

AN ABSTRACT OF THE THESIS OF

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Title The Synthesis of an Amino Alcohol Derived from 2,4-
Quinazolinedione-5-carboxylic Acid

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Method for the preparation of 5-(2-morpholine-1-hydroxyethyl)-1 (or 3)-methyl-2,4-quinazolinedione hydrochloride are given in detail using 2,4-quinazolinedione-5-carboxylic acid as the starting material. Several unusual reactions of the intermediate, 5-diazoacetyl-1,3-dimethyl-2,4-quinazolinedione such as permanganate oxidation, stannous chloride reduction and hydrobromic acid treatment are described. In these processes, one of the methyl substituents is invariably lost to give the corresponding monomethyl derivative.

In order to locate the position of the lost methyl group, both 1 and 3-methyl-2,4-quinazolinedione-5-carboxylic acid are prepared synthetically and are found to be not identical with the monomethyl-2,4-quinazolinedione-5-carboxylic acid obtained by the permanganate oxidation of 5-diazoacetyl-1,3-dimethyl-2,4-quinazolinedione. Also, the monomethyl-2,4-quinazolinedione-5-carboxylic acid upon methylation with diazomethane gave the methyl ester of a dimethyl-2,4-quinazolinedione-5-carboxylic acid which is isomeric but not identical to methyl-1,3-dimethyl-2,4-quinazolinedione-5-carboxylate.

It is, therefore, concluded that this monomethyl acid could be either a stereo isomer of 1 (or 3)-methyl-2,4-quinazolinedione-5-carboxylic acid or the methyl group is attached in some other manner.

THE SYNTHESIS OF AN AMINO ALCOHOL DERIVED
FROM 2,4-QUINAZOLINEDIONE-5-CARBOXYLIC ACID

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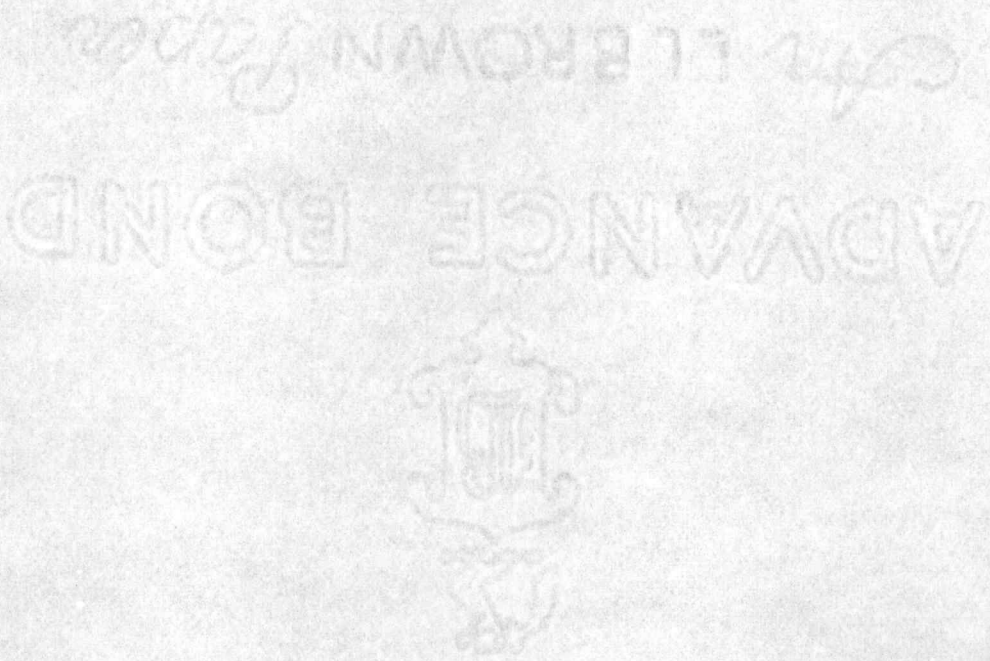
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THE SYNTHESIS OF AN AMINO ALCOHOL DERIVED
FROM 2,4-QUINAZOLINEDIONE-5-CARBOXYLIC ACID

I. INTRODUCTION

Methods for the synthesis of 2,4-dimethylquinazoline derivatives with an acetyl-substituent in the 7 and 8 positions have recently been described (4,5). The 5-isomer, however, could not be synthesized by these procedures due to the difficulties encountered in the attempted preparation of the necessary intermediates 3-acetamino-1,2-diacetylbenzene or 3-acetamino-2-acetylbenzoic acid required for the cyclization (11).

Since it would be useful to this laboratory to have a quinazoline compound with an amino alcohol substituent in the 5-position, the possibility of utilizing the easily prepared 2,4-quinazolinedione-5-carboxylic acid (I) as the starting material (See Fig. 1) was studied. This intermediate was converted to the acylchloride (II), which upon treatment with diazomethane formed the diazoketone and, at the same time, was simultaneously methylated in the 1,3 positions to yield 5-diazoacetyl-1, 3-dimethyl-2,4-quinazolinedione (III). This Diazoketone, upon treatment with dry hydrogen bromide gas, was converted to the bromomethylketone (IV); however, one of the methyl substituents (either 1 or 3) was lost in the process.

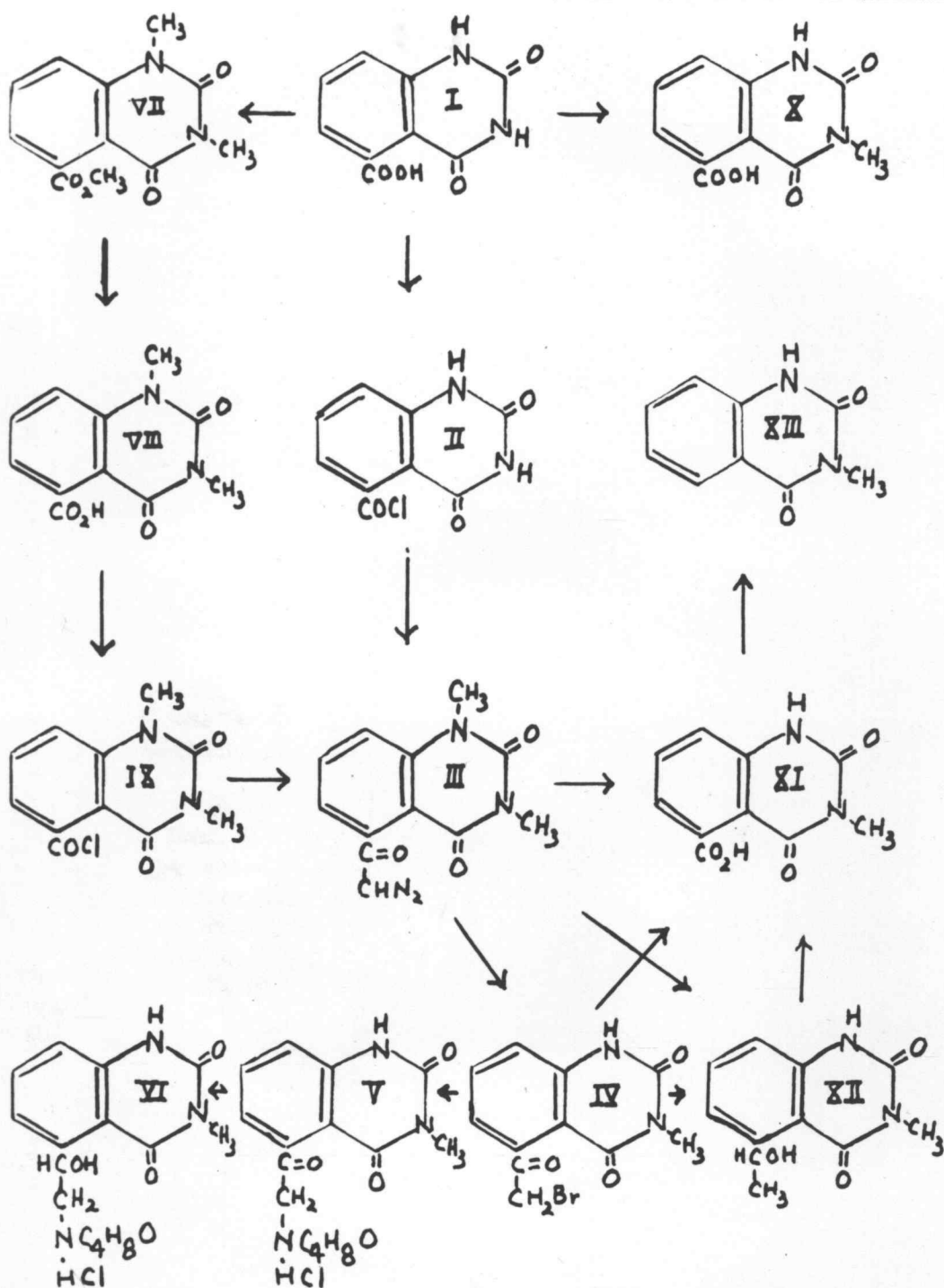


Fig. 1

The bromacetyl derivative (IV) readily combined with morpholine to yield an aminoketone (V) which was in turn catalytically reduced to the desired amino alcohol (VI).

In order to confirm the simultaneous methylation of the 1,3-positions of (II) during the diazomethane reaction, the starting material (I) was methylated with excess diazomethane. This gave an ester, (methyl 1,3-dimethyl-2,4-quinazolinedione-5-carboxylate (VII)) which was identical with that reported both by Scott and Cohen (9) as well as Lange, Chisholm and Szabo (7). These investigators had employed dimethyl sulfate as the methylating agent.

The ester (VII) was hydrolyzed to the acid (VIII) which, upon chlorination with thionyl chloride, gave a good yield of 1,3-dimethyl-2,4-quinazolinedione-5-carbonyl chloride (IX). When the acyl chloride (IX) was treated with diazomethane, a diazoketone identical with (III) was produced. These data confirmed the earlier observations of the methylation of the 1,3-positions of 2,4-quinazolinedione-5-carbonyl chloride with diazomethane.

Although (VII) on the basis of mixed melting point tests was identical with the ester prepared by Scott and Cohen, the acid (VIII) obtained by the hydrolysis of VII, was not the same as the 1,3-dimethyl-quinazolinedione-5-carboxylic acid reported by these workers (7, 9). Scott and Cohen originally

prepared the acid by the direct methylation of (I) using a limited amount of dimethyl sulfate. In order to confirm the earlier work, the methyl ester (VII) prepared in this laboratory by the method of Scott and Cohen was hydrolyzed to the free acid. This acid was found to be identical with (VIII) which was obtained as the hydrolysis product of the ester (VII) (prepared by the diazomethane reaction) and different from the dimethyl acid originally reported by these workers. In order to clarify these results, the free acid (X) was again prepared in this laboratory by the direct methylation procedure of Scott and Cohen; the methylation product was found to be a high melting compound as described by these workers. However, carbon and hydrogen data indicated an incomplete methylation yielding the 1(or 3)-methyl-2,4-quinazolinedione-5-carboxylic acid in place of the 1,3 homolog. Since the earlier work has been based on nitrogen analysis only, it is possible that the acid in question was the 1 or 3-methyl-2,4-quinazolinedione-5-carboxylic acid (X) and not the 1,3-dimethyl homolog as originally reported.

Because of the unpredictable ease with which the methyl substituent has been removed during the mild acid treatment of the diazoketone (III), further experiments with (III) were undertaken. The compound (III) upon oxidation with neutral

permanganate again lost the methyl substituent to the form 1 (or 3)-methyl-2,4-quinazolinedione-5-carboxylic acid (XI). The loss of a methyl substituent was again observed during reduction which yielded 5-(1 hydroxyethyl)-1(or 3)-methyl-2,4-quinazolinedione (XII). Both the bromomethylketone (IV) and the reduction product (XII) after a permanganate oxidation yielded acids which on the basis of mixed melting points tests were judged to be identical with (XI). From these results, as well as the analytical data, it was concluded that the same methyl substituent was quantitatively removed during each of the described operations.

The problem of determining the position of the remaining methyl group was approached through decarboxylation experiments. The acid (XI) after removal of the carboxyl group, gave a methyl-2,4-quinazolinedione (XIII) which melted sharply at 198°. This m.p. did not agree with 234° - 242° (3) reported for the 3-methyl-2,4-quinazolinedione or 147° or 265° (8) which had been reported for the 1-isomer (9).

A review of the literature reveals that Abt had prepared both the 3(and 1)-methyl-2,4-quinazolinediones (XIV) (XV) (m.p.'s 234, 147) by the cyclization of 2-aminomethylbenzamide and 2-methylaminobenzamide respectively with urea (See Figure 2). Both the 1 and 3-methyl-2,4-quinazolinediones

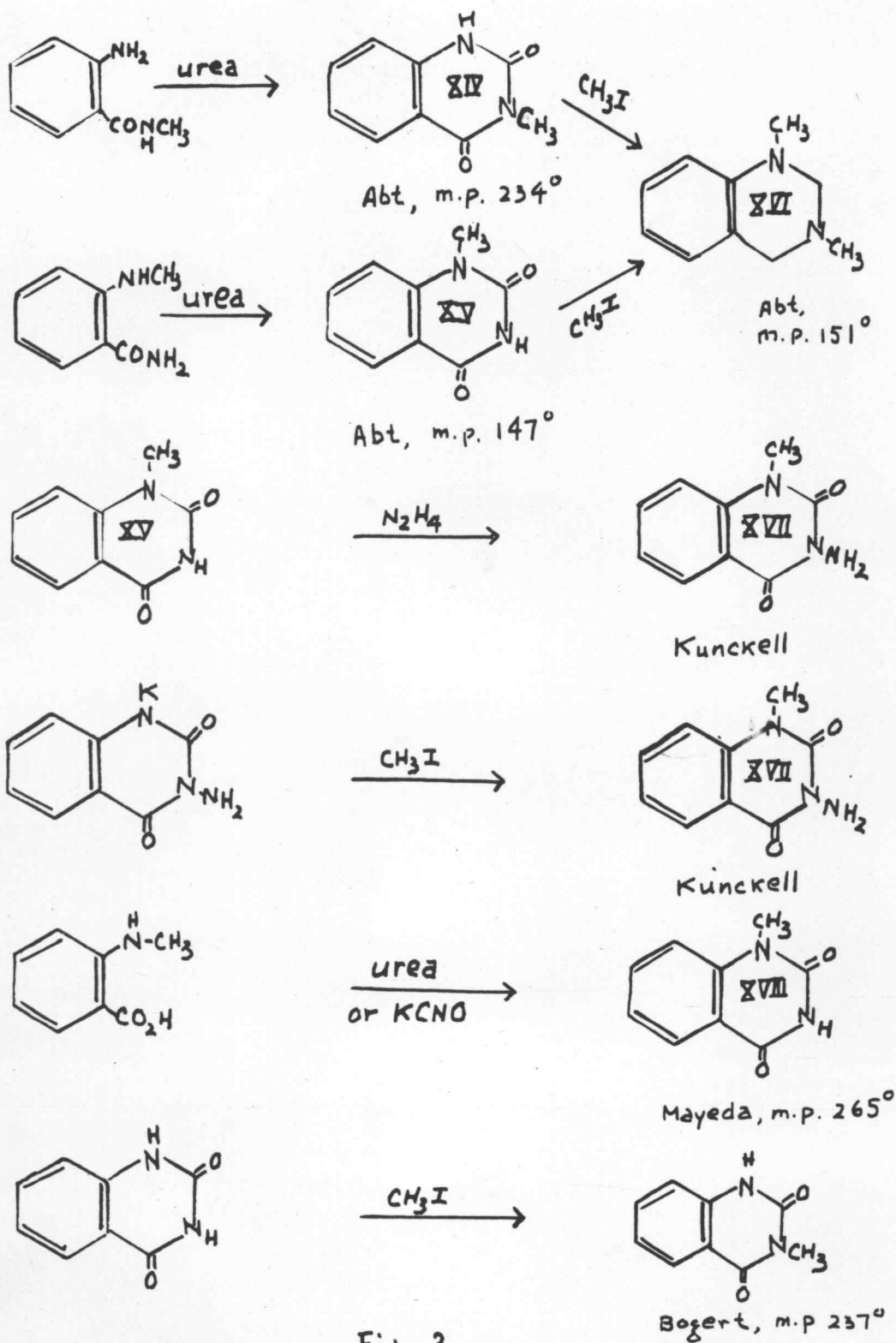


Fig. 2

prepared by Abt, after further methylation with methyl iodide, gave an identical known product 1,3-dimethyl-2,4-quinazoline-dione (XVI) m.p. 151° (1). Furthermore, Abt prepared by direct methylation using alkaline methyl iodide, a compound m.p. 147° which he concluded was 1-methyl-2,4-quinazolinedione (1).

The proof of structure of the 1-methyl isomer m.p. 147° was later confirmed indirectly by the experiments of Kunckell (6) who isolated 3-amino-1-methyl-2,4-quinazoline-dione (XVII) as the product of the reaction of the 1-methyl isomer (XV) with hydrazine. The identical compound had previously been obtained by the methylation of the potassium salt of 3-amino-2,4-quinazolinedione, with methyl iodide (6) (See Figure 2).

On the other hand, Mayeda cyclized 2-methylamino-benzoic acid with both urea and potassium cyanate and obtained the same product 1-methyl-2,4-quinazolinedione m.p. 265-6° (See Figure 2) (8). Confirmation of the existence of a 1-methyl-2,4-quinazolinedione m.p. 265-6° was later reported by Seide (10) who prepared this compound by an entirely different series of reactions.

Bogert (3) later reported that the product of the direct methylation of 2,4-quinazolinedione with alkaline methyl iodide was the 3-methyl isomer which he concluded was

identical with the 3-methyl-2,4-quinazolinedione (XIV) m.p. 234°, prepared by the cyclization procedures of Abt. Bogert's work has likewise been confirmed in this laboratory. It is possible that the different results obtained by Bogert and Abt upon direct methylation of 2,4-quinazolinedione (m.p.'s 234° and 147°) may be due to the different thermal conditions of the experiments.

In view of the anomalous m.p. data, mixed m.p. tests were run between each of the following: (1) 3-methyl-2,4-quinazolinedione (XIV), m.p. 242°, prepared by the method of Bogert with a small amount of 1-methyl-2,4-quinazolinedione (XVIII) m.p. 265° prepared by the method of Sentaro Mayeda (also vice versa); (2) compound XIV with the decarboxylation product (XIII) m.p. 198°; (3) compounds XVIII and XIII. In each test there was an appreciable lowering of the m.p. which proves that (XIII) could hardly be a mixture of (XIV) and (XVIII).

One must conclude that there is reasonable support for the structures proposed by Abt and Sentaro Mayeda for both the 1(and 3)-methyl-2,4-quinazolinediones. The only data which appears questionable are the m.p.'s which can best be explained on the basis (1) multiple melting points, (2) possibility of isomeric mixtures, or (3) the possibility of

stereoisomerism. However, the mixed m.p. behavior precludes the first two possibilities, leaving the only alternate explanation the existence of two stereoisomers of both 1(and 3)-methyl-2,4-quinazolines. A similar type of isomerism has been reported in the alkaloid literature (13). If such is the case, then the decarboxylation product (XIII) m.p. 198° appears to be the other stereoisomer of 3-methyl-2,4-quinazolidinedione, m.p. 242°.

If (XIII) is not a stereoisomer of 1-(or 3)methyl-2,4-quinazolidinedione, then the methyl substituent must be in some other position or attached in some other manner. This would change many of the accepted ideas regarding the methylation products of the quinazolones.

The preparation of the 3-methyl-2,4-quinazolidinedione by the method of Abt and the 1-methyl isomer by the method of Sentaro Mayeda were confirmed in this laboratory. However, repeated attempts to prepare the 1 methyl isomer m.p. 147° using two procedures suggested by Abt were unsuccessful. Although this laboratory obtained a crude cyclization product with a melting point of approximately 147°, this material was easily resolved on basis of acid solubility into two fractions, one melting at 265°C. and the other the starting product. From this work, it would appear that Abt's cyclization was only

partially complete and his product largely starting material contaminated with the 1-methyl-2,4-quinazolinedione m.p. 265°. This opinion finds additional support in the fact that the m.p. 147° is far out of line for compounds of this type.

In the search for an explanation of this puzzling question (the existence of what appears to be 3 compounds which are either 1-or 3-methyl substituted 2,4-quinazoline-diones) attention turned to the 5-substituted carboxylic acid intermediate to determine if the same anomaly existed among the 1-and 3-methyl-2,4-quinazolinedione-5-carboxylic acids.

Both the 1-methyl-2,4-quinazolinedione-5-carboxylic acid m.p. 320° and the 3-methyl isomer m.p. 332° were synthesized in this laboratory by methods which should leave little doubt as to the position of the methyl substituents. The 3-methyl-2,4-quinazolinedione-5-carboxylic acid was identified as the partial methylation product of 2,4-quinazolinedione-5-carboxylic acid reported earlier by Scott and Cohen (9) as the 1,3-dimethyl derivative but which was later found to be the mono methyl derivative.

Each of these compounds had different melting points which were much higher than the unknown isomeric oxidation product of 5-bromoacetyl-?-methyl-2,4-quinazolinedione. Furthermore, they were stable on melting in contrast to the latter acid which decomposed readily with gas evolution.

Diazomethane methylation of the 1-methyl-m.p. 320° and 3-methyl-m.p. 332° as well as 2,4-quinazolinedione-5-carboxylic acid gave identical products the methyl ester of 1,3-dimethyl-2,4-quinazolinedione-5-carboxylic acid m.p. 144°. This same product was likewise obtained with exhaustive dimethyl sulfate methylation of 2,4-quinazolinedione-5-carboxylic acid.

On the other hand, the methylation of ?-methyl-2,4-quinazolinedione-5-carboxylic acid with methyl iodide failed, while diazomethane in an ethereal solution gave the methyl ester. Exhaustive diazomethane methylation in ethereal methanol solution, however, invariably gave a syrupy product from which was isolated a small amount of crystalline material which was isomeric but not identical to methyl, 1,3-dimethyl-2,4-quinazolinedione-5-carboxylic acid.

The question of the structure of the original 5-bromoacetyl-?-methyl-2,4-quinazolinedione therefore still remains a mystery. Further experimentation is now under way to approach this interesting problem via tracer techniques.

The 1-methyl-2,4-quinazolinedione-5-carboxylic acid was synthesized in a sequence of reactions (See Figure 3) beginning with 2-amino-6-carbomethoxybenzoic acid hydrochloride. This compound was converted to methyl,2,4-dioxo-3,1,4-benzoxazine-

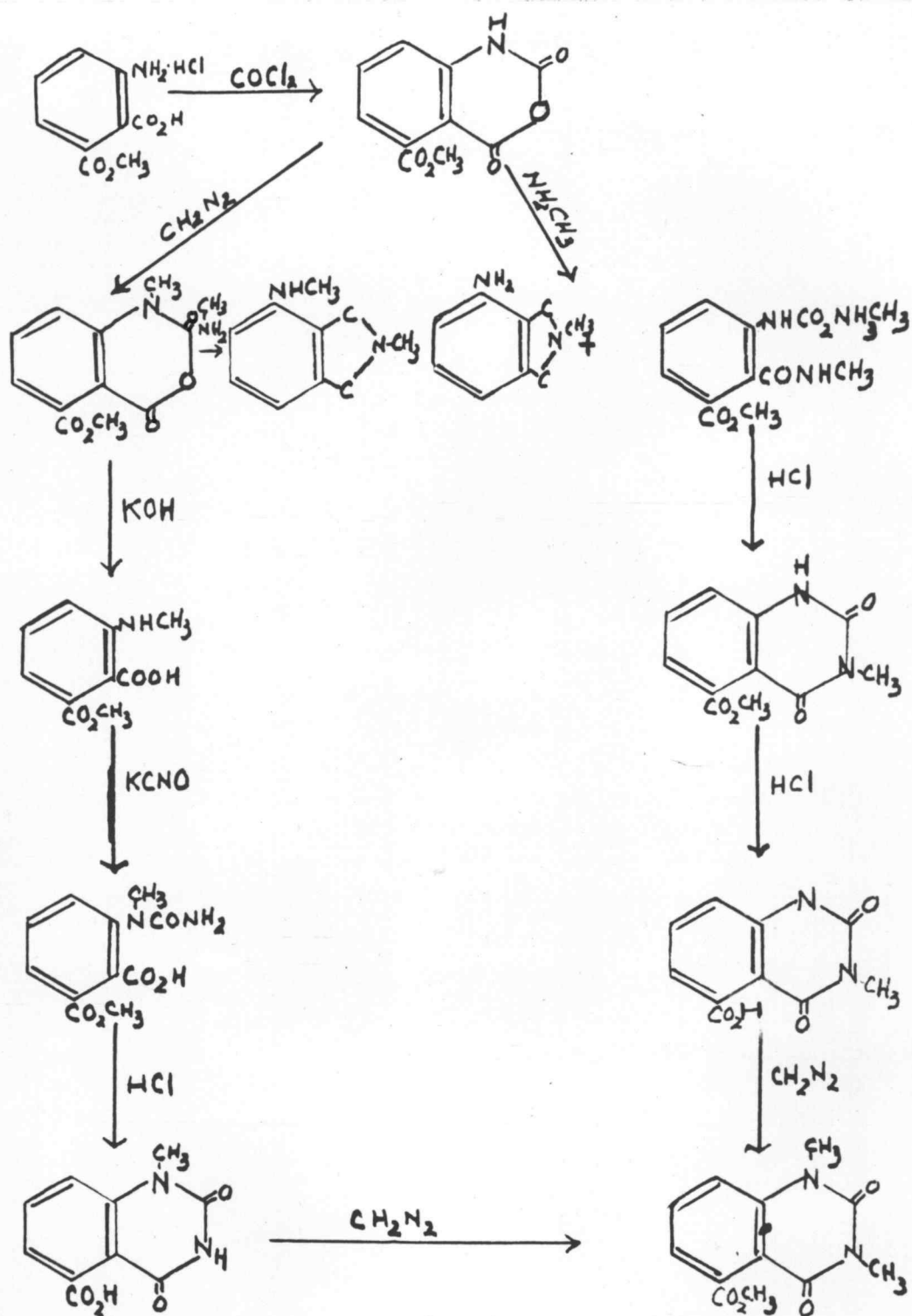


Fig. 3

5-carboxylate with phosgene which in turn on methylation with diazomethane gave methyl, 1-methyl-2,4-dioxo-3,1,4-benzoxazine-5-carboxylate.

Treatment of the benzoxazine derivative with potassium hydroxide, then hydrochloric acid gave 6-carbomethoxy-2-methylaminobenzoic acid. This intermediate was cyclized in usual manner with potassium cyanate and hydrochloric acid to 1-methyl-2,4-quinazolinedione-5-carboxylic acid.

The 3-methyl-2,4-quinazolinedione-5-carboxylic acid was likewise synthesized from methyl,2,4-dioxo-3,1,4-benzoxazine-5-carboxylate (See Figure 3) but by a different sequence of reactions. Ammonolysis of this compound with methylamine gave two products; 6-carbomethoxy-(N-methylamoniumcarboxy) anthranilicmethylamide which was easily cyclized by hydrochloric acid to methyl, 3-methyl-2,4-quinazolinedione-5-carboxylate, and 3-amino-N-methylphthalimide. The ester upon further diazomethane methylation was identical with the methyl, 1,3-dimethyl-2,4-quinazolinedione-5-carboxylate prepared by Wang and Christensen by the diazomethane methylation of 2,4-quinazolinedione-5-carboxylic acid, and by the dimethylsulfate methylation procedure of Scott (9) and Cohen.

In an attempt to prepare the 1,3-dimethyl-2,4-quinazolinedione-5-carboxylic acid by direct cyclization, the

methyl, 2,4-dioxo-3,1,4-benzoxazine-5-carboxylate was treated with methylamine hydrochloride but instead of the desired product, it gave N-methyl, 3-methylaminophthalimide. Concentrated ammonium hydroxide likewise gave the imide 3-methylaminophthalimide. It is evident that the predominant reaction is an ammonolysis of the ester followed by cyclization to the imide rather than direct cyclization to a quinazalone, as is ordinarily the case.

II. EXPERIMENTAL¹

5-Diazoacetyl-1,3-dimethyl-2,4-quinazolinedione (III).

-2,4-Quinazolinedione-5-carboxylic acid (I) was prepared and converted to the corresponding acid chloride by the method of Lange and co-workers. The addition of a few drops of quinoline to the thionyl chloride, besides materially shortening the time of chlorination, gave a purer product.

Twelve and four-tenths grams (0.0553 mole) of 2,4-quinazolinedione-5-carbonyl chloride (II) was pulverized into a fine powder and added gradually with stirring to 600 ml. of an ice-cold benzene solution of diazomethane prepared from 60 g. of N-nitroso-methylurea (0.40 mole of diazomethane). The reaction took place rather slowly as indicated by the rate of evolution of nitrogen gas. After stirring for six hours, the solution was allowed to warm to room temperature and then left standing overnight. The insoluble residue (0.5 g.) was removed by filtration and the solvent concentrated under reduced pressure to 100 ml. After standing in a refrigerator for two days the crystalline diazoketone was removed. The mother liquor was then evaporated to dryness under reduced pressure and the gummy residue redissolved in warm acetone. An additional amount of the diazoketone was obtained by the addition

¹All melting points are corrected.

ether to the acetone solution. The combined fractions weighed 10.1 g. (80%).

For analysis, a portion of the crude diazoketone was recrystallized twice from acetone yielding hard, colorless cubes which on standing decompose, m.p. 157-159°.

Anal. Calcd. for $C_{12}H_{10}O_3N_4$: C, 55.80; H, 3.91; N, 21.70. Found: C, 55.7; H, 3.88; N, 21.7.

The diazoketone was also prepared from 1,3-dimethyl-2,4-quinazolinedione-5-carboxylic acid (VIII) via the acyl chloride in a similar manner. The yield in this instance was only 40%.

5-Bromoacetyl-1(or 3)-methyl-2,4 quinazolinedione (IV)

Six grams (0.023 mole) of 5-diazoacetyl-1,3-dimethyl-2,4-quinazolinedione (III) was dissolved in 60 ml. of dry chloroform. The solution was cooled with an ice-bath and then treated with a stream of dry hydrogen bromide until the evolution of nitrogen ceased. The precipitated bromomethyl ketone was filtered, washed with ether and dried in a vacuum. Some additional product was obtained by concentration of the mother liquor. The combined yield weighed 6.6 g. (91%). A portion of this product was recrystallized twice from an alcohol-ether mixture to yield white crystals, m.p. 200-201°.

Anal. Calcd. for $C_{11}H_9O_3N_2Br$: C, 44.44; H, 3.05; N, 9.43; Br, 26.9. Found: C, 44.8; H, 3.15; N, 9.49; Br, 27.3.

5-(2-Morpholine-1-oxoethyl)-1(or 3)-methyl-2,4-quinazolinedione Hydrochloride (V).

Four and five-tenths grams (0.015 mole) of 5-bromo-acetyl-1(or 3)-methyl-2,4-quinazolinedione (IV) was suspended in 50 ml. of acetone. To this was added dropwise with shaking 2.6 g. (0.030 mole) of redistilled morpholine. The bromo-methyl ketone dissolved gradually accompanied by the precipitation of crystalline morpholine hydrobromide. After standing overnight, the morpholine hydrobromide was removed by filtration and the solvent concentrated under reduced pressure to 10 ml. Fifty milliliters of water was added to the concentrate; the precipitated crude amino ketone was filtered, washed thoroughly with water and vacuum dried. The crude product (m.p. 180° dec.) was then dissolved in 20 ml. of absolute ethanol, cooled with an ice-bath and dry hydrogen chloride gas was bubbled into the solution. The hydrochloride of the amino ketone precipitated upon the addition of dry ether in the form of a voluminous precipitate, which was separated from the mother liquor by means of centrifugation. The product (2 g.) after washing twice with dry ether was a hygroscopic white solid decomposing at about 150° .

Anal. Calcd. for $C_{15}H_{18}O_4N_3Cl$: N, 12.38; ionizable Cl, 10.44. Found: N, 12.5; ionizable Cl, 10.20.

The monopicrate of the amino ketone was prepared by dissolving a sample of the hydrochloride in water and adding saturated aqueous sodium picrate solution. The precipitate obtained after recrystallization from ethanol-ether mixture was a yellow mass. On heating, it turned brownish in color at about 120° and decomposed at 140° .

Anal. Calcd. for $C_{21}H_{20}O_{11}N_6$: C, 47.35; H, 3.80; N, 15.78. Found: C, 47.7; H, 4.03; N, 15.6.

5-(2-Morpholine-1-hydroxyethyl)-1(or 3)-methyl-2,4-quinazoline-dione Hydrochloride (VI).

A solution containing 0.56 g. (0.0016 mole) of the amino ketone hydrochloride (V) and 50 ml. of dry methanol was reduced in a low-pressure hydrogenation apparatus at 30 p.s.i. pressure in the presence of 200 mg. of 10% palladium-on-carbon catalyst. After shaking for two hours, the catalyst was removed by filtration and the solution concentrated to 10 ml. The amino alcohol hydrochloride precipitated by the addition of dry ether was separated by centrifuging and yielded 0.30 g. (53%) of a slightly colored, very hygroscopic solid. For analysis, a portion of this product was reprecipitated twice from ethanol

with dry ether, yielding a very hygroscopic white mass which decomposed without melting at about 200°.

Anal. Calcd. for $C_{15}H_{20}O_4N_3Cl$: N, 12.30; ionizable Cl, 10.38. Found: N, 12.52; Cl, 10.50.

The monopicrate was prepared by adding a saturated aqueous sodium picrate solution to an aqueous solution of the amino alcohol hydrochloride. The product after recrystallization from an alcohol-ether mixture was a yellow solid decomposing at about 150°.

Anal. Calcd. for $C_{21}H_{22}O_{11}N_6$: C, 47.17; H, 4.16; N, 15.72. Found: C, 47.6; H, 4.16; N, 15.6.

1,3-Dimethyl-2,4-quinazolinedione-5-carboxylic Acid (VIII).

Five grams (0.023 mole) of 2,4-quinazolinedione-5-carboxylic acid (I) was added in portions with stirring to 200 ml. of an ice-cold ethereal solution of diazomethane prepared from 20 g. of N-nitrosomethylurea (0.13 mole of diazomethane). The reaction appeared to take place rapidly as evidenced by the vigorous evolution of nitrogen gas. After standing at room temperature for six hours, the filtered ethereal solution was evaporated to dryness to yield 4.0 g. (66%) of slightly colored crystals. The crystals were purified by two recrystallizations from ethanol yielding 3.1 g. of colorless product, m.p. 142-143°.

This product (VII) was found to be identical with the ester obtained by Lange, Chisholm and Szabo from the complete methylation of 2,4-quinazolinedione-5-carboxylic acid with dimethyl sulfate and sodium hydroxide.

Three grams (0.013 mole) of the ester was hydrolyzed by refluxing with 20 ml. of 20% hydrochloric acid for three hours; toward the end of the hydrolysis, colorless crystals separated out. After standing in the refrigerator overnight, the mixture was separated by filtration giving 2.0 g. (70%) of needles. A portion of this product was recrystallized from ethanol for analysis, m.p. 250-253°.

Anal. Calcd. for $C_{11}H_{10}O_4N_2$: C, 56.39; H, 4.31; neut. equiv., 234. Found: C, 56.8; H, 4.50; neut. equiv., 238.

1,3-Dimethyl-2,4-quinazolinedione-5-carbonyl Chloride (IX).

One and six-tenths grams (0.072 mole) of 1,3-dimethyl-2,4-quinazolinedione-5-carboxylic acid (VIII) was refluxed for half an hour with 20 ml. of thionyl chloride containing three drops of quinoline. The resultant clear solution was concentrated to a few ml. and the crystalline acid chloride was removed by filtration, washed with a small amount of dry ether; yield 1.6 g., (95%), m.p. 178-180° with decomposition.

Anal. Calcd. for $C_{11}H_9O_3N_2Cl$: Cl, 14.68. Found: Cl, 14.3.

The acyl chloride (IX) upon treatment with diazomethane gave a diazoketone which was judged to be identical with (III) on the basis of mixed melting point tests.

1-(or 3)-Methyl-2,4-quinazolinedione-5-carboxylic Acid (X).

Scott and Cohen reported that limited methylation of 2,4-quinazolinedione-5-carboxylic acid with dimethyl sulfate in the presence of sodium hydroxide yields 2,4-dimethoxyquinazoline-5-carboxylic acid. However, Lange, Chisholm and Szabo later claimed that the product was actually 1,3-dimethyl-2,4-quinazolinedione-5-carboxylic acid. The acid obtained after repeating the work in this laboratory (after two recrystallizations from ethanol) was a monomethyl acid as shown by the analysis, m.p. 332-333° (uncor.).

Anal. Calcd. for $C_{10}H_8O_4N_2$: C, 54.54; H, 3.66; neut. equiv., 220. Found: C, 54.5; H, 3.85; neut. equiv., 221, 222.

5-(1-Hydroxyethyl)-1(or 3)-methyl-2,4-quinazolinedione (XII).

A suspension containing 1 g. (0.0034 mole) of 5-bromoacetyl-1(or 3)-methyl-2,4-quinazolinedione (IV) or 0.9 g. (0.0036 mole) of 5-diazoacetyl-1,3-dimethyl-2,4-quinazolinedione (III) and 10 ml. of a 10% stannous chloride solution in

concentrated hydrochloric acid was heated on a water-bath with stirring for two hours. The resultant clear solution was diluted with 20 ml. of water and, after standing overnight, yielded 0.7 g. (95%), and 0.35 g. (45%) of colorless crystals melting at 212-213°.

Anal. Calcd. for $C_{11}H_{12}O_3N_2$: C, 59.97; H, 5.50; N, 12.72. Found: C, 59.8; H, 5.21; N, 12.9.

1-(or 3)-Methyl-2,4-quinazolinedione-5-carboxylic Acid (XI).

One gram (0.0039 mole) of 5-diazoacetyl-1,3-dimethyl-2,4-quinazolinedione (III) or 1.0 g. (0.0034 mole) of 5-bromoacetyl-1(or 3)-methyl-2,4-quinazolinedione (IV) or 0.51 g. (0.0023 mole) of 5-(1-hydroxyethyl)-1(or 3)-methyl-2,4-quinazolinedione (XII) was suspended in 50 ml. of a water solution containing 1.25 g. (0.008 mole) of potassium permanganate. The mixture was maintained at 80° with stirring for one hour. After removing the precipitated manganese dioxide, the clear, slightly colored solution was carefully acidified with dilute hydrochloric acid. The crystals which formed on cooling were separated, yielding 0.60 g. (66%), 0.40 g. (62%) and 0.14 g. (27%) of product, respectively. A portion of each was purified by decolorizing with carbon and recrystallizing twice from aqueous alcohol, m.p. 230-237° with evolution of gas.

Anal. Calcd. for $C_{10}H_8O_4N_2$: C, 54.53; H, 3.66; neut. equiv., 220. Found: C, 54.9; H, 3.83; neut. equiv., 218.

1(or 3)-Methyl-2,4-quinazolinedione (XIII).

Two and a half grams (0.011 mole) of 1(or 3)-methyl-2,4-quinazolinedione-5-carboxylic acid (XI) was heated to 250° in a sublimation apparatus. After the evolution of carbon dioxide ceased, the residue was sublimed at 200° under reduced pressure. The sublimate (0.70 g., 35%) was triturated with a small amount of 1% sodium carbonate solution and the insoluble residue recrystallized from ethanol; hard needles, m.p. 198-199°.

Anal. Calcd. for $C_9H_8O_2N_2$: C, 61.34; H, 4.58. Found: C, 61.2; H, 4.80.

Methyl, 2,4-dioxo-3,1,4-benzoxazine-5-carboxylate.

A slow stream of phosgene was introduced through a sintered glass gas dispenser to a solution containing 20 g. of 6-carbomethoxy-2-aminobenzoic acid hydrochloride (2) (0.092 mole) over a period of thirty minutes. The reaction proceeded readily as evidenced by the precipitation in a few minutes of a white solid. After cooling, the precipitate was filtered and washed with a small amount of cold water. Yield 16.5 g. (81%).

A portion recrystallized from aqueous alcohol gave a colorless crystalline compound, m.p. 188-90°.

Anal. Calcd. for $C_{10}H_7O_5N$: C, 54.3; H, 3.17; neutral eq. 110.5. Found: C, 54.1; H, 3.19; neut. eq. 115.

Methyl, 2,4-dioxo-1-methyl-3,1,4-benzoxazine-5-carboxylate:

A suspension of 4.7 g. (0.0021 mole) of methyl, 2,4-dioxo-3,1,4-benzoxazine-5-carboxylate in 10 ml. of dry ether was placed in a three-necked flask equipped with a dropping funnel, a drying tube and a mechanical stirrer. Ten ml. of an ice-cold ethereal solution of diazomethane prepared from 1.0 g. of nitrosomethylurea was introduced into the flask with constant stirring which was continued for a period of three hours; nitrogen gas was evolved in the early stages of the reaction. The precipitate was removed by filtration, washed with a small amount of dry ether; yield 3.2 g. (64%). Recrystallization from alcohol gave a product m.p. 167.5-168.5°.

Anal. Calcd. for $C_{11}H_9O_5N$: C, 56.2; H, 3.83. Found: C, 55.8; H, 3.90.

1-Methyl-2,4-quinazolinedione-5-carboxylic acid:

To a suspension of 2.1 g. (0.009 mole) of methyl, 2,4-dioxo-1-methyl-3,1,4-benzoxazine-5-carboxylate in 10 ml. of

water was slowly added with constant stirring 50 ml. of a 10% potassium hydroxide solution. After standing for a few minutes, the mixture was neutralized with 6 N HCl and then acidified with 1.5 ml. of 6 N HCl. One gram of potassium cyanate was then stirred into the mixture. After standing 1.0 g. (45%) of a light yellow colored crystals were deposited which were identified as 2(N³ methyl) ureido-6-carbomethoxybenzoic acid. These were used immediately in the next step.

Anal. Calcd. for C₁₁H₁₂O₅N₂: neut. eq. 126.

Found: neut. eq. (by back titration) 128.

The 2(N³-methyl) ureido-6-carbomethoxybenzoic acid (0.8 g. - 0.003 mole) together with 1.5 ml. of conc. hydrochloric acid and 1 ml. of water were heated on a water bath with occasional stirring for ten minutes. The mixture which soon solidified was refluxed with 15 ml. of 6 N hydrochloric acid for an hour to complete the hydrolysis of the ester. The insoluble hydrolysis product was removed by filtration and redissolved in alkali and again refiltered to remove any insoluble residue. Upon acidification of the filtrate with hydrochloric acid, 0.5 g. (71%) of needles were obtained. Recrystallization from alcohol gave a product m.p. 320-1° (uncorrected).

Anal. Calcd. for C₁₀H₈O₄N₂: C, 54.5; H, 3.66;

neut. equiv. 220. Found: C, 54.5; H, 3.64; neut. eq. 215.

6-Carbomethoxy-(N-methylammoniumcarboxy) anthranilicmethylamide and 3-amino-N-methylphthalimide:

Six grams (0.027 mole) of methyl, 2,4-dioxo-3,1,4-benzoxazine-5-carboxylate were slowly added with constant stirring to 40 ml. of an ice-cold saturated solution of methylamine in methanol. This gave a clear yellow solution from which yellow crystals began to separate. After thirty minutes, the crystals were removed by filtration; yield 1.3 g. These crystals were identified as 3-amino-N-methylphthalimide, m.p. 201°.

Anal. Calcd. for $C_9H_8O_2N_2$: C, 61.3; H, 4.54; N, 15.9. Found: C, 61.4; H, 4.59; N, 15.5.

The filtrate was then evaporated under reduced pressure to a small volume from which the crystalline product separated on cooling. This product was removed by filtration and recrystallized from ethereal alcohol, yield 1.7 g. (22%). The colorless crystalline compound melted at 136° with gas evolution, resolidified and remelted at 198-200°.

Anal. Calcd. for $C_{12}H_{17}O_5N_3$: C, 50.8; H, 6.01. Found: C, 51.0; H, 6.23.

3-Methyl-2,4-quinazolinedione-5-carboxylic acid.

A solution of 0.7 g. (0.0025 mole) of 6-carbomethoxy-(N-methylammonium carboxy) anthranilicmethylamide in 10 ml. of

6N HCl was heated on a water bath with constant stirring for five minutes. Crystals soon separated which were collected after cooling, yield 0.55 g. (95%). Upon recrystallization from alcohol, the compound gave a m.p. of 190-3° with sublimation and was identified as the ester methyl,3-methyl-2,4-quinazolinedione-5-carboxylate.

Anal. Calcd. for $C_{11}H_{10}O_4N_2$: C, 56.4; H, 4.27.

Found: C, 56.0; H, 4.26.

The ester was hydrolyzed by refluxing in conc. hydrochloric acid to 3-methyl-2,4-quinazolinedione-5-carboxylic acid, m.p. 332-333° (uncorr.). The compound was judged to be identical with the monomethyl-2,4-quinazolinedione-5-carboxylic acid prepared by partial methylation of 2,4-quinazolinedione-5-carboxylic acid with dimethyl sulfate (2) on basis of a mixed melting point determination.

Methylation of 3-methyl-2,4-Quinazolinedione-5-carboxylic acid:

Eighty-five milligrams (0.000386 mole) of 3-methyl-2,4-quinazolinedione-5-carboxylic acid were added slowly with constant stirring to 10 ml. of an ice-cold ethereal solution of diazomethane prepared from 1.0 gram of N-nitrosomethylurea; nitrogen gas was slowly evolved as the mixture was gradually

up to room temperature. After standing for five hours, the evolution of gas ceased and the solution was evaporated then to half its original volume and filtered; yield 60 mg. This neutral product recrystallized from alcohol and gave a m.p. of 193-5°.

Anal. Calcd. for $C_{11}H_{10}O_4N_2$: C, 56.4; H, 4.28.

Found: C, 56.6; H, 4.60.

Thirty milligrams of the above neutral product was remethylated with 10 ml. of an ice-cold ethereal solution of N-nitroso-methyl urea and 5 ml. of dry methanol under same conditions. Upon completion of the reaction, the solution was evaporated to dryness and redissolved in hot alcohol-water mixture. After cooling for several days in the refrigerator, 5 mg. of a crystalline compound were obtained. M.P. 136-7°.

Anal. Calcd. for $C_{12}H_{12}O_4N_2$: C, 58.1; H, 4.63.

Found: C, 58.3; H, 4.77.

3-Methylamino-N-methylphthalimide.

A 1.0 g. sample of methyl, 2,4-dioxo-1-methyl-3,1,4-benzoxazine-5-carboxylate (prepared from diazomethane methylation of methyl,2,4-dioxo-3,1,4-benzoxazine-5-carboxylate) was suspended in 10 ml. of ethyl alcohol cooled by an ice bath; 15 ml. of a saturated alcoholic solution of methylamine was added

gradually with stirring. After the addition, stirring was continued for half an hour, while intensely yellow colored solid began to appear. The product was removed by filtration and additional product was obtained by evaporation of the mother liquor. The combined products were recrystallized from alcohol, yield 0.85 g. m.p. 158° . The product remained unchanged after refluxing with either concentrated hydrochloric acid or potassium hydroxide.

Anal. Calcd. for $C_{10}H_{10}O_2N_2$: N, 14.74. Found: N, 14.70.

III. SUMMARY

Method for the preparation of 5-(2-morpholine-1-hydroxyethyl)-1 (or 3)-methyl-2,4-quinazolinedione hydrochloride are given in detail using 2,4-quinazolinedione-5-carboxylic acid as the starting material. Several unusual reactions of the intermediate, 5-diazoacetyl-1,3-dimethyl-2,4-quinazolinedione such as permanganate oxidation, stannous chloride reduction and hydrobromic acid treatment are described. In these processes, one of the methyl substituents is invariably lost to give the corresponding monomethyl derivative.

In order to locate the position of the lost methyl group, both 1 and 3-methyl-2,4-quinazolinedione-5-carboxylic acid are prepared synthetically and are found to be not identical with the monomethyl-2,4-quinazolinedione-5-carboxylic acid obtained by the permanganate oxidation of 5-diazoacetyl-1,3-dimethyl-2,4-quinazolinedione. Also, the monomethyl-2,4-quinazolinedione-5-carboxylic acid upon methylation with diazomethane gave the methyl ester of a dimethyl-2,4-quinazolinedione-5-carboxylic acid which is isomeric but not identical to methyl-1,3-dimethyl-2,4-quinazolinedione-5-carboxylate.

It is, therefore, concluded that this monomethyl acid could be either a stereo isomer of 1 (or 3)-methyl-2,4-quinazolinedione-5-carboxylic acid or the methyl group is attached in some other manner.

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