

THE SYNTHESIS OF A NEW AMINO ALCOHOL
DERIVED FROM QUINAZOLINE

by

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DISCUSSION

For purposes of documentation it became necessary to prepare a series of quinazoline compounds with an amino alcohol substituent in the 5, 6, and 8 positions. This laboratory had previously synthesized such a compound with the alcohol in the 7 position (2) by the use of the Mannich reaction on a 7-acetylquinazoline. The present study deals with the synthesis of one of its isomers containing the amino alcohol substituent in the 8 position.

The two most general methods for the preparation of such compounds involve either (one) the Mannich reaction on the methyl ketone or aldehyde derivative or (two) the coupling of the bromomethyl ketone directly with the desired amine. Utilization of the latter method is generally preferred since it requires the more easily obtainable acid intermediate rather than the acetyl derivative.

In order to prepare a quinazoline with an acid, acetyl or aldehyde substituent in the 8 position one is limited to the use of 2-nitro-isophthalic acid or one of its derivatives. Two-nitro-isophthalic acid was synthesized from meta-toluidine through a series of

reactions. The toluidine was converted by the Sandmeyer reaction (3) to m-tolunitrile which on acid hydrolysis gave an almost quantitative yield of m-toluic acid. The latter was nitrated according to E. Muller's directions (6) giving a mixture of 2, 4, and 6-nitro-m-toluic acids. The majority of the desired 2 isomer was easily separated from the others. The 4 and 6 isomers yield identical oxidation products and could possibly be used for the preparation of an amino alcohol of quinazoline with the desired substituent in the 6 position.

Two-nitro-m-toluic acid was readily oxidized in good yield to the nitro-isophthalic acid. The nitro compound was reduced to 2-amino-isophthalic acid catalytically using 2 atmospheres of hydrogen with PtO_2 or 10% Pd on charcoal catalyst and by the use of stannous chloride and hydrochloric acid at 80-90°. The latter method has the advantage of being applicable to larger quantities. Scott and Cohen (10) report the stannous chloride reduction as being run in the cold. In this laboratory the reaction was found to proceed much more satisfactorily and in about 90% yields at the elevated temperature.

The 2-amino-isophthalic acid was then heated with formamide at about 130° (7) to give about a 50% yield

of 4-hydroxy-8-quinazolinecarboxylic acid. The acid chloride hydrochloride was prepared by treatment of the acid with thionyl chloride. Lange and co-workers (5) have shown that under the conditions used the OH group is not affected.

The acid chloride reacted quite rapidly with diazomethane in a benzene solution to form a benzene soluble diazo ketone while at the same time it also methylated the hydroxyl group. The diazo ketone was converted directly into the bromomethyl ketone by the use of dry hydrogen bromide. It was necessary to avoid an excess of the hydrogen bromide to prevent the formation of the hygroscopic hydrobromide of the bromomethyl ketone. The latter immediately turned to a dark oil on exposure to the air. Attempts to couple the bromomethyl ketone with dimethyl amine, morpholine and piperidine were not successful. In the cases of the latter two, it appeared a reaction took place but the solution almost immediately turned very dark and it was not possible to isolate any of the desired product.

Gilman and Nelson (4) report a method for converting an acid chloride into a methyl ketone by the use of dimethyl cadmium. A similar reaction was carried out on the quinazolinecarboxylic acid chloride but there was no yield of its ketone derivative. There were

indications that the acid chloride had reverted back to an acid.

Since both the coupling experiments and the attempt to convert the quinazolinecarboxylic acid chloride directly into an acetylquinazoline had failed another approach was tried. Either 1,3-diacetyl-2-nitrobenzene or 2-nitro-isophthalaldehyde would be desirable intermediates to produce a quinazoline nucleus containing an aldehyde or an acetyl group in the 8 position. The 2-nitro-isophthaloyl chloride seemed to be a convenient starting intermediate.

The di-acid chloride of 2-nitro-isophthalic acid was prepared by heating the acid with an excess of phosphorus pentachloride and phosphorus oxychloride. The acid chloride was isolated in good yields and in a fairly pure condition by pouring the warm reaction mixture into an ice-water mixture. The cadmium alkyl reaction failed to produce the desired diacetyl compound. The sodium aceto acetic ester condensation (9) with the di acid chloride also failed to give the diacetyl compound. According to the Rosenmund method of reduction (8) it is possible to reduce certain acid chlorides to the aldehyde with a palladium catalyst. Reduction of the 2-nitro-isophthaloyl chloride with the palladium catalyst gave a compound which is probably

isomeric with one described by Suida (11). When this worker treated a solution of nitro-terephthaldehyde in xylene with sunlight he obtained 2-nitroso-4-formylbenzoic acid. The compound obtained in this case has entirely similar properties. It can not be purified by recrystallization due to its insolubility in the ordinary organic solvents. Attempts to purify it by dissolving in soda solution and reprecipitating with sulfuric acid resulted in decomposition.

The 2-nitro-isophthaloyl chloride, however, reacted readily with diazomethane in benzene solution. The diazo ketone which was formed was not stable and hence was immediately decomposed by suspending in ether and treating with 48% hydrobromic acid. The bromo methyl ketone which was formed in excellent yield was, however, stable.

Reduction of the 1,3-di-bromoacetyl-2-nitrobenzene with stannous chloride and hydrochloric acid at 80-90° gave 2-amino-1,3-diacetylbenzene in about 90% yields. Christensen, et al. (2) were able to acylate the isomer (2-amino-1,4-diacetylbenzene) with acetic anhydride and pyridine in the cold. Under similar conditions with 2-amino-1,3-diacetylbenzene there was no reaction. At 140° with acetic anhydride the compound was acylated in about a 30% yield. Carrying the reaction out in a sealed

tube with acetic anhydride or using ketene as the acylating agent failed to increase the yield.

Bischler and Burkart (1) prepared 2,4-dimethylquinazoline by treating 2-acetylamino-acetophenone with alcoholic ammonia in a bomb at 130° for seven hours. A similar cyclization under more mild conditions with 2-acetylamino-1,3-diacetylbenzene produced 8-acetyl-2,4-dimethylquinazoline. The yields varied from 20 to 40% with the lower yields predominating. No explanation can be given for this.

A Mannich reaction on the acetylquinazoline with dimethylamine hydrochloride and aqueous formaldehyde gave about a 40% yield of the amino ketone. Reduction of the ketone with palladium on charcoal catalyst at 2 atmospheres of hydrogen pressure gave a product which was very hygroscopic. Analysis was not attempted on this compound. Rather it was converted to the dipicrate and analyzed as such.

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EXPERIMENTAL

2-Nitro-isophthalic acid.--The mixture 70 g. (0.44 mole) of potassium permanganate, 24 g. (0.44 mole) of potassium hydroxide, 700 cc. of water and 39 g. (0.22 mole) of 2-nitro-m-toluic acid was placed in a one liter three-necked flask equipped with a Trubore stirrer and a condenser. The mixture was stirred on a steam bath until all of the permanganate had disappeared. This usually required between two and two and one-half hours. The cooled liquid was filtered from the brown manganese dioxide and the latter washed with water. While the yellowish green filtrate was being stirred about 150 cc. of 6 N hydrochloric acid were slowly added to it. The precipitated white solid was filtered and washed with a little water. Air dried, it weighed 38 g. (87 percent yield).

Analysis calculated for $C_8H_5NO_6$: Neutral equivalent, 105.5. Found: Neutral equivalent, 107.

2-Amino-isophthalic acid.

Stannous chloride reduction:--2-Nitro-isophthalic acid (33 g.) was slowly added to a stirred solution of 140 g. of stannous chloride dihydrate in 370 cc. of concentrated hydrochloric acid. The mixture was heated with stirring on a hot water bath for three hours. A little hydrochloric acid was added from time to time

to keep the volume constant. At the end of the three hours there remained in the flask a white solid. The mixture was cooled and poured with stirring into one liter of water. The resulting light yellow solid was filtered and washed with water. It weighed 25 g. (88.5 percent yield).

Analysis calculated for $C_8H_7NO_4$: Neutral equivalent, 90.5. Found: Neutral equivalent, 90.5.

Catalytic reduction:--Five grams of 2-nitro-isophthalic acid were dissolved in 100 cc. of 95% ethyl alcohol and reduced with hydrogen at 30 pounds pressure using either platinum oxide catalyst (50 mg.) or 10% palladium on charcoal catalyst (200 mg.). The theoretical amount of hydrogen had been taken up in about one hour. Another 100 cc. of alcohol were added and the mixture brought to boiling and filtered, thus separating the catalyst. Cooling the filtrate yielded 3.0 g. of yellow crystals. By diluting the filtrate with an equal volume of water another 0.4 g. of the product was obtained. The total yield was 79.5 percent of theoretical.

Analysis calculated for $C_8H_7NO_4$: Neutral equivalent, 90.5. Found: Neutral equivalent, 89.5.

4-Hydroxy-8-quinazolinecarboxylic acid.--Eleven grams of 2-amino-isophthalic acid and 20 cc. of

formamide were heated in an oil bath under a reflux condenser at a temperature of about 130° for seven hours. After cooling, the solid mass was treated with 100 cc. of water and filtered. The residue was mixed well with another 100 cc. of water, filtered and washed several times with water. Air dried, the light yellow solid weighed 5.5 g. (47.5 percent). A neutral equivalent on this material indicated only 95% purity. A sample for analysis was prepared by recrystallization from water with the aid of charcoal. The light yellow crystals melted at 310-315° with decomposition.

Analysis calculated for $C_9H_6N_2O_3$: C, 56.85; H, 3.18; N, 14.73; Neutral equivalent, 190. Found: C, 56.98, 57.10; H, 3.75, 3.64; N, 14.54; Neutral equivalent, 187.

4-Hydroxy-8-quinazoline acid chloride hydrochloride.--4-Hydroxy-8-quinazolinecarboxylic acid (4.3 g.) was refluxed for two hours with 45 cc. of thionyl chloride. At no time did complete solution result. After cooling the mixture, it was filtered and washed with several portions of dry ether and then dried in a vacuum desiccator over sodium hydroxide. There were obtained 4.8 g. of a light yellow, very finely divided crystalline solid which was insoluble in the ordinary inert solvents such as a chloroform, carbon tetrachloride

and benzene. Attempts to recrystallize it were unsuccessful.

Analysis of the crude material calculated for $C_9H_6Cl_2N_2O_2$: Cl, 29.0. Found: Cl, 27.0.

8-Bromoacetyl-4-methoxyquinazoline.--To 180 cc. of a cold benzene solution of diazomethane (0.125 mole) were added in portions and with stirring 4.0 g. (0.016 mole) of 4-hydroxy-8-quinazoline acid chloride hydrochloride. There was an immediate evolution of a gas and the solution turned from yellow to orange during the two hours it was allowed to warm to room temperature. There was filtered from the reaction mixture 0.9 g. of material with a low chloride content. It was not identified. The filtrate was treated in portions with dry hydrogen bromide. Care was taken that the gas delivery tube did not come into contact with the solution and also that an excess of the hydrogen bromide was not used. Either of these things caused the formation of the hydrobromide which turned to a dark gummy substance on exposure to the air. A total of 2.6 g. (57 percent yield) of crude material were obtained. Because of solubility characteristics, the crude material was not easily purified by recrystallization. A sample was prepared for analytical purposes by dissolving the crude product in acetone, treating with charcoal, filtering

and then adding heptane which precipitated a flocculent light yellow precipitate. The material melted from 165-185° with decomposition.

Analysis calculated for $C_{11}H_9BrN_2O_2$: Br, 28.5; N, 9.96. Found: Br, 28.5; N, 9.90.

2-Nitro-isophthaloyl chloride.--Twenty five grams of 2-nitro-isophthalic acid, 100 g. of phosphorus pentachloride, and 40 cc. of phosphorus oxychloride were heated under gentle reflux for ten hours. A light colored product was most easily obtained if the phosphorus pentachloride was added to the reaction flask first followed by the other two constituents. The mixture was then very gently heated until the reaction started. Soon after the reaction started the mixture turned almost entirely to a liquid. At the end of the ten hours refluxing the warm reaction mixture was slowly poured onto about 900 g. of cracked ice. The mixture was continually stirred until all of the phosphorus pentachloride was destroyed. Care was taken that an excess of ice was always present. The light yellow solid was filtered, washed well with water and dried in a vacuum desiccator over sodium hydroxide. A chloride analysis on the crude acid chloride (27.1 g., 92 percent yield) indicated about 93% purity. The acid chloride was recrystallized for analytical purposes from heptane

with the aid of charcoal to give a white crystalline solid, m.p. 125-127°.

Analysis calculated for $C_8H_5Cl_2NO_4$: Cl, 28.6; N, 5.64. Found: Cl, 28.0; N, 6.10.

1,3-Di-bromoacetyl-2-nitrobenzene.--Twenty five grams (0.10 mole) of finely powdered 2-nitro-isophthaloyl chloride were added in portions to a 900 cc. of a stirred cold benzene solution of diazomethane (0.625 mole). There was an immediate evolution of a gas. After all of the acid chloride had been added, the ice bath was removed and stirring continued for another hour. The cream colored diazo ketone was filtered from the reaction mixture, washed with a little benzene but not sucked dry since it readily discolored. It was immediately suspended in about 300 cc. of ether and was decomposed while the mixture was being stirred by the addition in portions of 50 cc. of 48 percent hydrobromic acid. After the evolution of nitrogen had ceased, which usually required about an hour, the white fluffy solid was filtered and washed well with water. After drying in a vacuum desiccator over sodium hydroxide the 1,3-di-bromoacetyl-2-nitrobenzene weighed 31.3 g. (84 percent yield). It was recrystallized from either heptane or chloroform to give a white silky solid, m.p. 143°.

Analysis calculated for $C_{10}H_7Br_2NO_4$: Br, 43.8;

N, 3.83. Found: Br, 44.5; N, 4.23.

2-Amino-1,3-diacetylbenzene.--Fifteen grams of 1,3 di-bromoacetyl-2-nitrobenzene were added in portions to a mechanically stirred solution of 75 g. of stannous chloride dihydrate in 200 cc. of concentrated hydrochloric acid. After the addition of all of the compound the mixture was heated on a water bath with stirring for two and one-half hours. The solid almost completely dissolved to give a light red solution. After cooling, the mixture was filtered from a small amount of impurity and poured with good stirring into 1100 cc. of water. A yellow precipitate immediately settled, which was filtered and washed with water. Air dried at 60°, it weighed 6.4 g. (88 percent yield). A sample recrystallized from water with the aid of charcoal melted at 143-145°.

Analysis calculated for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.92; H, 6.50; N, 7.58.

2-Acetylamino-1,3-diacetylbenzene.--Two grams of 2-amino-1,3-diacetylbenzene were heated under reflux in an oil bath with 10 cc. of acetic anhydride at 140° for one and one-half hours. At the end of this time there remained an almost black solution. The solution was poured into 100 cc. of an ice-water mixture and allowed to stand for an hour. The mixture was filtered and the

filtrate evaporated to dryness on a steam bath leaving a very dark red viscous mass. The latter was extracted thoroughly with three 40 cc. portions of warm ether. Each time the ether was filtered from the dark residue. The ether was taken by reduced pressure leaving 1.13 g. of crude product. This solid was dissolved in 60 cc. of hot Skelly L, treated with charcoal and filtered. Cooling yielded 0.84 g. (34 percent yield) of very light yellow crystals, m.p. 101-103°.

Analysis calculated for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.17; H, 6.27; N, 6.02.

8-Acetyl-2,4-dimethylquinazoline.--A solution of 2-acetylamino-1,3-diacetylbenzene (1.2 g.) in 125 cc. of cold saturated ammoniacal alcohol was heated in a bomb at 105° for one hour. The alcohol was evaporated using reduced pressure. The residue (sometimes a light yellow orange solid, other times a red oil) was almost completely dissolved in 100 cc. of water, treated with charcoal and cooled. Crystallization was very slow. The yield of white fibers varied from 0.25 g. (23 percent yield) to 0.50 g. (46 percent yield). Usually another small crop of crystals could be obtained by concentrating the mother liquor. The crystals melted at 97-98°.

Analysis calculated for $C_{12}H_{12}N_2O$: C, 71.97; H, 6.04; N, 13.99. Found: C, 72.09; H, 6.37; N, 13.75.

8-(3-Dimethylamino-1-oxopropyl)-2,4-dimethylquinazoline hydrochloride.--A solution of 8-acetyl-2,4-dimethylquinazoline (1.0 g., 0.005 mole), dimethylamine hydrochloride (0.43 g., 0.005 mole), and 0.37 cc. of 40 percent formaldehyde solution (0.005 mole) in 25 cc. of absolute ethyl alcohol was shaken for four and one-half hours at room temperature. Twenty cubic centimeters of dry ether were added and the solution placed in the refrigerator overnight. Four-tenths of a gram of a yellow powder was obtained. Concentration of the filtrate and addition of more ether gave another 0.3 g. The total yield of almost pure product was 41 percent. The product was recrystallized from a small amount of isopropyl alcohol and melted at 131-133°.

Analysis calculated for $C_{15}H_{20}ClN_3O$: Cl, 12.07
N, 14.30. Found: Cl, 11.96; N, 14.44.

8-(3-Dimethylamino-1-hydroxypropyl)-2,4-dimethylquinazoline hydrochloride.--8-(3-Dimethylamino-1-oxopropyl)-2,4-dimethylquinazoline hydrochloride (0.4 g.) was dissolved in 25 cc. of methyl alcohol. Ten percent palladium on charcoal catalyst (0.2 g.) was added and the compound was reduced at two atmospheres of hydrogen pressure and at room temperature. After two hours of shaking in the hydrogenation apparatus the catalyst was filtered and the alcohol was evaporated under reduced

pressure. The residue was a light yellow viscous liquid. Drying at 50° in a good vacuum gave a light yellow plastic solid which was very hygroscopic. A melting point could not be obtained for the compound.

The di-picrate of the amino alcohol was prepared from an ether solution of the free base and ethereal picric acid. The resulting precipitate after being washed with ether and dried, melted at 92-94°.

Analysis calculated for $C_{27}H_{27}N_9O_{15}$: C, 45.20; H, 3.79; N, 17.57. Found: C, 45.62; H, 3.81; N, 17.25.

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SUMMARY

4-Hydroxy-8-quinazolinecarboxylic acid was prepared from 2-amino-isophthalic acid by reaction with formamide. Application of the Arndt-Eistert synthesis to the carboxylic acid chloride gave 8-bromoacetyl-4-methoxyquinazoline. Attempts to couple the latter with several secondary amines failed. The use of the cadmium alkyl reaction on the carboxylic acid chloride was also not successful.

Chlorination of 2-nitro-isophthalic acid gave 2-nitro-isophthaloyl chloride. Use of the Arndt-Eistert synthesis on the acid chloride gave 1,3-di-bromoacetyl-2-nitrobenzene. Reduction of this compound with stannous chloride gave 2-amino-1,3-diacetylbenzene. Acylation of this compound followed by cyclization in the presence of ammonia produced 8-acetyl-2,4-dimethylquinazoline. By the use of the Mannich reaction on the acetyl quinazoline followed by catalytic reduction, 8-(3-dimethylamino-1-hydroxypropyl)-2,4-dimethylquinazoline was synthesized.

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