[CONTRIBUTION FROM THE ROSS CHEMICAL LABORATORY, ALABAMA POLYTECHNIC INSTITUTE]

Some Derivatives of 7-Methylquinoline

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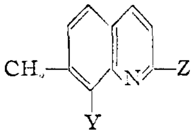
Some experiments were undertaken to determine how well reactions used previously for the preparation of certain substituted quinolinearsonic acids[1] could be applied to some substituted 7-methylquinolines, and the results were recorded for this paper. In general it was found that the reactions proceeded satisfactorily, and conditions were worked out for the synthesis of compounds I through IX.



I $Z = H, Y = NO_2$
II $Z = H, Y = NH_2$
III $Z = H, Y = C_6H_5CONH—$
IV $Z = H, Y = AsO_3H_2$
V $Z = Cl, Y = NO_2$
VI $Z = Cl, Y = NH_2$
VII $Z = Cl, Y = C_6H_5CONH—$
VIII $Z = Cl, Y = AsO_3H_2$
IX $Z = OH, Y = AsO_3H_2$

During the course of the work, it was noted that the nitration of 7-methylquinoline yielded mainly (67%) 7-methyl-8-nitroquinoline (I), a compound whose structure was proved by an unambigous synthesis starting with 2-nitro-*m*-toluidine. From the mixture of other substances formed in the nitration, there was isolated a small amount (6%) of a pure compound m.p. 133–134°, which was not analyzed, but which was shown to be different from 7-methyl-6-nitroquinoline and from 7-methyl-5-nitroquinoline. The latter compounds were obtained by applying the Skraup synthesis to 6-nitro-*m*-toluidine and to 5-nitro-*m*-toluidine. In both Skraup reactions two methylnitroquinolines were formed, representing the two directions in which ring closure can take place; in view of the non-identity of the direct nitration product with any of the four Skraup products, the absolute orientations of the latter were not determined.

Experimental

Nitration of 7-Methylquinoline.[2] A.—Solution A was prepared by mixing 17.0 ml. of nitric acid (sp. gr. 1.42) with 26.0 ml. of sulfuric acid (sp. gr. 1.84) and cooling to room temperature. The slow addition of 90.0 ml. of sulfuric acid (sp. gr. 1.84) to 33.0 g. of 7-methylquinoline, that was agitated, gave a solution B, which was cooled to room temperature. Solution A was then added dropwise to solution B with stirring. After standing for three hours in a flask surrounded by the atmosphere of the room, the resulting solution A-B was kept at 100° for one and one half hours and poured slowly into 2.5 liters of cracked ice and water. The pale yellow solid S (30.8 g.) resulting was separated by filtration and washed with water. Upon dissolving solid S in 135 ml. of hot glacial acetic acid, filtering, and cooling slowly, **7-methyl-8-nitroquinoline** (I) crystallized. This was washed with glacial acetic acid followed by water and dried at 65°. The filtrate from this crystallization was treated with norite (charcoal), boiled for several minutes before adding hiflo super cel[3] to coagulate fine carbon particles, and filtered. Concentration by distillation followed by slow cooling gave an additional quantity of 7-methyl-8-nitroquinoline. Twenty-nine grams (67% yield) of 7-methyl-8-nitroquinoline melting at 186–187° was finally obtained.

Anal. Calcd. for $C_{10}H_8N_2O_2$: N, 14.89. Found: N, 14.91.

The original filtrate from solid S was treated with ammonia water to obtain several solid fractions that possessed melting points lower than that of 7-methyl-8-nitroquinoline. Sublimation at 3 mm. pressure failed to yield a separation of these fractions into a pure component. Steam distillation using superheated steam gave no promising results. Several attempts to take advantage of possible differences in basicity characteristics of the components in the apparent mixture resulted in the isolation of approximately a 6% over-all yield of a substance melting at 133–134°.

B.—Twenty-five grams of 7-methylquinoline was added dropwise during twenty-five minutes to 80.0 ml. of nitric acid (sp. gr. 1.5) that was stirred mechanically and kept below 20°. The temperature of the system gradually was increased to 55–60° and maintained for fifteen minutes. A pale yellow solid formed upon pouring slowly into agitated water and ice mixture. Upon filtering, washing with water, and drying, this solid melted at 183°. Purification from glacial acetic acid according to procedure given in A yielded 7-methyl 8-nitroquinoline melting at 186–187°.

Treating the original filtrate with ammonia water revealed that nitration was incomplete and that a low melting solid similar to that obtained by nitrating 7-methylquinoline with nitric acid (sp. gr. 1.42) in sulfuric acid (sp. gr. 1.84) was produced.

7-Methyl-8-nitroquinoline (I).—2-Nitro-*m*-toluidine (4.23 g.) (from 2,3-dinitrotoluene[4]), arsenic pentoxide (6.00 g.), anhydrous glycerol (10.0 ml.) and sulfuric acid (sp. gr. 1.84, 7.00 ml.) were mixed well and heated for three hours under a reflux condenser by means of an oil-bath maintained at 160–165°. The cooled mass was poured with stirring into a mixture of cracked ice and water, made alkaline with ammonia water, filtered, and washed with water. Upon dissolving in a minimum quantity of dilute sulfuric acid and water solution, treating with norite (charcoal), boiling for several minutes, adding hiflo super cel and filtering, a clear solution resulted. The addition of a saturated solution of sodium acetate in water, while stirring, caused the crude 7-methyl-8-nitroquinoline to separate. Crystallization from glacial acetic acid gave some 7-methyl-8-nitroquinoline that melted at 185–186°.

Methylnitroquinolines.—6-Nitro-*m*-acetotoluidide (5.40 g.) (from *m*-acetotoluidide[5]), arsenic pentoxide (6.00 g.) anhydrous glycerol (10.0 ml.) and sulfuric acid (sp. gr. 1.84; 7.00 ml.) were mixed well and heated for three hours under a reflux condenser by means of an oil-bath maintained at 160–165°. The reaction mixture was treated similarly to that obtained from subjecting 2-nitro-*m*-tolui-

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(1) J. D. Capps and C. S. Hamilton, THIS JOURNAL, **60**, 2105 (1938).

(2) Compare with work reported by Tomisek, Graham, Griffith, Pease and Christensen, *ibid.*, **68**, 1588 (1946), which appeared after the first draft of this manuscript was submitted to the Editor of THIS JOURNAL.

(3) A product of Johns-Manville, 22 East 40th St., New York 16, N. Y.

(4) H. Burton and J. Kenner, *J. Chem. Soc.*, **119**, 1051 (1921).

(5) J. B. Cohen and H. D. Dakin, *ibid.*, **83**, 333 (1903).

dine to ring closure excepting that fractional crystallization from the purified dilute sulfuric acid solution by the gradual addition of saturated sodium acetate–water solution was used to separate the two isomeric methylnitroquinolines resulting. A combination of treatments with norite in hot ethanol–water solutions followed by crystallizations gave a substance D melting at 167–168° and a substance E melting at 119–120°.

5-Nitro-*m*-toluidine (3.70 g.) (from 3,5-dinitrotoluene[6]), arsenic pentoxide (4.23 g.), dry glycerol (7.20 ml.) and sulfuric acid (sp. gr. 1.84, 2.70 ml.) were mixed well and heated for one hour under reflux condenser by means of an oil-bath maintained at 130–135°. The temperature of the oil-bath was then increased to 150–155° for four additional hours. The resulting mixture was worked up similarly to a mixture obtained from subjecting 6-nitro-*m*-acetotoluidide to ring closure. Brown-yellow needles from ethanol–water solution melting at 131–132° and greenish colored needles from ethanol–water solution melting at 109–110° were isolated.

7-Methyl-8-aminoquinoline (II).—A solution of 5.00 g. of 7-methyl-8-nitroquinoline in 100 ml. of reagent grade acetone was reduced at 50° in presence of Raney nickel catalyst with hydrogen at 35–40 pounds per square inch pressure. Hiflo super cel was added to coagulate finely divided nickel, and the solids were removed by filtration. An oil was obtained by driving off the acetone under reduced pressure while heating in a water-bath. The oil crystallized upon pouring into a porcelain evaporating dish. A minimum quantity of 95% ethanol was used to dissolve the crude amine (4.40 g.) before treating with norite, coagulating the finely divided norite with hiflo super cel and filtering. Dilution of the filtrate with water until a slight cloudiness appeared, followed by the addition of a seed crystal, caused golden yellow needles to form; these melted down at 61–62° and the system cleared completely at 68–69°. Upon standing in a desiccator over sulfuric acid (sp. gr. 1.84) at 3 mm. pressure, the color and general appearance of the crystals changed.

Anal. Calcd. for $C_{10}H_{10}N_2$: N, 17.62. Found: N, 17.70.

7-Methyl-8-nitroquinoline (5.00 g.) was also reduced in 125 ml. of absolute ethanol containing suspended Raney nickel catalyst to give 7-methyl-8-aminoquinoline. A deep orange colored salt precipitated when 25 ml. of hydrochloric acid (sp. gr. 1.19) was added to the alcoholic solution of the amine.

7-Methyl-8-benzamidoquinoline (III).—A mixture of 1.00 g. of 7-methyl-8-aminoquinoline, 2.0 ml. of benzoyl chloride, and 20 ml. of 5% sodium hydroxide in water was shaken until no more solid was formed. Upon dissolving in 95% ethanol, decolorizing with norite, and standing overnight, colorless needle-like crystals appearing as spangles through a microscope developed. Dilution of mother liquor gave additional crystals of 7-methyl-8-benzamidoquinoline; 0.80 g. over-all recovery; m. p. 145–146°.

Anal. Calcd. for $C_{17}H_{14}N_2O$: N, 10.68. Found: N, 10.75.

7-Methyl-8-quinolinearsonic Acid (IV).—7-Methyl-8-aminoquinoline (4.40 g.) was converted into 7-methyl-8-quinolinearsonic acid by means of the procedure reported by Capps and Hamilton[1] for converting certain 2-chloroaminoquinolines into 2-chloroquinolinearsonic acids. The resulting 7-methyl-8-quinolinearsonic acid (2.70 g.) was dried in a vacuum dryer at 118°; clusters of long tan needles.

Anal. Calcd. for $C_{10}H_{10}NAsO_3$: As, 28.05. Found: As, 28.08.

2-Chloro-7-methyl-8-nitroquinoline (V). A.—7-Methyl-8-nitroquinoline (25.0 g.) was converted into 1,7-dimethyl-8-nitro-2-quinolone according to conditions described by Capps[7] for changing 6-methyl-8-nitroquinoline into 1,6-dimethyl-8-nitro-2-quinolone. The solid weighed 23.6 g. when dried at 65° and demonstrated instability toward light. Recrystallization of small quantities from methanol gave yellow plates melting with decomposition at 154–155°.

1,7-Dimethyl-8-nitro-2-quinolone (23.6 g.), phosphorus pentachloride (23.6 g.), and phosphorus oxychloride (12.0 ml.) were heated together under a reflux condenser in an oil-bath at 125° for one and one-quarter hours.[8] The resulting solution was poured slowly with good agitation into 400 ml. of cracked ice and water mixture. Upon filtering to separate the crude 2-chloro-7-methyl-8-nitroquinoline and washing with water, it was purified by decolorizing in acetic acid with norite and crystallizing; flesh colored needles; yield 15.4 g.; m. p. 133–134°.

Anal. Calcd. for $C_{10}H_7N_2ClO_2$: N, 12.59. Found: N, 12.64.

B.—7-Methylquinoline (78.0 ml.) was treated slowly with 57.0 ml. of dimethyl sulfate, while shaking, and permitted to stand forty minutes. Then 410 ml. of water followed by a solution of 450 g. of potassium ferricyanide in 1500 ml. of water was added. While stirring vigorously mechanically, a solution of 234 g. of sodium hydroxide pellets in 468 ml. of water was added from a dropping funnel during thirty minutes. Stirring was continued for two hours and the system stood overnight. The 1,7-dimethyl-2-quinolone[9] was extracted with benzene and the benzene solution washed free of alkali with water. After drying with anhydrous sodium sulfate, the benzene solution was concentrated by distillation and poured with stirring into cold petroleum ether. The quinolone was separated by filtering, washed with petroleum ether, and dried; 81.3 g. yield.

1,7-Dimethyl-2-quinolone (74.3 g.), phosphorus pentachloride (108.8 g.) and phosphorus oxychloride (12.8 ml.) were mixed well and heated under reflux condenser in oil-bath maintained at 135–140° for four hours. The excess phosphorus oxychloride was distilled off by changing the position of the condenser and raising the temperature of the oil-bath. The resulting mixture was poured into cracked ice and water, filtered, and the solid washed with water. Upon dissolving in sulfuric acid and water, treating with charcoal, and finally making alkaline with sodium hydroxide solution, the 2-chloro-7-methylquinoline[9] was extracted with benzene. The benzene solution was washed free of alkali with water and most of the benzene removed by distillation. Crystallization occurred as the remaining benzene evaporated from a porcelain dish; yield 63.4 g.

A cooled solution of 5.00 ml. of nitric acid (sp. gr. 1.42) in 10.0 ml. sulfuric acid (sp. gr. 1.84) was added slowly to an agitated solution of 10.0 g. 2-chloro-7-methylquinoline in 30.0 ml. sulfuric acid (sp. gr. 1.84) that was surrounded by running tap water. After standing for twenty hours at room temperature, the resulting solution was poured slowly with stirring into 400 ml. of cracked ice and water. The solid was separated by filtration and washed with water; yield 11.5 g. when dry. Fractional crystallization of the solid from acetic acid and water mixtures eventually resulted in the recovery of approximately 1.0 g. of 2-chloro-7-methyl-8-nitroquinoline, a larger quantity (6.0 g.) of an almost colorless less basic solid melting at 121–122°, and some of a waxy, tan to brown colored substance that possessed physical properties characteristic of a mixture.

2-Chloro-7-methyl-8-aminoquinoline (VI) A.—2-Chloro-7-methyl-8-nitroquinoline (0.20 g.) in acetone containing suspended Raney nickel catalyst was reduced at 50° with hydrogen under 35–40 pounds per square inch pressure. Removal of the catalyst followed by the acetone, under reduced pressure, gave a brown-colored oil. The oil was dissolved in diethyl ether, dried with anhydrous sodium sulfate, and the ether removed by evaporation

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(6) O. L. Brady, J. N. E. Day and W. J. W. Rolt, *J. Chem. Soc.*, **121**, 528 (1922).

(7) J. D. Capps, THIS JOURNAL, **68**, 176 (1946).

(8) Temperatures of 170–180° seemed to cause decomposition of the quinolone before conversion to the 2-chloroquinoline occurred.

(9) A. Kent, D. McNeil and R. M. Cowper, *J. Chem. Soc.*, 1861 (1939).

from a dish placed over a burning 300-watt electric light bulb. The residue was dried in a desiccator over sulfuric acid (sp. gr. 1.84) at 3 mm. pressure for four hours. Upon exposure to air and standing at room temperature, long brown colored needles slowly formed.

Anal. Calcd. for $C_{10}H_9N_2Cl$: N, 14.54. Found: N, 14.62.

After dissolving some of the oil in absolute ethanol and adding an excess of hydrochloric acid (sp. gr. 1.19), the colored solution was evaporated over a burning 300-watt electric light bulb to dryness. Further heating seemed to cause some softening of the orange-yellow solid accompanied by the evolution of a small amount of a gas. The residue was dried further over sulfuric acid (sp. gr. 1.84) under 3 mm. pressure.

Anal. Calcd. for $C_{10}H_9N_2Cl \cdot HCl$: N, 12.24. Found: N, 12.47.

B.—2-Chloro-7-methyl-8-nitroquinoline (5.00 g.) dissolved in 200 ml. of 95% ethanol was treated slowly with a solution of 14.2 g. stannous chloride crystals in 25 ml. hydrochloric acid (sp. gr. 1.19) at 60–70°. After standing in atmosphere of room for five hours, the temperature was increased to 60° and the system made alkaline by the slow addition of ammonia water. Sufficient hiflo super cel was added to prevent gelatinous precipitate from clogging the filter while filtering the hot system. The solid on filter paper was extracted several times with small quantities of hot ethanol to completely remove the amine. Sulfuric acid was used to acidify the combined alcoholic extracts which were concentrated by distillation. An oil formed when the residue from distillation was made alkaline with ammonia water. The amine (oil) was extracted with diethyl ether, dried with anhydrous sodium sulfate, and the ether removed by evaporation; yield 4.5 g.

2-Chloro-7-methyl-8-nitroquinoline dissolved in absolute ethanol containing a large excess of hydrochloric acid reacted with stannous chloride at 65–70° to give a different amine. Analysis of this amine (m. p. 172–173°) for nitrogen and chlorine content gave results indicating the presence of two chlorine atoms per molecule and the benzoyl derivative (m. p. 178–179°) depressed the melting point of 2-chloro-7-methyl-8-benzamidoquinoline.

2-Chloro-7-methyl-8-benzamidoquinoline (VII).—A mixture of 1.3 g. of 2-chloro-7-methyl-8-aminoquinoline, 3.0 ml. of benzoyl chloride, and 30 ml. of 5% sodium hydroxide in water was shaken for twenty minutes. The green colored oil which settled to the bottom was separated by decantation and treated with 95% ethanol. While stirring, a solid formed that was removed by filtration and washed with 50% ethanol–water solution. Crystallization from 95% ethanol gave small, almost colorless needles that were washed on a filter with 50% ethanol–water solution followed by water. After drying at 65°, the solid melted at 172–173°.

Anal. Calcd. for $C_{17}H_{13}N_2ClO$: N, 9.44. Found: N, 9.42.

2-Chloro-7-methyl-8-quinolinearsonic Acid (VIII).—The subjection of 2-chloro-7-methyl-8-aminoquinoline to conditions similar to those used for synthesizing 7-methyl-8-quinolinearsonic acid gave 0.50 g. of flesh-colored 2-chloro-7-methyl-8-quinolinearsonic acid; decomposition began at approximately 240° and continued above 250°. Low solubility of the amine hydrochloride made diazotization in presence of cracked ice difficult. The arsonic acid was dried under reduced pressure at 118°.

Anal. Calcd. for $C_{10}H_9AsNClO_3$: As, 24.86. Found: As, 24.80.

2-Hydroxy-7-methyl-8-quinolinearsonic Acid (IX).—2-Chloro-7-methyl-8-quinolinearsonic acid (0.30 g.) was added to a solution of 0.5 g. of metallic sodium in 30 ml. of methanol and the system refluxed for sixteen hours. Upon diluting with 40 ml. of water, filtering and making acid to congo red paper by adding dilute hydrochloric acid, small, tablet-like crystals slowly formed; 0.25 g. yield. Qualitative test indicated absence of chlorine and heat caused decomposition to occur between 260 and 270°. Product was dried at 118° under reduced pressure.

Anal. Calcd. for $C_{10}H_{10}AsNO_4$: As, 26.48. Found: As, 26.50.

Treatment with 12 parts by weight of hydrochloric acid (sp. gr. 1.19) at 120–125° for two hours failed to accomplish hydrolysis of the 2-chloro-7-methyl-8-quinolinearsonic acid.

Summary

1. A solution of 7-methylquinoline in sulfuric acid (sp. gr. 1.84) reacted with nitric acid (sp. gr. 1.42) to give 67% of 7-methyl-8-nitroquinoline, 6% of a substance (m.p. 133–134°) that was shown to be neither 7-methyl-6-nitroquinoline nor 7-methyl-5-nitroquinoline, and a solid mixture that was not separated into pure components. Nitric acid (sp. gr. 1.5) converted 7-methylquinoline incompletely in the absence of sulfuric acid into the same products.

2. 2-Chloro-7-methyl-8-nitroquinoline was obtained in approximately 10% yield when 2-chloro-7-methylquinoline was nitrated with nitric acid (sp. gr. 1.42)–sulfuric acid (sp. gr. 1.84) mixture. The major nitration product (60% yield, m.p. 121–122°) seemed to be less basic than 2-chloro-7-methyl-8-nitroquinoline but was not identified.

3. 7-Methyl-8-nitroquinoline was converted into 2-chloro-7-methyl-8-nitroquinoline *via* the methyl sulfate salt and the 2-quinolone.

4. 2-Chloro-7-methyl-8-nitroquinoline and 7-methyl-8-nitroquinoline were reduced with hydrogen in the presence of Raney nickel to 2-chloro-7-methyl-8-aminoquinoline and 7-methyl-8-aminoquinoline, respectively. 2-Chloro-7-methyl-8-aminoquinoline was also obtained when 2-chloro-7-methyl-8-nitroquinoline was dissolved in 95% ethanol and treated with stannous chloride in a limited amount of hydrochloric acid (sp. gr. 1.19). When absolute ethanol, a large excess of hydrochloric acid, and a temperature of 65–70° were used for the reduction, a dichloroamine resulted as the chief product.

5. 7-Methyl-8-benzamidoquinoline and 2-chloro-7-methyl-8-benzamidoquinoline were prepared from the corresponding amines by the action of benzoyl chloride in presence of sodium hydroxide solution.

6. 7-Methyl-8-quinolinearsonic acid was synthesized from 7-methyl-8-aminoquinoline, and 2-chloro-7-methyl-8-aminoquinoline was changed to 2-chloro-7-methyl-8-quinolinearsonic acid. 2-Chloro-7-methyl-8-quinolinearsonic acid hydrolyzed to 2-hydroxy-7-methyl-8-quinolinearsonic acid.

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