AN ABSTRACT OF THE THESIS OF

Ferdinand Power Konrad for the M.S. in Chem.
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Title The Synthesis of 2 methyl-1, 4 dihydro-quinazoline

Abstract Approved Redacted for privacy
(Major Professor)

2 methyl-1, 4 dihydro quinazoline is synthesized in a three step process starting with anthranilic acid. The anthranilic acid is reduced electrolytically to O-amino benzyl alcohol. The alcohol is acetylated with a 100 percent excess of acetic anhydride to form O-acetamino benzylacetate which is separated from a mixture of acetylated products by fractional crystallization out of petroleum ether. The O-acetamino benzylacetate is condensed with alcoholic ammonia at a pressure of 2,000 p.s.i. and a temperature of 170°-180° to give 2 methyl-1, 4 dihydroquinazoline. Derivatives of the quinazoline were prepared and analyzed in order to identify the compound. Oxidation of the methyl quinazoline, undertaken with the intent to form quinazoline carboxylic acid, caused a ring rupture and the subsequent formation of a mono-nitrogen acid.

THE SYNTHESIS OF
2 METHYL-1, 4 DIHYDRO-QUINAZOLINE

by

FERDINAND POWER KONRAD

A THESIS

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APPROVED:

Redacted for privacy

Professor of Chemistry

In Charge of Major

Redacted for privacy

Chairman of Department of Chemistry

Redacted for privacy

Chairman of School Graduate Committee

Redacted for privacy

Chairman of State College Graduate Council

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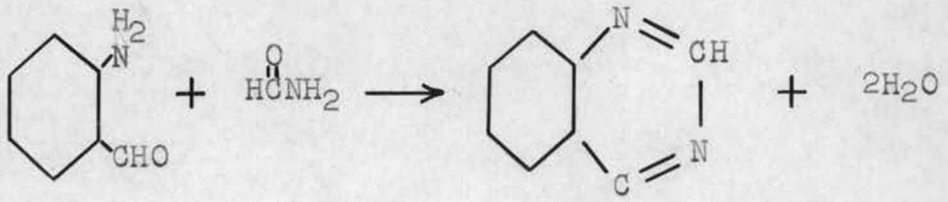
INTRODUCTION

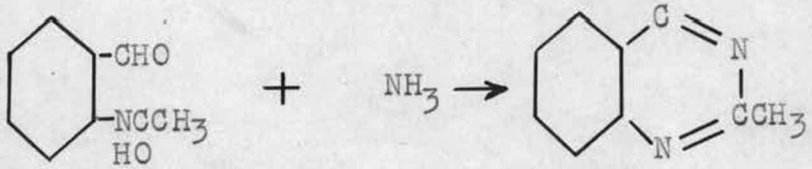
This laboratory has been very interested in the problem of devising a method for synthesizing quinazoline carboxylic acid, a compound which is not described in the literature. One method which immediately suggests itself is the conversion of 2-methyl quinazoline to the acid by the usual oxidation procedures. The problem then centers about a practical method of making this intermediate in sufficient quantities for research purposes. The methods described in the literature for making 2-methyl quinazoline could not be used because the intermediate compounds employed, O-amino benzaldehyde and O-amino benzyl acetamide are not available and there is no satisfactory method for synthesizing them. Therefore a new method of making 2-methyl quinazoline, using some readily obtainable material, had to be devised. In the method described herein, the starting material is anthranilic acid, readily available in any quantities. It is converted to 2, methyl 1, 4 dihydro quinazoline by the three step process in 41% yield.

The general methods given in the literature for making quinazolines involve a condensation of ammonia or formamide with N-substituted O-amino-benzaldehydes, and benzo-ketones; also by the elimination of a molecule of water from N-substituted O-aminobenzylamines. Keto-quinazolines, the

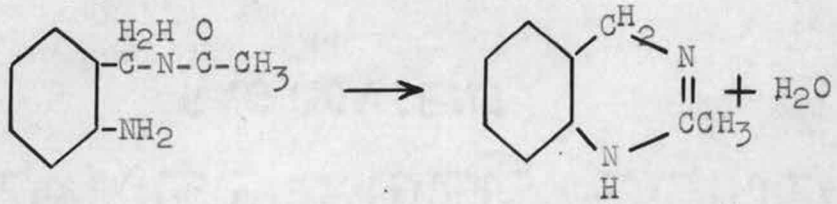
quinazolones, are formed by the reaction of formamide with anthranilic acid. These possess both feeble phenol and basic characters, hence can be regarded as hydroxy-quinazolines. Quinazoline with no substituted groups on it is made by a ring condensation of the first type, treating O-amino-benzaldehyde with formamide: (6)



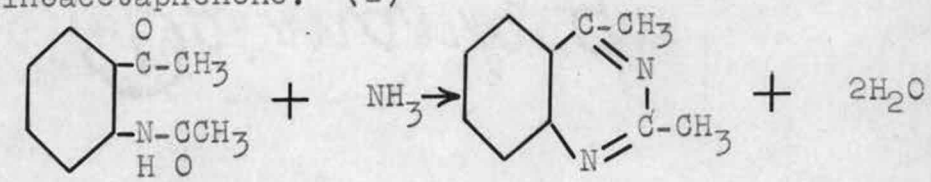
2, methyl quinazoline is produced when O-acetaminobenzaldehyde is treated with alcoholic ammonia: (1)



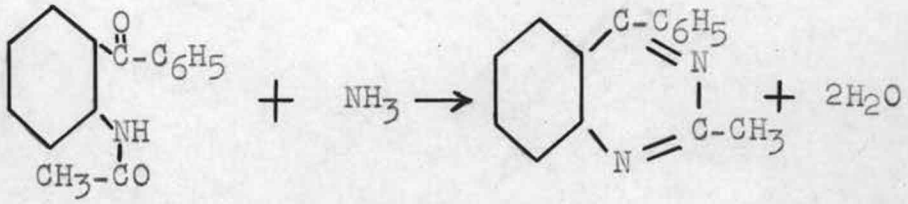
By heating O-aminobenzylacetamide to 200° to drive off one molecule of water 2, methyl-1, 4 dihydroquinazoline is produced: (4)



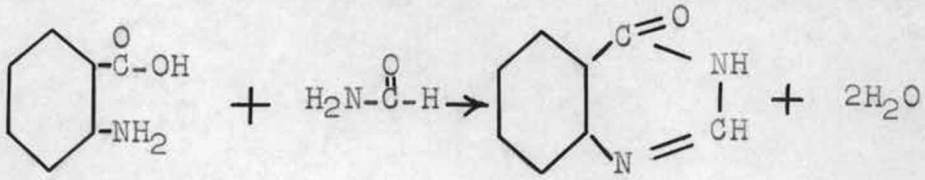
Dimethyl quinazoline results when ammonia condenses with O-acetaminoacetaphenone: (2)



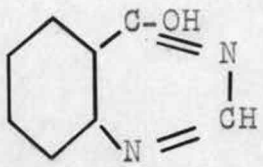
O-acetaminobenzophenone gives a methyl phenyl substituted quinazoline: (1)



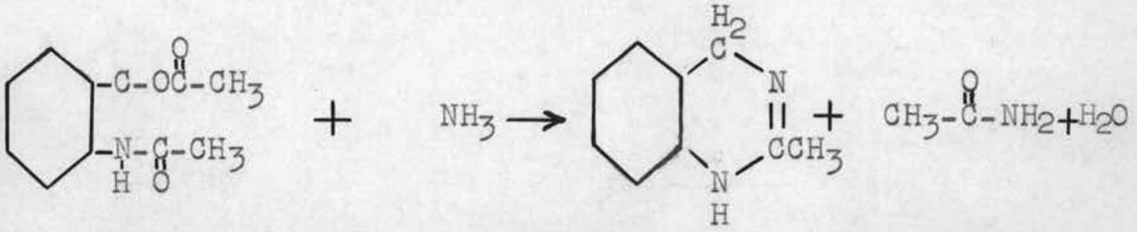
Anthranilic acid with formamide gives quinazolone: (6)



This can also be considered as hydroxy quinazoline: (6)



All these methods of synthesis present two difficulties, either the condensing intermediates are too difficult to obtain or, as in the case with anthranilic acid, quinazalones are produced. An intermediate, one which had never been condensed before, solved both of these difficulties. It is O-acetamino benzylacetate - - easily made in 68 percent yield from anthranilic acid by first reducing the acid electrolytically to O-amino benzyl alcohol and then acetylating this alcohol with acetic anhydride. The anilide so formed is then condensed at high temperature and pressure with alcoholic ammonia:



In the electrolytic reduction of anthranilic acid, Coleman(3) reports a 78 percent yield of alcohol after 60-70 ampere-hours. This yield was duplicated, but the reaction time had to be doubled. Beyond 120 ampere-hours the yield again decreases owing to the formation of resin-like polymerization products. To obtain a pure product from the reduction mass, the amino benzyl alcohol is re-crystallized out of petroleum ether. Coleman recommends a petroleum ether fraction of 65°-75°; but the alcohol has such a limited solubility in this low-fraction, that extremely large amounts are necessary. However, a fraction boiling at 105°-110° was used, in which the alcohol is about 8 times more soluble. It was just as selective -- giving a white crystalline product with the same melting point as that obtained from the low-boiling fraction.

The second step, the acetylation of O-amino benzyl alcohol, is carried out with a hundred percent excess of acetic anhydride, to form the di-substituted derivative O-acetamino benzylacetate. The acetylation does not give solely the di-substituted product but a mixture of mono-, di- and tri-. Widman (6) merely states that if the reaction is carried out in the cold, then the mono- is formed,

O-acetaminobenzyl alcohol; and that refluxing for a short time yields the di-, while refluxing for a longer time results in the tri-, di-acetamino benzylacetate. Numerous runs were made to determine the actual time necessary to obtain the best yield of the desired di-acetylated product. Yields ranged from 40 to 88% with a variation in refluxing times of no more than 10 minutes. In the separation of these products, for which no method is given in the literature, fractional crystallization out of petroleum ether was found to be the best. Other solvents were tried, but they gave practically no separation whatsoever.

In the third step, the condensation, the amount of reactants used is based on the solubility of ammonia in absolute alcohol at 0° and noting that two ammonia molecules react with one of the anilide. The ammonia is used in 100 percent excess. The quinazoline is separated from acetamide, formed during the reaction, by precipitating quinazoline hydrochloride. The best yield obtained under various conditions of pressure, temperature and time for this step was approximately 60%. Below 115° practically no condensation takes place, while above 180° the increase in polymerization products lowers the yield.

Due to the presence of impurities the nitrogen content of the quinazoline was 1.5% below the theoretical

value; therefore, derivatives, prepared and analyzed to prove the identity of the 2-methyl 3, 4 dihydroquinazoline, were the hydrochloride, the picrate, the chlorophatinate and the dichromate.

Oxidation with potassium permanganate gave a nitrogen containing acid, but its neutralization equivalent and nitrogen content did not agree with that of quinazoline carboxylic acid. Apparently potassium permanganate was too vigorous an oxidizing agent, because, according to the analysis, the ring was broken, even when the oxidation was carried out in the cold.

EXPERIMENTAL

Reduction:

The reduction (3) of the anthranilic acid is carried out in four cells connected in series. Each cell consists of a one liter beaker, a porous cup, a mechanical stirrer, and sheet lead electrodes each having a total surface area of 100 sq. cm. In each porous cup, the anode is placed 200 cc. of 15% sulfuric acid. In the cathode space of each cell are placed 25 g (0.18 mol.) of anthranilic acid and 400 cc. of 15 percent sulfuric acid. The cells are connected in series with an ammeter and a suitable resistance also in the circuit. The stirrers are

started, the current (110 volts D.C.) turned on, and the resistance so adjusted that the ammeter records 10-12 amperes. The temperature of the solution in the cells is maintained at 20°-30° by surrounding them with a bath of cool water. The reduction is complete after 120 ampere-hours. This fact is indicated by the increased evolution of hydrogen and the complete solution of the anthranilic acid.

The cathode liquid is removed from the cells and neutralized with solid ammonium carbonate or concentrated aqueous ammonia. The solution is filtered to remove any resinous material, then saturated with ammonium sulfate and extracted with five 80 cc. portions of chloroform. Ether can also be used as the extracting agent, but the benzyl alcohol is not so soluble in it as in chloroform. The chloroform solution is dried with 20 g. of anhydrous sodium or magnesium sulfate; filtered, and the chloroform distilled off. The yield of O-aminobenzyl alcohol obtained from the four cells is 62-70 g.; 69-78 percent of theoretical amount. This product has a light brown color and melts at 75°-80°. After one recrystallization from petroleum ether the melting point is 80°-81°. Petroleum ether, boiling at 105°-110°, is used.

Acetylation:

This O-amino-benzyl alcohol is acetylated (6) with a hundred percent excess of acetic anhydride. One mole (123 g.) of the alcohol is placed in a 500 cc. erlenmyer with four moles (408 g.) of acetic anhydride, and refluxed for 20 minutes. The contents are then transferred to a liter beaker and the excess acetic anhydride decomposed by cautiously adding a saturated solution of sodium carbonate. The light brown solid which precipitates out is filtered off and washed with cold water. The filtrate is extracted with four 100 cc. portions of chloroform; the chloroform distilled off and the residue combined with the light-brown solid from the first filtration. The solid is recrystallized out of petroleum ether (105°-110°), to give white crystals of O-acetaminobenzylacetate with a melting point of 91°.

Condensation:

The condensation of the anilide is carried out in the bomb with a 100 percent excess of ammonia dissolved in absolute ethyl alcohol. 100 g. of alcohol in an erlenmeyer are saturated at 0° with ammonia (approximately 1.5 moles dissolving) transferred to the bomb and 72 g. (0.37 moles) of O-acetaminobenzylacetate added. The bomb is

sealed and the temperature control set at 170°-180°, generating a pressure of about 2,000 p.s.i. The reaction is complete after 16 hours. After which time the contents of the bomb are removed, the alcohol and excess ammonia distilled off, and 200 cc. of water added to the residue. The oil which thereupon settles to the bottom, constituting about 65% of the total yield of quinazoline, is filtered off and the filtrate extracted with four-50 cc. portions of benzene. The benzene is dried with 25 g. of anhydrous sodium sulfate, saturated with gaseous HCl and the precipitated quinazoline hydrochloride filtered off. The hydrochloride is dissolved in 25 cc. of water, neutralized with 28% ammonium hydroxide and the free base extracted with four-25 cc. portions of benzene. The benzene is distilled off, leaving the quinazoline as a clear yellow oil.

Derivatives:

Yellow crystals of the quinazoline picrate were precipitated out of a 10% solution of picric acid in acetone. The picrate, corresponding to the formula $C_6H_2OH(NO_2)_3 \cdot C_9H_{10}N_2$, melted at 185°. A micro-Dumas determination gave a nitrogen content of 18.42 percent; the theoretical content is 18.01 percent. The characteristic red crystals

of quinazoline dichromate were precipitated in the cold out of a 10% solution of potassium dichromate in water. Crystals of quinazoline hydrochloride were made by dissolving five grams of the quinazoline in 25 cc. of dilute HCl, evaporating to dryness on the steam bath, and recrystallizing twice out of methanol. Ionizable chloride determination gave a chlorine content of 19.70 percent; the theoretical chlorine content is 19.43 percent. A Dumas on this hydrochloride gave 15.61 percent nitrogen; the theoretical value is 15.42 percent. The chloroplatinate, $(C_9H_{10}N_2)_2PtCl_6$, was made by reacting two parts of quinazoline with two parts of HCl and one part of platinic chloride. A micro-muffle determination gave a platinum content of 27.58 percent, and a Dumas determination gave a nitrogen content of 8.12 percent; the theoretical values in the two cases being 27.80 percent and 8.10 percent respectively.

Oxidation:

For the oxidation, 2 g. of quinazoline were dissolved in 40 cc. of water in an erlenmeyer flask, 3.6 g. of $KMnO_4$ were added and the flask was placed in an ice bath. The reaction was complete after two hours, as seen by the disappearance of the $KMnO_4$. The MnO_2 was filtered off and

to the filtrate was added a 10% solution of neutral lead acetate, immediately precipitating the lead salt of the acid. Lead acetate was added until no more precipitation occurred. The precipitated lead salt was filtered off, washed with water, suspended in 40 cc. of water in an erlenmeyer and then saturated with H_2S. The lead sulfide was filtered off and the filtrate evaporated to dryness on the steam bath, leaving a light brown crystalline mass. The acid thus isolated had a neutral equivalent of 152 and a nitrogen content of 6.70%.

CONCLUSION

A new method for synthesizing 2 methyl 1, 4 di-hydro quinazoline has been developed. The compound was identified by the preparation and analysis of several derivatives. In attempts to oxidize the methyl quinazoline to quinazoline carboxylic acid, $KMnO_4$ was found to be too vigorous an oxidizing agent. According to the low nitrogen content of the acid formed, the ring must have been ruptured and one of the nitrogens split off.

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