1-Chloro-2-diethylaminopropane.—To a chilled solution of 182 g. of pure thionyl chloride in 500 ml. of dry benzene was added 100 g. of 2-diethylaminopropanol-1 at such a rate that the temperature did not exceed 25°. After heating the mixture at 50–60° for three hours, it was concentrated to dryness and the residue was made alkaline with 40% potassium hydroxide solution with cooling. The oily amino chloride was extracted with ether and distilled yielding 94 g. (82%) of material boiling at 79–80° (50 mm.) $n^{2}D$ 1.4310.

Anal. Calcd. for $C_7H_{16}ClN$: C, 56.2; H, 10.8. Found: C, 56.1; H, 10.8.

5-Diethylaminohexanone-2.—To a refluxing solution of ethyl sodio acetoacetate prepared from 11.5 g. of sodium and 65 g. of ethylacetoacetate in 250 ml. of absolute alcohol was added over one and one-half hours 75 g. of 1-chloro-2-diethylaminopropane. After refluxing for an additional fourteen hours, the precipitated sodium chloride was filtered off and the alcohol distilled from the filtrate. The crude ester was stirred for twenty hours at room temperature with 600 ml. of 5% sodium hydroxide solution. After separation of a small insoluble portion, the solution was acidified with hydrochloric acid and warmed on the steam-bath until evolution of carbon dioxide ceased. After cooling, the solution was made alkaline and saturated with potassium carbonate. The amino ketone was extracted with several portions of ether and distilled yielding 36 g. (42%) of material boiling at 94–95° (16 mm.) or 105–107° (22 mm.); $n^{25}D$ 1.4337.

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.1; H, 12.4. Found: C, 70.4; H, 12.3.

5-Diethylamino-hexanol-2.—The above ketone was reduced catalytically over Raney nickel,[27] yielding 85% of the alcohol boiling at 110° (15 mm.).

Anal. Calcd. for $C_{10}H_{23}NO$: C, 69.3; H, 13.4. Found: C, 69.0; H, 13.2.

2-Bromo-5-diethylaminohexane.—The above alcohol was converted to the oily bromide hydrobromide with thionyl bromide in benzene. Since no crystalline salt of the bromoamine could be found, it was used directly for subsequent work.[2]

3-(3′-Diethylaminopropoxy)-propanol-1.—To a solution of 50 g. of sodium in 400 g. of dry redistilled trimethylene glycol in 200 ml. of dry xylene at 120° was added 360 g. of 3-diethylamino-1-chloropropane. After cooling, the salt was filtered off and the filtrate was fractionated carefully yielding 192 g. (51%) of product boiling at 147–148° (10 mm.).

Anal. Calcd. for $C_{10}H_{23}NO_2$: C, 63.5; H, 12.2. Found: C, 63.7; H, 12.3.

3-(3′-Diethylaminopropoxy)-1-chloropropane.—This was prepared from the above alcohol with thionyl chloride in benzene. The free base boiled at 118–119° (10 mm.).

Anal. Calcd. for $C_{10}H_{22}ClNO$: C, 57.3; H, 10.6. Found: C, 57.5; H, 10.6.

1-Ethylaminobutene-3.—Reaction of 1-bromobutene-3[2] (77 g.) with ethylamine (300 ml.) in a bomb at 100° for twelve hours and then at room temperature for forty-eight hours as in the preceding cases gave 42% of 1-ethylaminobutene-3 boiling at 108–109°.

Anal. Calcd. for $C_6H_{13}N$: C, 72.7; H, 13.2. Found: C, 72.9; H, 13.3.

The acetyl derivative of the above amine boiled at 115–117° (30 mm.).

Anal. Calcd. for $C_8H_{15}NO$: C, 68.0; H, 10.7. Found: C, 68.1; H, 10.9.

1-Bromo-2-hydroxy-4-ethylaminobutane.—To a solution of 30 g. of 1-ethylaminobutene-3 in 27 ml. of acetic acid and 100 ml. of water was added over thirty minutes 42 g. of N-bromoacetamide.[29] After stirring for two hours the bromoacetamide all dissolved. After addition of 75 ml. of 48% hydrobromic acid the solution was concentrated under reduced pressure to a thick mush of oil and crystals. This was triturated with 20 ml. of absolute alcohol and the insoluble ammonium bromide was filtered off. The oily bromoamine hydrobromide was used for condensations with 6-methoxy-8-aminoquinoline without further purification because of its marked tendency to form a pyrrolidine derivative.

Summary

1. A general method for the synthesis of amino-halides of the type $CH_3CHX(CH_2)_3NR_2$, where R = alkyl or hydrogen, has been described.

2. The synthesis of a variety of other amino halides has been described.

(28) Linstead and Rydon, *J. Chem. Soc.*, 1995 (1934).

(29) Likhosherstov and Alekseev, *J. Gen. Chem.* (U. S. S. R.), **3**, 927 (1933), described the reaction of N-bromoacetamide with butene-2.

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

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Synthesis of 5-Substituted Derivatives of 6-Methoxy-8-aminoquinoline and of 5-Chloro-6-methoxyquinoline[1]

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Derivatives of 5,6-dimethoxy-8-aminoquinoline, carrying alkylamino side chains in the 8-position have been reported in the literature[2,3] to possess antimalarial properties superior to those of similar substances not carrying the 5-methoxyl group. In a succeeding paper of this series, the synthesis of a number of such drugs is described. In the present communication we wish to present the results of a study of the synthesis of 5,6-dimethoxy-8-aminoquinoline itself. Various syntheses of this substance are given in the patent literature[4] of which the most direct consists in the reaction of 5-chloro- or 5-bromo-6-methoxy-8-nitroquinoline with sodium methoxide. However, possibly because of a lack of sufficient detail in the patents, we have been unable to duplicate the available syntheses.

(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) Schönhöfer and Andersag, German Patent 536,447; *Friedlander*, **18**, 2718 (1931).

(3) Schönhöfer, *Z. physiol. Chem.*, **274**, 1 (1942).

(4) Schönhöfer, U. S. Patent 1,879,538, Sept. 27, 1932.

Attention was then turned to use of the Skraup reaction using 4-amino-5-nitroveratrole for the synthesis of 5,6-dimethoxy-8-nitroquinoline. When the reaction was carried out under the usual conditions, no pure product could be isolated from the tarry crude reaction product. By cutting down the time of the reaction to about ninety seconds, it has been possible to secure yields of 40% of 5,6-dimethoxy-8-nitroquinoline. The primary reason for poor yields appears to be the extreme lability of the methoxyl group in the position para to the nitro group either in the veratrole or quinoline derivative. This lability was demonstrated by the ease of hydrolysis of 5,6-dimethoxy-8-nitroquinoline to 5-hydroxy-6-methoxy-8-nitroquinoline when the former was boiled with dilute alcohol containing very small amounts of mineral acid.

Since such favorable results were obtained in the above case when the reaction time was radically shortened, other Skraup reactions were carried out using various amines and reaction times of from one to fifteen minutes. The yields from these were uniformly low or nil. Accordingly, the following generalization appears to apply to such reactions. If the aminobenzene derivative contains an activating group orienting so as to favor closure of the pyridine ring, the maximum yield of quinoline derivative will be obtained when a short reaction time is used. This is particularly the case when a competing reaction (*e.g.*, hydrolysis of the 5-methoxyl group in the compound under discussion) takes place.

In the course of the above studies, the preparation of 6-methoxyquinoline by the Skraup reaction previously described by several workers[5,6] has been greatly improved. By introducing a period during which the reaction mixture is preheated to a moderate temperature before subjecting it to the final temperature, the violence of the reaction can be effectively controlled. In this way 6-methoxyquinoline has been repeatedly prepared on a six mole or larger scale without losing control of the reaction. The product, obtained in improved yield, is of much higher quality and may be directly extracted from the diluted reaction mixture without the necessity of the very tedious steam distillation from accompanying tar which is necessary when the older procedures are used.

6-Methoxyquinoline undergoes a reaction characteristic of β-naphthylmethylethers when heated with phosphorus pentachloride[7,8] with the formation of 5-chloro-6-methoxyquinoline. The latter substance was also obtained by reaction of 6-methoxyquinoline with chlorine in acetic acid according to the procedure of Robinson and Tomlinson[9] for the chlorination of 6-methoxy-8-acetaminoquinoline.

5,6-Dimethoxy-8-aminoquinoline was obtained by reduction of the nitro compound with stannous chloride. The susceptibility of the 5-methoxyl group in 5,6-dimethoxy-8-nitroquinoline to hydrolysis made necessary careful temperature control during the reduction to the amino-derivative, a fact not obvious from previous reports.[4] Provided due precautions are observed, substantially quantitative yields were obtained. Improper temperature control resulted in appreciable hydrolysis of the group in question.

It has been postulated in the past that one of the reasons for the relatively high toxicity of Pamaquine (Plasmochin) may be due to oxidation in the 5-position with formation of an aminophenol derivative. Derivatives of Pamaquine in which the 5-position is blocked by such groups as methyl or chlorine[10] suffer marked loss in activity against avian malaria. The use of fluorine for such blocking has not been investigated. Accordingly, a study of the synthesis of 5-fluoro-6-methoxy-8-nitroquinoline has been made. The fluorine atom in the above substance shows a striking lability and is practically completely hydrolyzed during the Skraup reaction with 2-fluoro-4-amino- (or 4-acetamino)-5-nitroanisole with the result that the yield of the desired 5-fluoroquinoline derivative was exceedingly low under all experimental conditions. The fluorine atom does not exert as strong an orienting effect tending to promote ring closure as does the methoxyl group in the preceding case, so that longer reaction times are necessary. When conditions were set to give the best yield of quinoline derivatives, the product was not the desired 5-fluoro derivative but rather 5-hydroxy-6-methoxy-8-nitroquinoline exclusively. Attempted replacement of the amino group in 5-amino-6-methoxyquinoline by fluorine by the use of the diazonium reaction was unsuccessful. The diazonium fluoborate was obtained in 83% yield, but decomposition of it under all conditions resulted only in the formation of tars.

Experimental[11,12]

5,6-Dimethoxy-8-nitroquinoline.—"Dynamite" glycerol was dried by heating it in an evaporating dish at 165–170° for fifteen minutes. While still above 150°, 365 ml. was poured into a 5-liter flask and to it was added 70 g. of arsenic acid anhydride and 120 g. of 4-acetamino-5-nitroveratrole[13] (m. p. 198–199°). The mixture was thoroughly slurried by shaking and 150 ml. of sulfuric acid was added slowly down the sides of the flask, the contents of which were agitated by swirling. After a few seconds, a vigorous exothermic reaction set in. Unless the reactants are added rapidly to the hot glycerol, the temperature falls below 150° and the exothermic reaction does not start spontaneously. It is then necessary to heat the mixture carefully, with shaking, to start the reaction. The contents of the flask were swirled under the hood for ninety seconds and then poured into 1.5 liters of ice water. If the exothermic

(5) Skraup, *Monatsh.*, **6**, 672 (1885).
(6) Iwamiya, *J. Pharm. Soc. Japan*, **49**, 792 (1929).
(7) Autenrieth, *Ber.*, **30**, 2379 (1897).
(8) Autenrieth and Mühlinghaus, *ibid.*, **39**, 4098 (1906).
(9) Robinson and Tomlinson, *J. Chem. Soc.*, 1524 (1934).
(10) Antimalarial Drugs 1941–1945. Published by the Survey of Antimalarial Drugs, in press.
(11) All melting points are corrected.
(12) Microanalyses by the Misses Lois May and Lathrope Baker.
(13) Jones and Robinson, *J. Chem. Soc.*, **111**, 914 (1917).

reaction is allowed to continue for but sixty seconds, considerable amounts of deacetylated 4-acetamino-5-nitroveratrole are recovered. A longer reaction time leads to the formation of excessive amounts of alkali soluble material, presumably arising from cleavage of the 5-methoxyl group. The acid solution was filtered from insoluble nonbasic material, and the filtrate was made alkaline with a solution of about 400 g. of sodium hydroxide. The precipitate of crude 5,6-dimethoxy-8-nitroquinoline was washed thoroughly with water, dissolved in 400 ml. of 10% hydrochloric acid, and reprecipitated from the filtered acid solution with ammonia. After recrystallization from 600 ml. of 70% alcohol, 47 g. (40%) of tan needles melting at 127–128° was obtained. 5,6-Dimethoxy-8-nitroquinoline is reported as melting at 126–128°[4].

5-Hydroxy-6-methoxy-8-nitroquinoline.—In the course of recrystallizing one batch of crude 5,6-dimethoxy-8-nitroquinoline (without reprecipitation) from 240 g. of 4-acetamino-5-nitroveratrole, the aqueous alcoholic solution was boiled for one and one-half hours. A red crystalline solid (33 g.) separated. The clear filtrate from this was boiled for a total of three and one-half hours longer, and a total of 80 g. of the material was obtained. After recrystallization from water containing a little hydrochloric acid, the substance formed red square plates which melted at 243–245° (d). It was soluble in dilute alkali.

Anal. Calcd. for $C_{10}H_8N_2O_4$: C, 54.6; H, 3.7. Found: C, 54.7; H, 4.0.

5,6-Dimethoxy-8-aminoquinoline.—To a well-stirred solution of 104 g. of stannous chloride dihydrate in 300 ml. of hydrochloric acid (sp. gr. 1.19) cooled to below 10° in an ice-bath was added dropwise a solution of 26 g. of 5,6-dimethoxy-8-nitroquinoline in 100 ml. of hydrochloric acid (sp. gr. 1.19). After the addition was complete, the solution was stirred for an hour at 10° and then allowed to come to room temperature and stirred for an additional two hours. Unless the temperature is held within the limits indicated up to this point, the yield suffers because of cleavage of the labile 5-methoxyl group. The canary yellow tin complex was completely dissolved by addition of warm water. The orange red solution, cooled in an ice-bath, was made strongly alkaline by careful addition of concentrated sodium hydroxide solution, ice being added to keep the temperature below 20°. If the mixture is allowed to warm up at this point, the product occludes considerable amounts of the stannic chloride addition complex. The tin salt precipitated first, then redissolved in the excess alkali and 5,6-dimethoxy-8-aminoquinoline separated as micro plates. After washing thoroughly with water, 22 g. (96%) of pure material melting at 148–149° was obtained. Schönhöfer[4] reports a melting point of 148°. The amine is somewhat unstable and susceptible to atmospheric oxidation.

2-Fluoro-4-nitroanisole.—The following modification of the procedure of Holmes and Ingold[14] represents a considerable improvement over the procedure given by Schiemann and Miau.[15] To a solution of 50 g. of 2-fluoroanisole in 195 ml. of acetic anhydride cooled to 0° in an ice–salt bath was added with stirring, dropwise over a period of one hour, a mixture of 20 ml. of fuming nitric acid (sp. gr. 1.50) and 8 ml. of glacial acetic acid, the temperature being kept at 0 to −2°. The mixture was stirred for three hours longer at the same temperature and was then poured into 800 ml. of cold water. This mixture was stirred for thirty minutes and left in the refrigerator overnight, after which the product had separated as a thick paste consisting of solid material mixed with some oil (probably a mixture of other nitro compounds). This was filtered off on a coarse sintered glass funnel and the solid was pressed and washed with cold water to remove as much of the oil as possible. Two crystallizations from alcohol gave 28.4 g. (41%) of 2-fluoro-4-nitroanisole which melted at 104–105°.

Reduction of 2-fluoro-4-nitroanisole to the corresponding amine by means of stannous chloride and hydrochloric acid has been described by English, Mead and Niemann,[16] and by Schiemann and Miau.[15] However, the direct conversion of the nitro compound to the acetamino compound, as well as the properties of the latter, apparently are not recorded.

A suspension of 51 g. of 2-fluoro-4-nitroanisole, prepared according to English, Mead and Niemann,[16] in 75 ml. of acetic anhydride was shaken with 0.2 g. of Adams platinum oxide catalyst in an Adams shaker under 30–40 lb. of hydrogen pressure. The calculated amount of hydrogen was taken up in about one and one-half hours. After filtering off the catalyst, 75 ml. of water was added to the filtrate cautiously, and the mixture was boiled for about an hour. It was then poured into 300 ml. of water and 41 g. (77%) of pinkish crystals separated. The acetamino compound was recrystallized from benzene or a mixture of benzene and petroleum ether and melted at 112–112.5°.

Anal. Calcd. for $C_9H_{10}FNO_2$: C, 59.1; H, 5.5. Found: C, 59.4; H, 5.6.

2-Fluoro-4-acetamino-5-nitroanisole.—In a 250 ml., three-necked flask equipped with a thermometer, mechanical stirrer, and a dropping funnel chilled in an ice–salt freezing bath, 18 g. of 2-fluoro-4-acetaminoanisole was dissolved in 30 ml. of 98% sulfuric acid, care being taken that the temperature did not rise above 0°. To this solution 15 ml. of nitric acid (sp. gr. 1.42) was added dropwise at such a rate that the temperature did not rise above −1°. After all the nitric acid had been added, the viscous orange mass was poured onto 300 g. of cracked ice and the mixture was thoroughly stirred. The yellow crystals which separated were filtered off and thoroughly washed with water, yielding 19 g. of crude product which upon recrystallization from 500 ml. of alcohol gave 17 g. of yellow crystals melting at 163–164°. The yield was 75%.

Anal. Calcd. for $C_9H_9FN_2O_2$: C, 47.4; H, 4.0. Found: C, 47.6; H, 4.2.

2-Fluoro-4-amino-5-nitroanisole.—A suspension of 2 g. of 2-fluoro-4-acetamino-5-nitroanisole in 25 ml. of water, 25 ml. of hydrochloric acid (sp. gr. 1.19) and 10 ml. of alcohol was refluxed for thirty minutes. On cooling, red orange crystals separated which were recrystallized from alcohol. The yield of material melting at 142.5–143.5° was 80%.

Anal. Calcd. for $C_7H_7FN_2O$: C, 45.2; H, 3.8. Found: C, 45.2; H, 4.1.

5-Fluoro-6-methoxy-8-nitroquinoline.—To a mixture of 46 g. of "Dynamite" glycerol (previously dried by heating at 170° for ten minutes), 6.0 g. of arsenic acid anhydride, and 11.5 g. of 2-fluoro-4-acetamino-5-nitroanisole, was slowly added 27.5 g. of 98% sulfuric acid. The mixture was heated under an air condenser over a small free flame, and after the reaction started, the mixture was maintained at a gentle boil for fifteen minutes. During this time hydrogen fluoride was evolved in copious amounts. After cooling the mixture was poured into 400 ml. of ice water. A red solid separated which was identified as 5-hydroxy-6-methoxy-8-nitroquinoline by mixed melting point with the substance obtained as described above. The filtrate was made alkaline with 200 ml. of 50% sodium hydroxide solution. The dark brown mass which separated was recrystallized from isopropanol (carbon), yielding 2 g. of brown crystals. On sublimation this gave 1 g. of yellow material which melted at 155–156°.

Anal. Calcd. for $C_{10}H_7FN_2O_3$: C, 54.1; H, 3.2. Found: C, 54.5; H, 3.5.

When the Skraup reaction was carried out according to the method of Fourneau, Tréfouel and Benoit[17] for the preparation of 5-chloro-6-methoxy-8-nitroquinoline but using 2-fluoro-4-amino-5-nitroanisole and a reaction time of seven hours at 130–140°, the yield of 5-hydroxy-6-methoxy-8-nitroquinoline was 54% and none of the fluoroquinoline was obtained.

The Skraup reaction carried out in a vacuum according

(14) Holmes and Ingold, *J. Chem. Soc.*, **129**, 1328 (1926).

(15) Schiemann and Miau, *Ber.*, **66**, 1179 (1933).

(16) English, Mead and Niemann, THIS JOURNAL, **62**, 350 (1940).

(17) Fourneau, Tréfouel and Benoit, *Ann. Inst. Pasteur*, **44**, 744 (1930).

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.

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

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

[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).