to Strukov,[18] a procedure which has given excellent results in the synthesis of other quinolines in our hands, over ten hours at 125–130° yielded only about 5% of the fluoroquinoline.

6-Methoxyquinoline.—Into a 5-liter round-bottom flask fitted with an efficient reflux condenser and inside thermometer, was weighed 2024 g. of "Dynamite" glycerol (previously dried by heating at 170° for ten minutes), 492 g. of *p*-anisidine (technical grade) and 306 g. of *p*-nitroanisole. To this well stirred mixture was slowly added with cooling 586 g. of 98% sulfuric acid at such a rate that the temperature did not rise above 40°. The mixture was then gradually heated with a small flame to 135° over a period of seventy-five to ninety minutes and the temperature was held at 135–140° for two hours. It was found that this preliminary heating resulted in a much smoother reaction. During the period at 135–140° very little outside heat was required. When this preliminary heating period was omitted, the reaction, especially on a larger scale, got out of control, but no trouble was encountered when the above procedure was rigidly adhered to. The reaction mixture was cooled to 90° and a second portion of 314 g. of 98% sulfuric acid was added during the course of twenty to thirty minutes. During the addition of the sulfuric acid, the temperature rose and, at the end of the addition, it was cautiously brought to 140° and held at this point at gentle reflux for three hours.

After the period of reflux, the dark reaction mixture was cooled to 90°, poured into its own volume of ice-water, and allowed to stand overnight. Unreacted *p*-nitroanisole was collected on a Buchner funnel. In order to remove completely the *p*-nitroanisole, the filtrate was extracted with 1 liter of benzene. (In one run the crude filtrate was not extracted with benzene at this point, but was diazotized directly. This resulted in saving about one and a half days time, but the yield was lowered to 44%.) The aqueous acid solution was made basic by addition of a solution of 1050 g. of sodium hydroxide in 3 liters of water with stirring and cooling, and then extracted with five 1-liter portions of benzene. The combined benzene extracts were filtered through a gravity filter for the removal of a black, gummy impurity, and the filter was thoroughly washed with benzene. After removal of the benzene at the water pump, the residue was dissolved in a mixture of water (1 liter) and hydrochloric acid (sp. gr. 1.19) (1.5 liters). The chilled solution was then diazotized, for the removal of unreacted *p*-anisidine, with stirring by slow addition of a solution of 50 g. of sodium nitrite in 800 ml. of water at 0–5° and any diazonium compounds formed were destroyed by boiling the acid solution for three hours. The mixture was then cooled to room temperature and filtered. To the cooled and stirred filtrate was added a solution of 850 g. of sodium hydroxide in 2 liters of water, and the liberated 6-methoxyquinoline was extracted with benzene. The crude product, after drying, was distilled under reduced pressure. 6-Methoxyquinoline distils as follows: 112–117° (0.7 mm.); 126–130° (5 mm.); 165–168° (25 mm.). The substance melts at 18–20°. The yield was 402 g. (66%).

5-Chloro-6-methoxyquinoline.—To 16 g. of 6-methoxyquinoline contained in a 200-ml. flask equipped with a stirrer, reflux condenser, and an addition flask connected by means of Gooch tubing was added 21 g. of phosphorus pentachloride slowly and with constant stirring. Considerable heat was evolved, and a rather vigorous evolution of hydrogen chloride occurred. After most of the phosphorus pentachloride had been added, the mixture began to solidify. It was heated with a free flame for ten minutes to melt the mixture and insure complete reaction. After cooling slightly, 40 ml. of water was added dropwise to decompose the phosphorus trichloride. All the solid material dissolved. The solution was then cooled and made alkaline with 3 *N* sodium hydroxide solution and finally extracted with ether. The ether extract was dried over magnesium sulfate and, after removal of the solvent, the residual oil was crystallized three times from petroleum ether, yielding 12 g. (62%) of colorless plates melting at 99–99.5°.

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.0; H, 4.2. Found: C, 62.0; H, 4.2.

Chlorination of 6-methoxyquinoline with chlorine gave a 71% yield of the 5-chloro derivative.

(18) Strukov, *Org. Chem. Ind.* (U. S. S. R.), **4**, 523 (1937); *C. A.*, **32**, 4987 (1938).

Summary

1. 5,6-Dimethoxy-8-nitroquinoline has been prepared by the Skraup reaction.

2. 5-Hydroxy-6-methoxy-8-nitroquinoline has been described.

3. A study of the preparation of 5-fluoro-6-methoxy-8-nitroquinoline by the Skraup reaction has been made.

4. An improved procedure for the synthesis of 6-methoxyquinoline has been described.

5. Chlorination of 6-methoxyquinoline with either phosphorus pentachloride or chlorine yields 5-chloro-6-methoxyquinoline.

NEW YORK 27, N. Y. RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Syntheses of Certain 8-Nitroquinolines[1]

BY ARTHUR TOMISEK, BRUCE GRAHAM, ARVON GRIFFITH, C. S. PEASE, AND BERT E. CHRISTENSEN

This paper describes the preparation of 7-methyl-, 5 methyl- and 5-methoxy-8-nitroquinolines which were necessary intermediates in the syntheses of antimalarials in the 8-aminoquinoline series.

The principal product resulting from the nitration of 7-methylquinoline was found to be 7-methyl-8-nitroquinoline. The structure of this compound was established by comparison with the product obtained from the Skraup reaction upon 2-nitro-3-toluidine. Particular attention was given to simplifying the procedures and establishing optimum conditions in the series of reactions leading to the preparation of this latter intermediate.

5-Methyl-8-nitroquinoline was prepared as indicated in reactions I to IV. The Skraup synthesis using the Richter and Smith procedure[2] was applied to 4-nitro-3-aminotoluene. 3-Nitro-4-aminotoluene was used as the starting material

(1) The work described in this paper was done under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Oregon State College. Published with the approval of the Monographs Publication Committee, Oregon State College, as Research Paper No. 102, School of Science.

(2) Richter and Smith, THIS JOURNAL, **66**, 397 (1944).

since it was converted to the 4-nitro-3-amino-toluene in fewer operations and in greater yield than with the intermediates employed by Manske, Marion and Leger.[3]

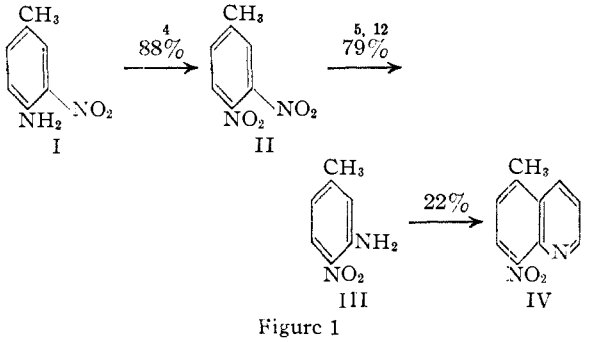


Figure 1

5-Methoxy-8-nitroquinoline was prepared by the sequence: quinoline → 5-nitroquinoline → 5-aminoquinoline $\xrightarrow{6}$ 5-bromoquinoline $\xrightarrow{6}$ 5-bromo-8-nitroquinoline → 5-methoxy-8-nitroquinoline.

Experimental[7]

m-Tolunitrile.—The directions given in "Organic Syntheses"[8] for the preparation of *o*- and *p*-tolunitrile from their respective toluidines were found to apply equally well to the synthesis of the meta[9] isomer. The product was isolated by distillation through a 10-inch, helix-packed column. A preliminary experiment indicated that little if any phenolic compound was formed. Three hundred and twenty-one grams of *m*-toluidine gave a yield of 241 g. (59%) of a colorless liquid, b. p. 98–100° (20 mm.).

m-Toluic Acid.—A mixture consisting of 100 cc. of water, 100 cc. of conc. sulfuric acid and 45 g. of *m*-tolunitrile was refluxed for four hours and then diluted with 100 cc. of water, which was added through the top of the condenser. The flask was stoppered and shaken under a cold water tap until the oily layer solidified as granules. After further cooling with ice, the granules were removed by filtration, dissolved in base and reprecipitated with concd. hydrochloric acid. The cooled mixture was then filtered and washed twice with water. A yield of 50.3 g. (96%) of *m*-toluic acid with m. p. 108.5–111° was obtained.

2-Nitro-3-toluic Acid.—Fifty grams of *m*-toluic acid was added slowly with stirring to 200 cc. of fuming nitric acid[10] (d. 1.5). Lumps of Dry Ice were added directly to the reaction mixture to maintain the temperature between 0 and 5° during the addition of the toluic acid and for a half hour thereafter. The mixture was then allowed to warm to 5°, filtered as dry as possible (using a sintered glass funnel), washed and dried. Thirty grams (48%) of 2-nitro-3-toluic acid, m. p. 213–220°, was obtained. Nitration temperatures as low as −50° were used without materially affecting the yield.

7-Methyl-8-nitroquinoline (by Skraup Synthesis).—The 2-nitro-3-toluic acid was converted to its amide[11] and this in turn subjected to the Hoffman degradation.[11] Sixteen and two-tenths grams of the orange-colored 2-nitro-3-toluidine was subjected to the Skraup synthesis using molar quantities and conditions as given by Richter and Smith.[2] The reaction mixture was diluted with 100 cc. of water, cooled to about 0° and filtered. The solid material was extracted with boiling dil. hydrochloric acid. The acid solution was neutralized with ammonia and the crude 7-methyl-8-nitroquinoline was removed by filtration and washed with water and dried. The yield was 8.7 g. (43%) of black needles. The original mother liquors were treated with excess ammonia and the solid was removed by filtration. The precipitate was dissolved in hydrochloric acid, and this solution was diazotized over a period of three hours by the addition of a large excess of sodium nitrite. The mixture was heated to 80°, cooled to 0° and filtered. The filtrate was made strongly basic with sodium hydroxide, and the resulting precipitate was washed with water. The product, after treatment with charcoal and recrystallization from alcohol, gave 2.5 g. (12%) additional material. These crude products were fractionally recrystallized from alcohol. The second crop of crystals gave a relatively pure yellow product, m. p. 181–183°.

7-Methyl-8-nitroquinoline (by Direct Nitration).—Forty grams of 7-methylquinoline was added gradually with cooling to 100 cc. of cooled concd. sulfuric acid. After the mixture had cooled to room temperature, 16 cc. of fuming nitric acid (d. 1.5) was added in one portion. After standing for three hours, the mixture was poured into 1.2 liters of water. The amorphous product was filtered and washed with water. The product was dissolved in hot alcohol, treated with charcoal, and then recrystallized. A yield of 31.7 g. (61%) of short white rods, m. p. 183°, was obtained. Mixed m. p. tests indicated an identical product with that obtained from the Skraup reaction.

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29: N, 14.89. Found: C, 63.87; H, 4.51; N, 14.72.

5-Methyl-8-nitroquinoline.—The Richter and Smith procedure[2] for the Skraup synthesis was applied to 207 g. of 3-amino-4-nitroquinoline.[5,12] The reaction mixture was then diluted, cooled and filtered. Additional solid material was precipitated from the liquors by ammonia and was removed by filtration, washed with water and redissolved in dil. hydrochloric acid. This solution was diazotized and treated as described for 7-methyl-8-nitroquinoline. The filtrate was made strongly basic with sodium hydroxide, and the resulting precipitate was washed with water and thoroughly air-dried. This crude material was extracted with boiling benzene and the boiling filtrate was treated with charcoal. The product which crystallized on cooling was removed and the remainder recovered by evaporation of the solvent. After two recrystallizations from alcohol 56 g. (22%) of pale tan plates, m. p. 136.5–137.5°, were obtained. Manske and co-workers[3] reported the same yield, with m. p. 138°.

5-Methoxy-8-nitroquinoline.—To a solution of sodium methoxide prepared from 11.5 g. (0.5 mole) of sodium in 1500 cc. of dry methanol was added 208 g. (0.427 mole) of 5-bromo-8-nitroquinoline.[6] The mixture was refluxed gently for thirty minutes, then cooled and 72 g. of crude product (81%) was removed by filtration. Further purification was accomplished readily by charcoal treatment of a hot toluene solution, followed by recrystallization from mixtures of di-isopropyl ether with either benzene or absolute alcohol. Pale yellow crystals, m. p. 117.5–118° were obtained.

Summary

7-Methyl-8-nitroquinoline was prepared by the direct nitration of 7-methylquinoline. The structure of this compound was established by comparison with the product obtained by the Skraup reaction upon 2-nitro-3-toluidine.

(3) Manske, Marion and Leger, *Canadian J. Research*, **20B**, 133 (1942).

(4) Page and Heasman, *J. Chem. Soc.*, 3235 (1923).

(5) Elson, Gibson and Johnson, *ibid.*, 2739 (1929).

(6) Dickshoorn, *Rec. trav. chim.*, **48**, 550 (1929).

(7) All melting points are corrected.

(8) Clarke and Read, "Organic Syntheses," Coll. Vol. 1, John Wiley & Sons Inc., New York, N. Y., 2nd ed., 1941, p. 514.

(9) Buchka and Schachtebeck, *Ber.*, **22**, 841 (1889), mentioned this reaction, omitting the yield and other details.

(10) Muller, *ibid.*, **42**, 430 (1909).

(11) Geerling and Wibaut, *Rec. trav. chim.*, **53**, 1015 (1934).

(12) The yield of 3-amino-4-nitrotoluene was increased to 79% by evaporating the alcoholic recrystallization liquors to dryness and extracting the residue with boiling ligroin, from which the product crystallized on cooling. The use of reaction temperatures over 155° resulted in considerably reduced yields.

5-Methyl-8-nitroquinoline was prepared by a modification of the procedures of Manske, Marion and Leger.

5-Methoxy-8-nitroquinoline was prepared by methoxylation of 5-bromo-8-nitroquinoline.

CORVALLIS, OREGON RECEIVED APRIL 5, 1946

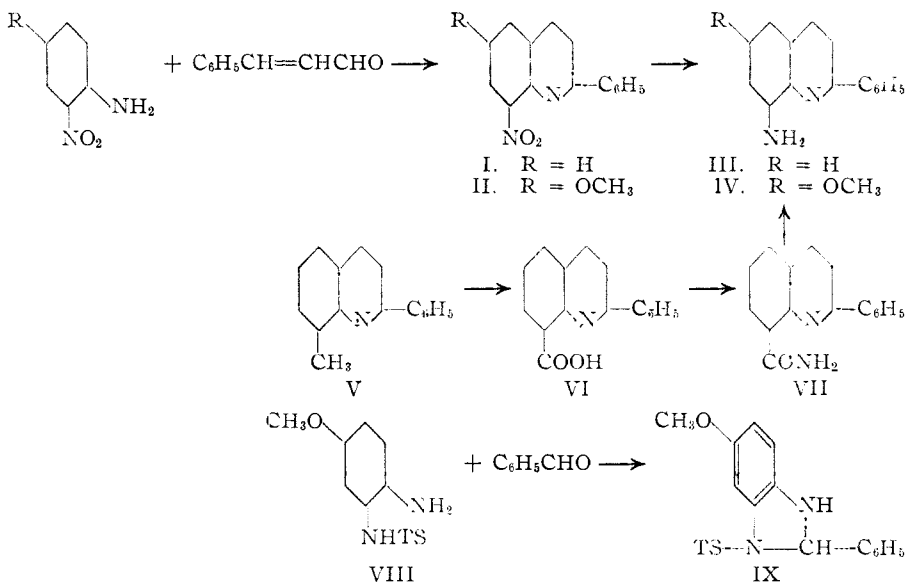
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Synthesis of Simple 2-Phenyl-8-aminoquinoline Derivatives[1]

BY ROBERT C. ELDERFIELD, WALTER J. GENSLER, THOMAS H. BEMBRY, THURMOND A. WILLIAMSON AND HENRY WEISL

In a preceding paper[2] the synthesis and reasons therefor of certain 2-phenyl-4-chloroquinolines to be used as intermediates in the preparation of antimalarial drugs of the 4-aminoquinoline series has been described. For exactly similar reasons it was desired to ascertain the effect of the introduction of a phenyl group in the 2-position in the 8-aminoquinoline series. In the present paper we wish to present the results of a study of the synthesis of 2-phenyl-8-aminoquinoline and certain of its derivatives. The conversion of these substances to drugs of the Pamaquine (Plasmochin) series is described in a succeeding paper.[3]

The synthesis of 2-phenylquinoline by the general Doebner–Miller method has been studied by Murmann.[4] Apparently the method has not been applied to the synthesis of other derivatives of 2-phenylquinoline. We have now extended the method to the synthesis of 2-phenyl-8-nitroquinoline (I) and 2-phenyl-6-methoxy-8-nitro-quinoline (II), although the yields leave something to be desired Since the possibility of the formation of a 4-phenylquinoline derivative by the above method is not completely eliminated, the structure assigned to I was definitely proved by synthesis of 2-phenyl-8-aminoquinoline (III) from 2-phenyl-8-methylquinoline (V-III).[5] Samples of III obtained by either method were identical.



An attempted alternative synthesis of II involved application of the familiar Pfitzinger method to the reaction of 2-(*p*-toluenesulfonamido)-4-methoxyaniline (VIII) with benzaldehyde and pyruvic acid. When VIII was warmed with benzaldehyde, the expected anil was not obtained, although the analytical figures agreed with those for the anil. Since the product of the reaction was insoluble in dilute alkali and since it did not react with pyruvic acid in the desired sense, it is assigned the structure of the isomeric 2-phenyl-3-(*p*-toluenesulfonyl)-5-methoxy-1,2-dihydrobenzimidazole (IX). When IX was allowed to stand in ether solution with pyruvic acid at room temperature, a product furnishing analytical figures agreeing with those demanded by VIII was obtained. However, this substance was not identical with VIII. Its nature was not investigated further.

Finally, use was made of the method of Gilman and Spatz[6] involving the use of phenyllithium for the preparation of IV. The reaction failed when applied to 6-methoxy-8-aminoquinoline itself, but was successful when applied to 6-methoxy-8-acetaminoquinoline. Introduction of a phenyl group into other 8-aminoquinoline derivatives by this method was investigated. The results are shown in Table I. From this it appears neces-

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

(2) Elderfield, *et al.*, THIS JOURNAL, **68**, 1272 (1946).

(3) Elderfield, *et al.*, *ibid.*, **68**, 1516 (1946).

(4) Murmann, *Monatsh.*, **25**, 621 (1904).

(5) Doebner and Gieseke, *Ann.*, **242**, 298 (1887).

(6) Gilman and Spatz, THIS JOURNAL, **66**, 621 (1944).