing 10 g. of the hydrindone from 150 ml. of a 2:1 ethanol–water mixture in the presence of 3.5 g. of activated carbon. There was obtained 8.2 g., m.p. 163–164°; reported m.p. 160°[1] and 161°.[7]

Hydrastic Acid.—A mixture of 100 g. (0.57 mole) of 5,6-methylenedioxyhydrindone-1, 6 g. (0.03 mole) of vanadium pentoxide, 1200 ml. of distilled water, and 300 ml. of concentrated nitric acid was heated in a 5-l. flask under reflux until the reaction started, and then for 1.5 hours, with occasional swirling, after the violent phase of the reaction had subsided. The hot reaction mixture was quickly filtered through asbestos to remove the vanadium pentoxide before some of the hydrastic acid crystallized. The filtrate was neutralized to litmus with 15% sodium hydroxide solution, acidified with glacial acetic acid to a congo red endpoint, and then heated to the boiling point. Lead acetate solution (500 ml., 10%) was added until the lead salt of hydrastic acid was completely precipitated, the mixture allowed to cool, filtered, and the yellowish-white precipitate washed with three 100-ml. portions of 3% acetic acid.

The lead salt was converted to crude hydrastic acid by making a slurry with 900 ml. of tap water, heating to boiling, and adding concentrated nitric acid (75 ml.) dropwise from a buret until solution was effected. The hot solution was filtered by gravity through a heated funnel, and the filtrate cooled slowly to ice-bath temperature, allowed to stand 0.5 hour, filtered, washed with two 75-ml. portions of ice-water, and air-dried (yield 66 g.). An additional 17 g. of crude hydrastic acid was obtained from the filtrate by neutralizing as before to precipitate the hydrastic acid as lead hydrastate, filtering, washing and converting this to the crude hydrastic acid as above. The material was often contaminated with small amounts of lead hydrastate.

The combined, crude fractions of hydrastic acid were purified by two precipitations as the lead salt and a recrystallization from water. This was done by dissolving the material in 800 ml. of boiling tap water (adding a little nitric acid if an appreciable amount of the insoluble lead hydrastate was present), and precipitating the lead hydrastate with 10% lead acetate solution (approximately 500 ml. was required). If nitric acid was added, an equivalent amount of sodium hydroxide was added at this point. The lead salt was filtered, dissolved again in dilute nitric acid, filtered, neutralized to litmus with sodium hydroxide solution and acidified to congo red with acetic acid as before, and the lead hydrastate then converted to hydrastic acid as before. The yield was 57 g., solubility temperature 86.1° at 12:1 (corresponding to a purity of 98%), with a neutralization equivalent of 104.7 (theory, 105.0). An additional 5 g. was recovered from the filtrate by precipitating the lead salt, etc., as previously described. The combined 62 g. of pale yellow hydrastic acid was recrystallized from 620 ml. of distilled water, using 6 g. of activated carbon (Darco G-60) to remove the color. An almost white product resulted (53 g., 44.5% of theory), solubility temperature 86.5° at 12:1. This material was used to prepare the anhydride.

A pure white product, having the same solubility temperature, was obtained after three more recrystallizations from water with activated carbon. *Anal.* Calcd. for $C_9H_8O_6$: C, 51.44; H, 2.88. Found: C, 51.42; H, 2.91. The following solubility temperatures were determined: 12:1, 86.5°; 25:1, 73.8°; 50:1, 58.7°; 100:1, 42.8°; 150:1, 33.9°.

Hydrastic Anhydride.—This was prepared by stirring and heating 50 g. of hydrastic acid for 5 minutes after melting in a 1000-ml. beaker immersed in an oil-bath maintained at 190°.[4] A light tan product (44 g., 96%), m.p. 178.5–181° was obtained. This was dissolved in 1000 ml. of hot benzene, 9 g. of activated carbon added, filtered hot through asbestos, cooled to 10°, and filtered. There was obtained 29 g. of a pure white product (64% of theory), m.p. 179–180° (determined in a sealed tube); reported m.p., 175°.[4] *Anal.* Calcd. for $C_9H_4O_5$: C, 56.59; H, 2.11. Found: C, 56.48; H, 2.30. An additional 9 g. of white material, m.p. 177.5–179.5°, was isolated by concentrating the filtrate (total yield, 83%).

(7) W. Borsche and W. Eberlein, *Ber.*, **47**, 1469 (1914).

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Quinazolines. XI. Synthesis of Several Aminoquinazolines and Their Sulfa Derivatives[1]

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Although the search for new sulfa drugs has been most extensive very little attention has been given to the sulfaquinazolines. For this reason the work in this Laboratory was extended to include the synthesis of a number of such compounds.

The principal task in the execution of such a program is the synthesis of the various aminoquinazolines required for the coupling. In this study all the isomeric aminoquinazolines were prepared with the exception of the 2- and 4-aminoquinazolines. The 2-aminoquinazoline in contrast to the 4-amino isomer, had been previously successfully coupled with acetylsulfanilyl chloride by Dewar.[2] Macbeth and Rodda,[3] however, report the successful preparation of a sulfaquinazoline using 4-aminoquinazoline but failed to give any details or analytical data. Earlier work in this Laboratory had indicated that it would be difficult if not impossible to couple the 4-amino isomer due to its amide-like characteristics, thus confirming the experiments of Dewar.

5-Aminoquinazoline was synthesized from 5-nitro-4-quinazolone which had been prepared according to the directions of Bogert.[4] This nitroquinazolone was converted to the 4-chloro derivative. The reduction of 4-chloro-5-nitroquinazoline was extremely difficult; it was necessary to subject this material to prior purification using Raney nickel, remove the nickel and then proceed with the reduction using palladized calcium carbonate at 0° following essentially the directions of Elderfield.[5] This critical operation yields the dihydro-derivative of 5-aminoquinazoline which was found to be very sensitive to air oxidation. For this reason it was necessary to remove the palladized

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(2) Dewar, *J. Chem. Soc.*, **2**, 619 (1944).

(3) Macbeth and Rodda, *Nature*, **156**, 207 (1945).

(4) Bogert and Chambers, THIS JOURNAL, **27**, 649 (1905).

(5) Elderfield and co-workers, *J. Org. Chem.*, **12**, 405 (1947).

calcium carbonate by filtration. The dehydrogenation was then effected by immediately refluxing in the presence of palladized charcoal to yield 5-aminoquinazoline which was stable in air. No sulfaquinazoline could be isolated from the reaction product of the 5-amino derivative with acetylsulfanilyl chloride.

The 6-aminoquinazoline was prepared by the directions given by Elderfield. It was advantageous to carry out the final reduction of the 4-chloro-6-nitroquinazoline in a methylcellosolve rather than methanol solvent due to solubility characteristics. The reaction of this intermediate with acetylsulfanilyl chloride was straightforward.

7-Aminoquinazoline was obtained by essentially the same sequence of reactions from 7-nitro-4-quinazolone.[6] The 4-chloro-7-nitroquinazoline reduced readily to the dihydro derivative which was in turn dehydrogenated with ferricyanide to yield 7-aminoquinazoline. For some unknown reason, the coupling of 7-aminoquinazoline with acetylsulfanilyl chloride was not successful in either glacial acetic acid, dioxane or pyridine.

The preparation of 8-aminoquinazoline[6] was essentially the same as for the 6-amino isomer. The coupling of this intermediate with acetylsulfanilyl chloride did not pose any new problems.

The over-all yields in all these preparations were small by reasons of the great losses entailed in purifying the chloroquinazolines prior to reduction and low yields on hydrogenation–dehydrogenation operations. A number of the aminoquinazolines were light sensitive, making it necessary to carry out several of the operations in the absence of light.

Experimental

4-Chloro-5-nitroquinazoline.—Forty-two ml. of phosphorus oxychloride was added to a mixture consisting of 14 g. (0.073 mole) of 5-nitro-4-hydroxyquinazoline and 24 g. (0.12 mole) of phosphorus pentachloride. This mixture was heated under reflux for 2 hours, cooled for 1 hour, and the crystalline mass of 4-chloro-5-nitroquinazoline which formed removed by filtration. The crystals were washed several times with dry ether, ground with ether in a mortar, and again washed twice with more ether to remove the chlorides of phosphorus. The washed material was twice recrystallized from pure *n*-heptane to give 5.1 g. of white crystals, m.p. 137–139°.

The phosphorus oxychloride filtrate was evaporated to dryness under reduced pressure. The solid residue was then treated with ether and poured into a separatory funnel containing a cold mixture of chopped ice and water. The 4-chloro-5-nitroquinazoline was removed by extraction with ether; the ether extracts were shaken with sodium bicarbonate, decanted, and dried over anhydrous sodium sulfate. Evaporation of the ether solution gave a yellow material which on recrystallization from *n*-heptane yielded 2.7 g. of the chloro compound. The total yield of 4-chloro-5-nitroquinazoline was 7.8 g. (51%). An analytical sample was prepared by sublimation at 0.1 mm. and 140°, m.p. 138.5–139°.

Anal. Calcd. $C_8H_4ClN_3O_2$: C, 45.8; H, 1.9; N, 20.0. Found: C, 45.3; H, 2.2; N, 20.2.

5-Aminoquinazoline.—4-Chloro-5-nitroquinazoline (0.5 g., 0.0024 mole) was dissolved in 70 ml. of dry cold methyl cellosolve which had been placed in a round-bottom flask surrounded with ice. About 0.4 g. of Raney nickel was added and the flask vigorously swirled for a few minutes in order to assure thorough mixing. The Raney nickel was then allowed to settle and the supernatant liquid decanted into a cold hydrogenation bottle containing 1.5 g. of palladized calcium carbonate (2% Pd). The bottle was packed in ice, evacuated of air, and hydrogen admitted at 30 pounds pressure. After shaking for 30 minutes hydrogen absorption was virtually complete; the catalyst was then filtered and the brownish-yellow filtrate transferred to a flask containing 0.5 g. of palladized charcoal (10% Pd). After refluxing for 20 hours, filtration, and removal of the solvent *in vacuo*, the residue, 5-aminoquinazoline was isolated as a dirty yellow solid. The product was again dissolved in a 33% solution of potassium hydroxide and extracted with ether. Evaporation of the extracts gave 0.165 g. of a bright yellow solid, m.p. 183–187°; 47.8% yield. An analytical sample was prepared by sublimation and recrystallization from benzene, m.p. 192.5–193.5°.

Anal. Calcd. for $C_8H_7N_3$: C, 66.2; H, 4.83. Found: C, 65.6; H, 4.95.

7-Aminoquinazoline.—Two grams of palladized calcium carbonate (5% Pd) and 2 g. (0.0138 mole) 4-chloro-7-nitroquinazoline were added to 60 ml. of dry methanol in a hydrogenation bottle. Hydrogenation at 30 lb. initial pressure was complete in 30 minutes. The catalyst was then removed by filtration, the filtrate concentrated to approximately 5 ml. *in vacuo* and then diluted with 50 ml. of water. To this solution was added 15.2 ml. of 33% potassium hydroxide and gradually over a period of 20 minutes 50 ml. of a warm aqueous solution containing 6.5 g. of potassium ferricyanide. After standing 5 minutes, 63 ml. of 33% potassium hydroxide solution was added and the reaction mixture then extracted with ether. Evaporation of the dry ether extracts gave 0.67 g. of 7-aminoquinazoline; 48.4% yield. A sample which had been sublimed at 210° and 3 mm. after recrystallization from benzene gave a m.p. 190.5–191°.

Anal. Calcd. for $C_8H_7N_3$: C, 66.2; H, 4.83; N, 29.0. Found: C, 66.4; H, 5.13; N, 28.6.

N^1-Acetyl-N^4-6-quinazolylsulfanilamide.—N-Acetylsulfanilyl chloride (0.214 g., 0.0009 mole) was added in four portions at 10-minute intervals to a stirred solution of 0.120 g. (0.00083 mole) of 6-aminoquinazoline in 6 ml. of dry pyridine at room temperature following essentially the directions of Wolf.[7] The reaction mixture was then stirred for 1 hour at room temperature and for an additional half-hour at 60°. The amber colored solution which formed was placed in the refrigerator overnight; 75 mg. of yellow material in the form of lumps settled from the solution; yield 27.5%. Recrystallization of the solid from an alcohol–benzene mixture (1:2) yielded small irregular shape yellowish-white crystals which darkened at 285° and melted with decomposition at 290–292°.

Anal. Calcd. for $C_{16}H_{14}N_4O_3S$: C, 56.2; H, 4.1. Found: C, 55.9; H, 4.3.

N^1-Acetyl-N^4-8-quinazolylsulfanilamide.—A solution of 90 mg. (0.00062 mole) of 8-aminoquinazoline in 2 ml. of dry pyridine was added dropwise to a solution of 160 mg. (0.00069 mole) of N-acetylsulfanilyl chloride in 3 ml. of pyridine maintained at 60°. The entire reaction was carried out for 1 hour in semi-darkness, then the reaction mixture was concentrated *in vacuo* to 1 ml. and 30 ml. of water added. A cream-colored suspension formed together with a red gummy deposit. The suspension cleared upon standing in the refrigerator several hours. The supernatant liquid was then decanted and on storage overnight in the refrigerator a small amount of the sulfa derivative crystallized. The reddish gum remaining in the flask was dissolved in 2 ml. of half normal sodium hydroxide, diluted to 12 ml., filtered, and the clear filtrate neutralized with glacial acetic acid. The precipitates which formed were filtered and dried; yield of crude product 0.146 g. (69%). An analytical sample prepared by crystallization from ethyl alcohol had a m.p. of 215.5–216°.

Anal. Calcd. for $C_{16}H_{14}N_4O_3S$: C, 56.2; H, 4.1; N, 16.4. Found: C, 55.8; H, 4.3; N, 16.3.

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