

A STUDY OF THE PROPERTIES OF THE 2- AND  
4-METHYL SUBSTITUTED QUINAZOLINES

by

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A THESIS

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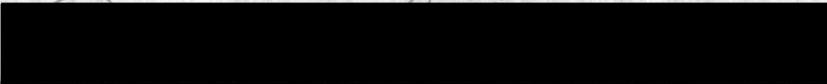
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A STUDY OF THE PROPERTIES OF THE 2- AND  
4-METHYL SUBSTITUTED QUINAZOLINES

For the past ten years there has been a great deal of interest in the physiological properties of the amino alcohols of the various nitrogen heterocycles (3, p.384; 8, p.1294; 11, p.401; 13, p.1813; 16, p.2186; 17, p.736). This has led to the development of synthetic procedures for the preparation of typical compounds which in turn have been tested for anti-malarial activity, pressor action, etc. In the course of this work, a number of amino alcohols of the quinazoline series (7, p.2001; 10, p.4061) were synthesized. This was accomplished by first preparing the acetyl-2,4-dimethylquinazoline intermediate and then converting it to an amino alcohol via the Mannich reaction. In each such instance, it was not possible to isolate a Mannich product from the reaction mixtures obtained by following the usual procedures as described for the condensation of methyl ketones (1, p.329). Only when aqueous formaldehyde was used in place of paraformaldehyde and the temperature maintained at approximately 25° was it possible to isolate such a product. Because of the unusually mild conditions of the reaction, it appeared likely that one of the methyl groups might have reacted, and hence it was not possible to assign definite structures to these amino alcohols. In view of this behavior, it was decided to investigate the 2- (and 4-) methyl substituted

quinazolines for methylenic character.

The methyl substituent in 2- (and 4-) methylquinazolines are members of entirely different structural units. The 2-methyl substituent is part of an amidine structure  $C-C \begin{matrix} \text{N}^- \\ \text{N}^+ \end{matrix}$  while the 4-methyl substituent is a typical ketimine  $-C \begin{matrix} \text{N}^- \\ \text{CH}_3 \end{matrix}$  which may well impart methylenic character to the 4-methyl substituent. The 4- position in the quinazoline compounds has been found by Tomisek and Christensen (19, p.2112) to be extremely reactive. Furthermore, similar structural units occurring in  $\alpha$ -picoline (9, p.1243; 12, p.95), 2-methylquinoline (9, p.1242; 15, p.2727) and 1- (and 3-) methylisoquinoline (15, p.2726; 6, p.1094) have been reported as having methyl substituents sufficiently active to undergo condensation reactions.

2-Methylquinazoline (5, p.1933) and 2,4-dimethylquinazoline (4, p.1350) were prepared for these studies by well known procedures. 4-Methylquinazoline was obtained through the formylation of o-aminoacetophenone which product in turn was cyclized to 4-methylquinazoline. As had been surmised, the methyl substituent in 2-methylquinazoline was sufficiently unreactive that it did not form condensation products with dimethylamine hydrochloride and aqueous formaldehyde; on the other hand, both the 4- and 2,4-dimethylquinazolines yielded the Mannich condensation products. In order to confirm the structure

assigned to the reaction product of 2,4-dimethylquinazoline, this derivative was subjected to hypobromite oxidation. This yielded a compound which was found to be identical to 2-methyl-4-quinazalone. When 2,4-dimethylquinazoline was subjected to a similar oxidation, it gave a white crystalline compound which was identified as 2-methyl-4-tribromomethylquinazoline; this compound on further treatment in hypobromite solution yielded in turn 2-methyl-4-quinazalone. Attempts to condense 4-methylquinazoline with benzaldehyde in the presence of zinc chloride gave tars from which no pure products could be isolated. This latter reaction at least confirmed the reactive properties of the 4-methyl substituent.

Although this laboratory has prepared the 7- (and 8-) acetyl-2,4-dimethylquinazolines (7, p.2001; 10, p.4061) and had failed to obtain the 5-acetyl (20, p.1440), it was decided to prepare the 6-acetyl isomer in order to complete the series and to obtain material for comparison with the unacylated methyl substituted quinazolines. The starting material for this sequence of reactions was m-tolunitrile which was converted to m-toluic acid and then to 4-nitro-m-toluic acid by well established procedures.

Permanganate oxidation of 4-nitro-m-toluic acid gave low yields; however, by changing to a dichromate oxidant in an 80% sulfuric acid medium and using the

procedures given by Magidson (14, p.869) and later modified by Albert (2, p.54T) for the oxidation of 2-chloro-4-nitrotoluene, reasonable yields of 4-nitro-isophthalic acid were obtained.

Treatment of the 4-nitroisophthalic acid with phosphorous pentachloride and phosphorous oxychloride mixtures gave the corresponding phthalylchloride which was converted to 1-amino-2,4-diacetylbenzene by means of a procedure which Isensee successfully used to make 2-amino-1,3-diacetylbenzene (10, p.4061). This process involved the use of diazomethane to form the bromomethyl ketone which was then reduced with stannous chloride. These operations give much better yield than the older methods described by Ruggli and Gassenmeier (18, p.496). Acylation of 1-amino-2,4-diacetylbenzene followed by cyclization yielded the final product 6-acetyl-2,4-dimethylquinazoline (see Fig. 1).

A hypobromite oxidation of 6-acetyl-2,4-dimethylquinazoline gave an acid which probably is 6-carboxy-2-methyl-4-quinazalone.

The 6-acetyl-2,4-dimethylquinazoline when subjected to the Mannich reaction under similar conditions as those used on the 7- (and 8-) acetyl isomer likewise yielded a Mannich product.

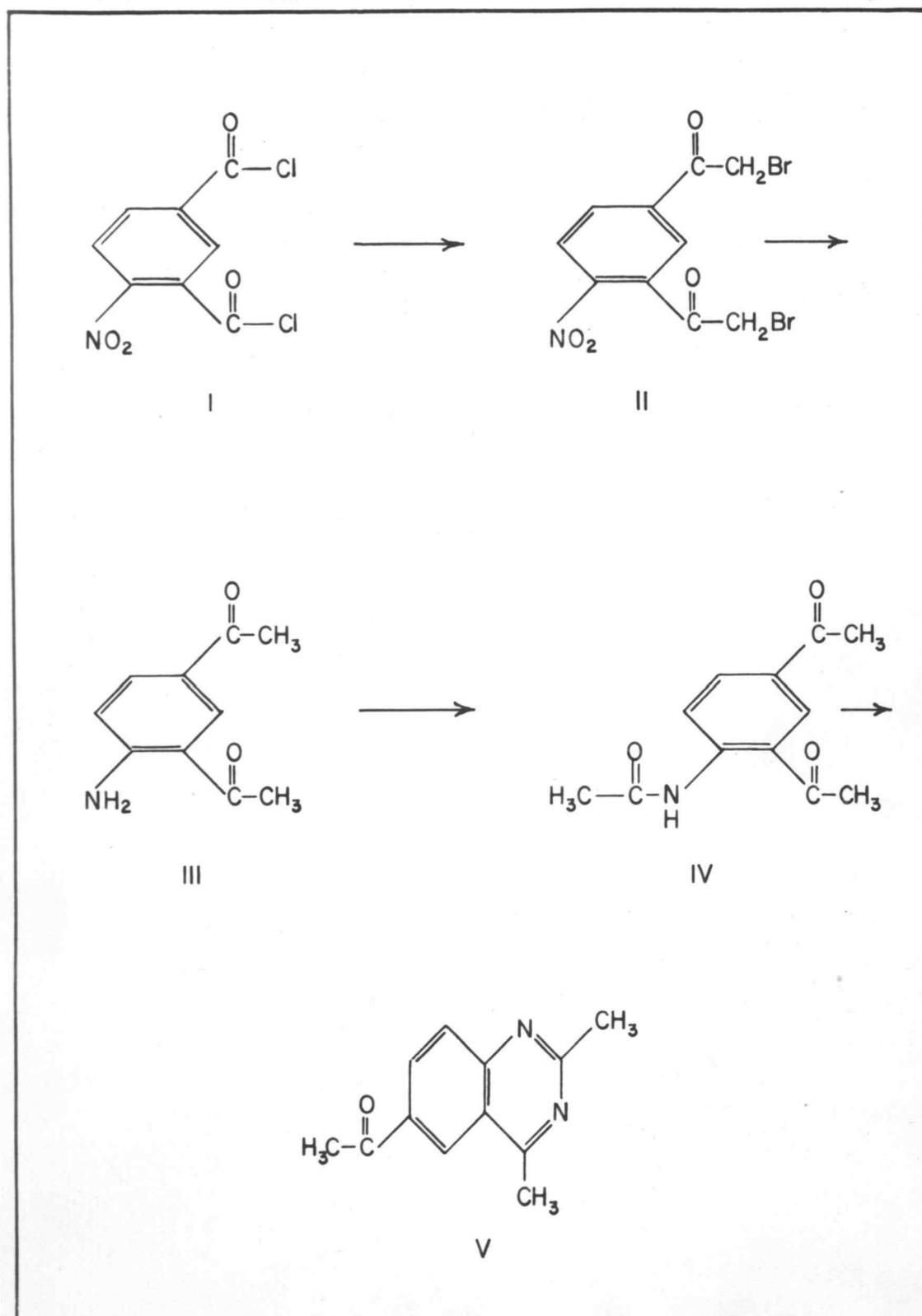


Figure 1

It was not possible to determine for certain that the condensation involved the 2-methyl substituent rather than the methyl of the methyl ketone. From the unusually mild conditions under which the Mannich condensation took place and the known activity of the 4-methyl position, it would appear that the 4-methyl rather than the methyl ketone was involved in the condensation.

## EXPERIMENTAL

o-Formamidoacetophenone: To a mixture containing 292 ml. of 90% formic acid and 50 ml. of acetic anhydride were added 20 g. (0.15 mole) of o-aminoacetophenone. The solution was heated to 80°, and the temperature was maintained between 85-90° for a period of 20 minutes by the slow addition of 56 ml. of acetic anhydride. The solution was allowed to cool for ten minutes and then poured onto 200 g. of ice. This ice-mixture was made basic with sodium carbonate immediately paying particular attention to maintaining ice-bath temperatures to avoid decomposition. The mixture was extracted with ether, and the ether in turn, extracted with both 3 N. hydrochloric acid until colorless and finally with water until neutral. Evaporation of the ether gave a crude product which, recrystallized from n-heptane, yielded 16 g. of white crystals (61-65%).

4-Methylquinazoline: Ten grams (0.061 mole) of o-formamidoacetophenone in 250 ml. of absolute alcohol were cooled in an ice-bath, saturated with ammonia, and then placed in a bomb which was maintained at 125-130° for 5 hours, and the alcohol was removed under vacuum. The residue was distilled in vacuo at 15 mm. and the fraction b.p. 126-128° was collected, yield light yellow oil, 7.35 g. (83-95%).

2-Methyl-4-(2-dimethylaminoethyl)-quinazoline

hydrochloride: To a mixture containing 2.0 g. (0.013 mole) of 2,4-dimethylquinazoline, 1.04 g. (0.013 mole) dimethylamine hydrochloride, 0.95 ml. of 37% formaldehyde solution, and 21 ml. of absolute alcohol were shaken for four and one-half hours at room temperature. After standing overnight in a refrigerator, the precipitate was filtered and washed with dry ether. The combined filtrates yielded a second crop of crystals. The total yield of colorless crystals, melting at 131.8-141.8°, was 1.28 g. (40.2%).

Anal. Calcd. for  $C_{13}H_{18}ClN_3$ : C, 62.0; H, 7.16; Cl, 14.15. Found: C, 62.15; H, 7.24; Cl, 14.0.

4-(2-Dimethylaminoethyl)-quinazoline hydrochloride:

The procedure was the same as given above. The yield of fine colorless crystals, melting at 133.4-134.4°, was 1.42 g. (40.6%). Anal. Calcd. for  $C_{12}H_{16}ClN_3$ : C, 60.5; H, 7.06; Cl, 14.9. Found: C, 60.4; H, 7.23; Cl, 14.8.

2-Methyl-4-(2-morpholinoethyl)-quinazoline hydro-

chloride: The procedure was the same as given above. The yield of colorless crystals, melting at 151.6-152.6°, was 1.32 g. (35.6%). Anal. Calcd. for  $C_{15}H_{20}ClN_3O$ : C, 61.3; H, 6.82; Cl, 12.1. Found: C, 61.6; H, 6.78; Cl, 12.2.

4-(2-Morpholinoethyl)-quinazoline hydrochloride:

The procedure was the same as given above. The yield of colorless crystals, melting at 156.2-158.2°, was 2.19 g. (54.8%). Anal. Calcd. for  $C_{14}H_{18}ClN_3O$ : C, 60.0;

H, 6.43; Cl, 12.7. Found: C, 60.03; H, 6.67; Cl, 12.7.

Mannich reaction with 6-acetyl-2,4-dimethylquinazoline: The procedure was the same as given above. The yield of light yellow crystals was 0.85 g. (24.5%), m.p. 149° decomp. Anal. Calcd. for  $C_{15}H_{20}ClN_3O$ : C, 61.2; H, 6.8; N, 14.3; Cl, 12.1. Found: C, 60.8; H, 7.0; N, 14.25; Cl, 12.11.

Oxidation of 2-methyl-4-(2-dimethylaminoethyl)-quinazoline hydrochloride: To a solution of 1.38 g. (0.0055 mole) 2-methyl-4-(2-dimethylaminoethyl)-quinazoline hydrochloride in 2.11 ml. of 10% sodium hydroxide and 13.2 ml. water was added 25 ml. of sodium hypobromite solution (1.52 ml. of bromine in 25 ml. of 10% sodium hydroxide). The mixture became cloudy; upon warming an oily substance separated. After 15 minutes, an additional 13.2 ml. of sodium hypobromite was added which turned the orange solution to a yellow color. The mixture was diluted to 88 ml., and a saturated solution of sodium bisulfite was added until starch iodide paper no longer gave a positive test. The solution was filtered, acidified with concentrated nitric acid, extracted with two 22 ml. portions of ether, and then placed in a refrigerator. After three days, the solution was filtered, yield 0.19 g. (19-21.6%) of a light yellow crystalline precipitate. A sample recrystallized from water was identified as 2-methyl-4-quinazalone on basis of mixed

m.p. and carbon and hydrogen data.

2-Methyl-4-tribromomethylquinazoline: Twenty-five ml. of water was added to 1.0 g. (0.0063 mole) of 2,4-dimethylquinazoline. The hydrate formed was filtered and air dried. The hydrate was dissolved in 25 ml. of dioxane and added very slowly with shaking to a solution of sodium hypobromite (1.06 ml. bromine in 25 ml. of 10% sodium hydroxide). The solution became warm and cloudy while a white solid separated. After the addition of 50 ml. of water, the solution was filtered and the precipitate air-dried, yield, 1.28 g. (48-56%). An analytical sample recrystallized from n-heptane melted at 133.4-135.4°. Anal. Calcd. for  $C_{10}H_7Br_3N_2$ : N, 7.09; Br, 6.06. Found: N, 6.95; Br, 6.02.

One gram (0.0025 mole) of 2-methyl-4-tribromomethylquinazoline was dissolved in 10 ml. of dioxane added in small portions to a solution of sodium hypobromite (0.425 ml. bromine in 10 ml. of 10% sodium hydroxide). The solution was warmed on a water-bath until the white solid which separated went back into solution. After the addition of the sodium hypobromite, the solution was decanted from the oil which separated, evaporated to a thick paste in front of a fan, and then acidified with dilute sulfuric acid. The resulting precipitate was filtered, washed with a small amount of water, air dried, yield 0.3 g. (74%) of white crystalline material. A

sample was recrystallized from n-heptane and identified by a mixed melting point as 2-methyl-4-quinazalone.

4-Nitroisophthalyl chloride: Twenty grams (0.095 mole) of 4-nitroisophthalic acid, 40 ml. of phosphorous oxychloride and 80 g. (0.74 mole) of phosphorous pentachloride were refluxed for eight hours during which time the solution became red in color. The excess phosphorous pentachloride was removed by filtration using a sintered glass funnel.

The excess phosphorous oxychloride was then removed by vacuum distillation using a water aspirator, the residual liquid was cooled and then filtered to remove the remaining phosphorous pentachloride. The dark red filtrate was now dissolved in dry ether and used in the next step of preparation.

An analytical sample was obtained by vacuum distillation of the crude red liquid acid chloride at a fraction of a mm. pressure. Under these conditions the acid chloride fraction distills between 145-150° as a light orange colored liquid. Anal. Calcd. for  $C_8Cl_2H_3NO_4$ : Cl, 28.6. Found: Cl, 28.7.

1,3-Diazoacetyl-4-nitrobenzene: Five hundred and seventy ml. of ether and 170 ml. of 40% potassium hydroxide were stirred in a liter erlenmeyer flask which was cooled with a Dry Ice-acetone-bath. Fifty-seven grams (0.55 mole) of N-nitrosomethylurea was then added slowly and

after solution was completed the yellow ethereal layer was separated and dried over potassium hydroxide pellets for four to six hours. The dried diazomethane solution was then transferred to a three necked flask equipped with mechanical stirrer, dropping funnel, and provided with a Dry Ice-acetone-bath.

One-half of the acid chloride solution prepared in the preceding operation (half portions were run for reasons of safety) was diluted to 125 ml. with dry ether and then added slowly to the diazomethane solution. The precipitate which separated was removed by filtration; crude yield, 9 g. (73%). This product was immediately suspended in ether for use in the next operation.

1,3-Dibromoacetyl-4-nitrobenzene: In a 3-liter erlenmeyer flask equipped with dropping funnel and mechanical stirrer were placed 1-liter of ether and 18.0 g. of the crude diazoketone from the preceding run. After the formation of a uniform suspension approximately 50-70 ml. of 48% hydrobromic acid was added dropwise with stirring. This was continued until further addition of the hydrobromic acid no longer caused gas evolution. The ethereal solution was separated and ether removed leaving a yellow orange residue. This was dissolved in a small excess of hot chloroform, decolorized with charcoal, filtered and then reprecipitated by addition of petroleum ether; yield 11.6 g. (33.4%), (based on the nitroisophthalic

acid), m.p. 104-105°. A white analytical sample was prepared by three precipitations from chloroform using petroleum ether and decolorizing with charcoal. Anal. Calcd. for  $C_{10}H_7Br_2NO_4$ : C, 32.9; H, 1.92; Br, 43.8. Found: C, 32.5; H, 1.88; Br, 43.5, 43.6, 43.9.

4-Amino-1,3-diacetylbenzene: 1,3-Dibromoacetyl-4-nitrobenzene (7.6 g. - 0.021 mole), 38 g. (0.030 mole) of stannous chloride dihydrate and 290 ml. of concentrated hydrochloric acid were stirred on a water-bath. After two and one-half hours the solution became yellow; the reaction mixture was then poured into 500 ml. of water and the resultant mixture made very basic with concentrated sodium hydroxide and then set aside in a refrigerator. A long yellow needled crystalline product was removed by filtration and recrystallized from water, yield 2.9 g. (78%), m.p. 139-140°. Anal. Calcd. for  $C_{10}H_{11}NO_2$ : C, 67.7; H, 6.21; N, 7.92. Found: C, 67.8; H, 6.46; N, 8.06.

4-Acetamino-1,3-diacetylbenzene: A flask containing 1.0 g. (0.0064 mole) of 4-amino-1,3-diacetylbenzene, 2.25 g. (0.022 mole) of acetic anhydride was placed in an oven at 42-46° overnight. The amino ketone went into solution, and the solution was poured into a small amount of water. An oily material which slowly crystallized separated, and after neutralization of the solution with sodium carbonate was removed by filtration. The precipitate

was recrystallized from n-heptane as long colorless needles, yield 1.1 g. (88%), m.p. 127-128°. Anal. Calcd. for  $C_{12}H_{13}NO_3$ : C, 65.6; H, 5.93; N, 6.40. Found: C, 65.75; H, 5.99; N, 6.44.

6-Acetyl-2,4-dimethylquinazoline: A solution containing 1.0 g. (0.0046 mole) of 4-acetamino-1,3-diacetylbenzene in 25 ml. of absolute alcohol was saturated with ammonia and then placed in a bomb. The bomb was maintained in an oven at 100-105° for seven and one-half hours. The yellow alcoholic reaction product was evaporated before a fan to dryness. A yellow residue was obtained which was dissolved in n-heptane, decolorized with charcoal and then recrystallized; yield 0.72 g. (76%) of white crystalline powder, m.p. 92°. Anal. Calcd. for  $C_{12}H_{12}N_2O$ : C, 71.9; H, 6.00; N, 14. Found: C, 71.6; H, 5.93; N, 13.7.

6-Carboxy-2-methyl-4-quinazalone: A solution of 1.0 g. (0.005 mole) of 6-acetyl-2,4-dimethylquinazoline, 10 ml. of water, and 8 ml. of dioxane was added slowly to 25 ml. of a sodium hypobromite solution (1.2 ml. bromine in 25 ml. 10% sodium hydroxide). Additional hypobromite solution was added to insure an excess of this reagent. The solution was decanted from an oily material which separated and treated with sodium bisulfite until it no longer gave a test with starch iodide paper. The mixture was then extracted several times with 25 ml. portions of ether and then acidified with concentrated nitric acid

and filtered; the yield, light tan colored crystals, 0.41 g. (41.8%). An analytical sample was prepared by dissolving it in dilute sodium hydroxide, treating with charcoal, and reprecipitating with nitric acid. The white powder gradually decomposed above 300°. Anal. Calcd. for  $C_{10}H_8N_2O_3$ : N, 13.71; neut. equiv., 204. Found: N, 13.3; neut. equiv., 203.5.

## SUMMARY

The methylenic character of the 4-methyl substituent in 4-methylquinazoline and 2,4-dimethylquinazoline has been demonstrated by condensation reactions. The 4-methyl substituent has been converted to the tribromomethyl derivative and finally to the 2-methyl-4-quinazalone.

The synthesis of 6-acetyl-2,4-dimethylquinazoline from 4-nitroisophthalic acid and a new procedure for the preparation of 4-methylquinazoline has been described in detail.

Several new compounds 4-(2-dimethylaminoethyl)-quinazoline hydrochloride, 4-(2-morpholinoethyl)-quinazoline hydrochloride, 2-methyl-4-(2-dimethylaminoethyl)-quinazoline hydrochloride, and 2-methyl-4-(2-morpholinoethyl)-quinazoline hydrochloride have been prepared from 4-methyl and 2,4-dimethylquinazoline respectively.

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