SOME SYNTHETICAL EXPERIMENTS WITH 4-QUINAZOLONE

Thesis by

Rafat Mirza

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ABSTRACTS

An exceedingly labile compound has been isolated by the direct acetylation of 4-quinazolone. The same compound was obtained by reacting silver acetate and 4-chlorquinazoline. Attempts to prepare 3-acetyl-4-quinazolone by the oxidation of 3-acetyl-3, 4-dihydroquinazoline were not successful, and only 4-quinazolone was isolated as the oxidation product.

Attempts to attach the alkylaminoalkyl side chains to 4-quinazolone showed that such secondary amines undergo self condensation rather than react with 4-quinazolone. However, it was possible to introduce a dialkylaminoalkyl side chain, and 3-(diethylaminoethyl)-4-quinazolone has been synthesized and is being tested for possible antimalarial activity.

3-Acetonyl-4-quinazolone gave a well defined crystalline solid with diethylamine under the conditions of the Mannich reaction. The analysis of this compound did not agree with the values for the expected compound, and the structure has not been elucidated.

ATTEMPTS TO SYNTHESIZE 3-ACETYL-4-QUINAZOLONE

INTRODUCTION

Although many substituted 4-quinazolones have been prepared, no reference to 3-acetyl-4-quinazolone is encountered in the literature. However it has been reported that attempts at direct acetylation, in hope of getting the 3-acetyl derivative were not successful.[1] The only 3-acetyl derivative encountered in the literature is the 2-phenyl-3-quinazolone, the preparation of which is reported by Shah and Ichaporia.[1] Their method of synthesis lies in the condensation of benzanilid imidochloride with acetylurethane, and the subsequent cyclisation of the product so formed. It is interesting to note that the same authors report that their attempts to acetylate 2-phenyl-4-quinazolone were not successful.

A series of experiments were performed in an endeavor to synthesize 3-acetyl-4-quinazolone. The problem was approached from different angles, and a new compound, whose elementary analysis agrees with that of the expected compound, was isolated. The mode of formation of this compound and the subsequent steps to prove its structure are recorded in the following pages.

PART I.

DIRECT ACETYLATION

By the direct acetylation of 4-quinazolone with acetic anhydride and acetyl chloride, an exceedingly labile compound, whose analysis agrees with that of the expected compound, 3-acetyl-4-quinazolone, was obtained. It was a colorless crystalline solid, m.p. 84.5 -86°. In contact with water, even at 0°, it was instantaneously decomposed to 4-quinazolone and acetic acid. The mode of formation of this compound is given below:

MODE OF FORMATION

Method I. Acetylation with acetyl chloride:

The potassium salt of 4-quinazolone was prepared by the addition of 47.2 ml. 1.145N alcoholic potassium hydroxide to 7.90 grams 4-quinazolone dissolved in 100 ml. alcohol, and removing the solvent at reduced pressure. The potassium salt was further dried in the Abderhalden apparatus over phosphorus pentoxide at 110° for twenty hours. From the above dried salt, 9.49 grams were introduced into a three neck flask, and dioxane which had just been refluxed over sodium was distilled directly into the reaction flask. Eight milliliters (100% excess) of freshly redistilled acetyl chloride was introduced into the flask, and the contents were refluxed. The end of the reaction was noted in the following manner.

Approximately 1 ml. of the mixture was removed from the flask, and quickly introduced into a small test tube already heated to 110° in a dibutylphthalate bath. The solvent was blown off with air dried over calcium chloride. The solid residue so obtained was dissolved in water and a drop of phenolphthalein was introduced. A pink coloration was taken as indicating the presence of the potassium salt and consequently of the incompleteness of the reaction.

After an hours refluxing the reaction had gone to completion. The solvent was stripped off at reduced pressure below 70°. The air that was passed through during the distillation was dried over sulfuric acid. A solid residue was obtained which was very soluble in benzene and could best be crystallized from benzene-ligroin mixture (3:1). Colorless chunky crystals, m.p. 84.5 -86°, were obtained. The yield was 5.5 grams. Anal: Found: C, 64.28; H, 4.23 . Calc. for $C_{10}H_8O_2N_2$ C, 63.82; H, 4.28.

In the above experiment, great care was necessary to minimize atmospheric exposures and to exclude water as much as possible. In several experiments, where rigid measures like drying the salt over phosphorus pentoxide and the dioxane over sodium were not taken, 4-quinazolone was the only product isolated.

The value for the carbon determination shows a difference of 0.46% from the expected value. The above value is perhaps not as close as one would like to get. However, in view of the fact that the compound under consideration was so labile, the inevitable exposures between the final crystallization and combustion were bound

to lead to some decomposition that subsequently showed itself in the analysis. A closer check on the compound was possible by the determination of the equivalent weight. Freshly recrystallized samples of the compound were hydrolyzed, and the liberated acetic acid was titrated against tenth normal sodium hydroxide, using phenolphthalein as the indicator. An equivalent weight of 189 was thus obtained. The close agreement of this with the expected value, 188.2, places the molecular formula beyond doubt.

Method II. Acetylation with acetic anhydride:

One gram of 4-quinazolone was refluxed for one hour with 25 ml. of acetic anhydride. The excess anhydride was removed at reduced pressure and temperature not exceeding 70°. A solid residue was obtained, which was recrystallized from benzene-ligroin mixture (3:1). Colorless chunky crystals were obtained, m.p. 84.5 -86°. A mixed melting point with the substance from the first experiment showed no depression. The yields in these experiments ranged from 45 to 80 percent. The yield was proportional to the amount of care taken in excluding the moisture during the process of stripping the solvent, and while crystallizing.

PART II.

PROOF OF THE STRUCTURE

Judging from the structure of 4-quinazolone, one would expect the acetylation, to give the N-acetyl derivative. However, to place the structure of the compound isolated by the direct acetylation on a more solid ground, a series of experiments was performed. The object of these investigations was not only to get direct evidence of the N-acetyl group, but also to get indirect evidence on the problem by synthesizing the other possible isomer, 4-acetoxyquinazoline. The following three schemes were devised and put to test.

SCHEME I

The object of this experiment was to synthesize 4-acetoxyquinazoline in order to confirm whether it is the same or different from the substance obtained from the direct acetylation. The synthesis was undertaken by refluxing 4-chlorquinazoline with anhydrous potassium-acetate in dry benzene and in dry dioxane. There was no reaction. The use of sodium acetate instead of the potassium acetate did not change the situation. However, the silver acetate reacted slowly with the 4-chlorquinazoline. The compound thus isolated proved to be the same as the one obtained in the direct acetylation experiments.

EXPERIMENTAL:

Silver acetate contained in a test tube wrapped in black paper was dried in Abderhalden apparatus over phosphorus pentoxide for twenty hours at 110°. From the above dried salt, 5.6 grams were weighed out into a flask. Freshly recrystallized 4-chlorquinazoline, 5.5 grams (equivalent quantity) was added, and 150 ml. dry dioxane was introduced. The mixture was refluxed, and the end point was determined as follows:

Approximately 0.5 ml. of the solution was pipetted out, and the suspended matter removed by centrifugation. The clear solution was decomposed with dilute nitric acid, and the resulting solution was tested for the chloride ion. A positive test with silver nitrate showed the presence of the chloro compound and, consequently, the incompleteness of the reaction.

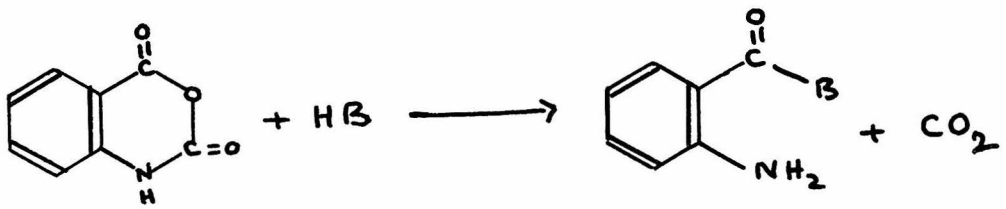
The reaction was found to go to completion in twenty hours. On filtration, a bright yellowish-green solution was obtained. The solvent was removed at reduced pressure below 70°. The solid residue gave a benzene soluble portion and a benzene insoluble portion. The benzene soluble portion proved to be the same as that obtained in the direct acetylation experiments, while the benzene insoluble portion was 4-quinazolone. The total yield of benzene soluble compound was 2.95 grams; the yield of 4-quinazolone was 2.3 grams.

SCHEME II

This scheme was devised in order to have a synthesis, in

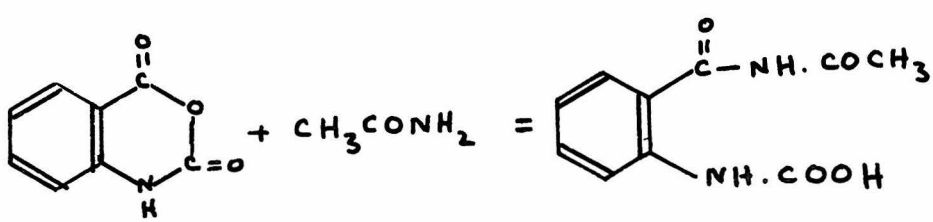
which the acetyl group is known to be attached to position three, on the basis of the well known mechanism formulated by Clark and Wagner[2] for the reaction of isatoic anhydride.

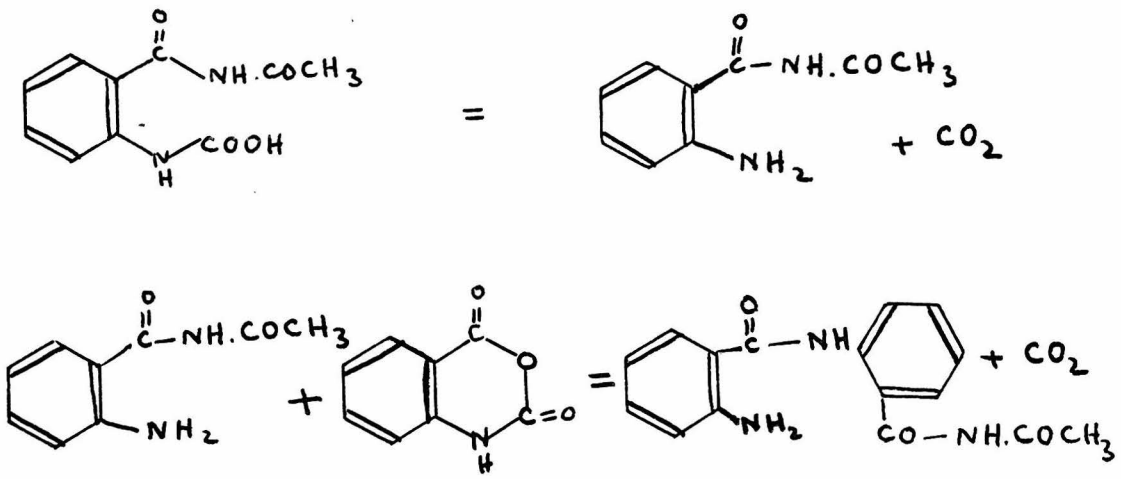
Clark and Wagner have investigated the reactions of isatoic anhydride of the following type.



B = $-NH_2$; $-NHR$; $-NHAR$ etc.

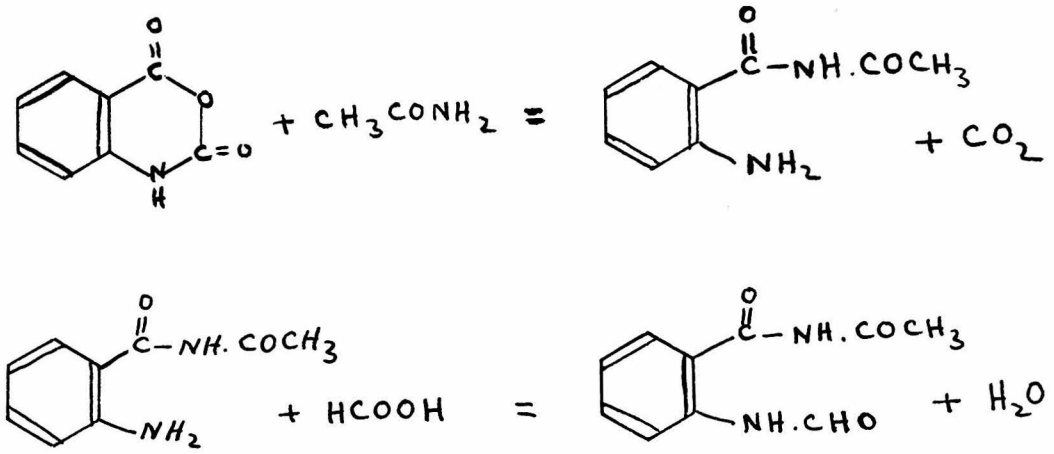
The above reaction in the case of acetamide had been found to go abnormally by Bell and Meyer[4], although the amount of the carbon dioxide given off is just as much as expected for the normal reaction. Clark and Wagner interpret this abnormality as due to the complications arising from the free amino group, produced by the decarboxylation of the product formed by the first step. They formulate their action as follows:

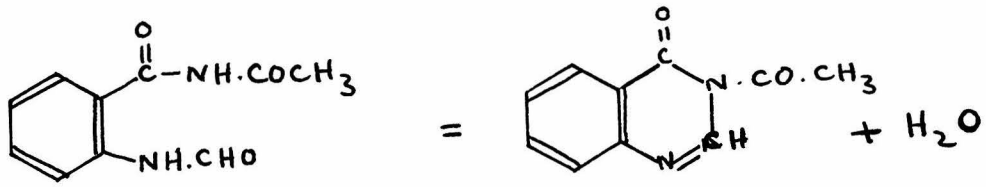




AND SO ON

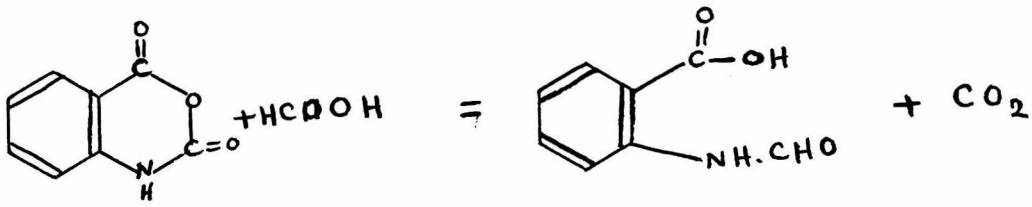
The interest in the above reaction lay in the fact that, if by some means it were possible to prevent polymerization, then by the reaction with formic acid it should be possible to affect the ring closure to give the desired product. The reaction as desired was as follows:





The above scheme was tested experimentally. On heating equimolar quantities of isatoic anhydride and acetamide at 160-180° until no more carbon dioxide was liberated, a pale yellow amorphous product resulted, in confirmation of the Meyer and Bellmann's observations.

As there was a clear indication that the free amino group was the cause of the aberration of the reaction from the desired path, experiments were devised in an attempt to block the amino group as soon as it is formed. Equivalent quantities of acetamide and isatoic anhydride were refluxed in anhydrous formic acid. The reaction gave only formylanthranilic acid. Apparently the course of the reaction was as follows:

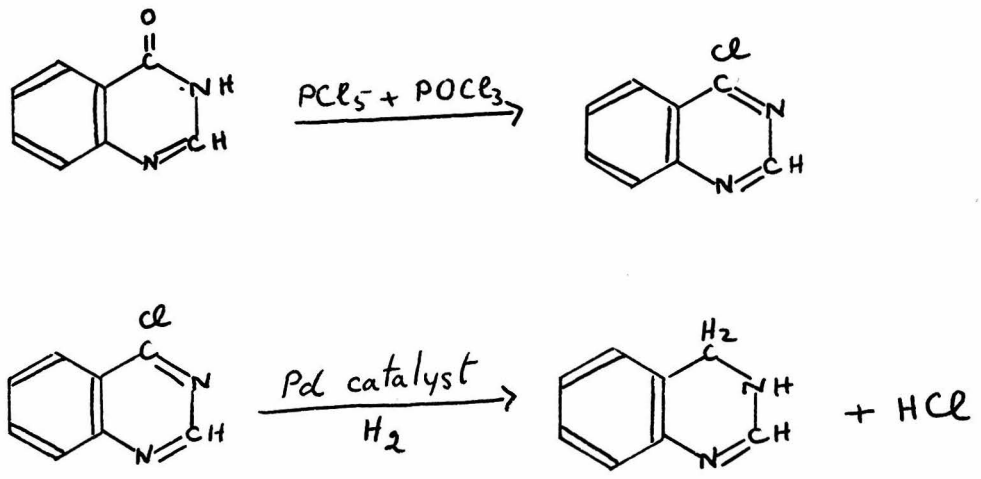


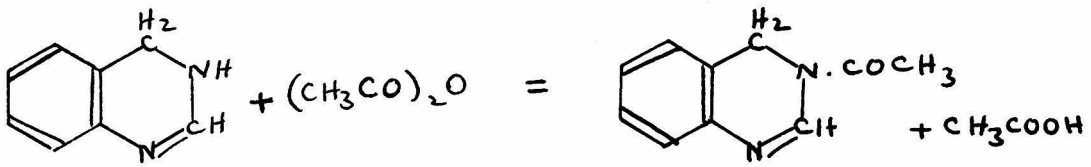
EXPERIMENTAL:

Three grams isatoic anhydride and 1.1 gram acetamide (equivalent quantities) were refluxed in 30 ml. anhydrous formic acid. The carbon dioxide was collected over water previously saturated with the gas. The reaction was completed in five hours. On cooling the solution crystals came out. Weight of the dry mass was 2.7 grams. The crystalline mass was identified as formyl anthranilic acid by mixed melting point.

SCHEME III Oxidations of 3-acetyl-3, 4-dihydroquinazoline

Another approach to the problem was possible due to the fact that 3-acetyl-3, 4-dihydroquinazoline can be synthesized. The synthesis of this compound has been recently reported by Elderfield in the following manner:





As the 3-acetyl-3, 4-dihydroquinazoline on oxidation would be expected to give 3-acetyl-4-quinazolone, a series of oxidation experiments were performed. The oxidations in aqueous medium with hydrogen peroxide gave an ill-defined product. By oxidation with potassium permanganate, only 4-quinazolone was formed. The removal of the acetyl group during the oxidation in aqueous medium suggested the use of an anhydrous medium for the oxidation, in order to prevent the hydrolysis of the acetyl group. Acetic acid seemed very appropriate as the reaction medium because it can be obtained in anhydrous form easily; because standard solutions of chromic anhydride and that of hydrogen peroxide can be conveniently prepared; and because its anhydride can be added to take up the water formed in the reaction.

Oxidations with anhydrous peroxide in the presence of acetic anhydride gave an ill-defined substance, which could not be crystallized. Oxidations with chromic anhydride solutions gave only 4-quinazolone, in 25 to 40% yields. The use of potassium permanganate and calcium permanganate in anhydrous acetic acid was not possible because of their insolubility.

EXPERIMENTAL:

Preparation of 4-quinazolone:

The method used was a modification of the one used by Niementowski[10]. One hundred grams of anthranilic acid was introduced into a beaker and 50 ml. formamide (100% excess) was added. The mixture was heated at 125 to 130° over an oil bath. The mass solidified in two and one-half hours. Heating was continued for two hours. A higher temperature reduced the yield immensely.

The solid lump was dissolved in the minimum quantity of 20% sodium hydroxide solution, and the solution was made up to 500 ml. The 4-quinazolone was precipitated by passing in carbon dioxide gas. The crude 4-quinazolone was washed with 100 ml. water and crystallized from about 800 ml. of 5 to 10% alcohol in water. The yield was 89 grams. An additional 6 to 8 grams were recovered from the mother liquors, m.p. 216 - 217°, with sublimation at 180°.

Preparation of 4-chlorquinazoline:

The method given by Gabriel and Stelzer[6], and its modification given by Bogert and May[7] was tried several times, but very poor yields were obtained. The following method has been worked up, based on a suggestion of Christensen[8] that the chlor-compound is quite stable in the presence of base. The yield by this method is higher than that claimed by others for their methods.

4-quinazolone, 22 grams, was introduced in a 300 ml. flask, and 120 ml. phosphorus oxychloride was added. Phosphorus pentachloride,

34 grams (10% excess), was gradually added. On refluxing for an hour, a clear solution was obtained. Phosphorus oxychloride was removed at reduced pressure (90 to 100 ml.).

Eighty grams sodium hydroxide was dissolved in about 200 ml. water, and 500 grams of crushed ice was added. With vigorous shaking, the contents of the flask were added to sodium hydroxide solution. A white precipitate immediately separated out. The mass was extracted with one litre of carbon tetrachloride in three batches. The extracts were dried over sodium sulfate, and the solvent stripped off. The solid residue left in the flask was crystallized from 60 - 80 ml. petroleum ether (60 - 70° fraction). The yield was 17.3 grams, m.p. 95.5 - 96.5°.

In working with 4-chlorquinazolone, it is advisable to use rubber gloves and to take precautions not to let it come in contact with the skin. Painful blisters resulted when, because of the ignorance of this fact, it was handled without any precautions. The physiological effect was confirmed by the application of the chlor-compound to the skin, which caused blisters in less than twenty hours.

Preparation of Palladium Catalyst:

The method is essentially the same as that of Busch and Stove[9]. One gram of the palladium chloride was dissolved in the minimum quantity of concentrated hydrochloric acid, and the solution was made to 100 ml. with distilled water. Fifty grams of reagent

precipitated calcium carbonate was introduced in a litre conical flask and 300 ml. distilled water was added. To this solution the palladium chloride solution was added gradually with constant whirling. The contents turned brown immediately. After all the palladium solution had been added, the contents was warmed to 80°, for five minutes. The flask was then allowed to cool. The suspension was filtered off on a medium porosity sintered glass funnel. The catalyst was further washed six to eight times with cold distilled water (total washings were about 150 ml.). The washed catalyst was dried below 80°, powdered, and stored in a glass stoppered bottle. The catalyst had a light brown color.

Preparation of 3, 4-dihydroquinazoline:

Eight grams of freshly recrystallized 4-chlorquinazoline was dissolved in 200 ml. twice redistilled methanol. Eight grams of the above prepared catalyst were added, and the reduction was done on the Adam's machine at 32 pounds pressure. The catalyst was reduced in one minute and the whole solution became black. The theoretical amount of hydrogen was absorbed in 12 to 15 minutes. The redistilled methanol was much preferred for the job, as in several experiments where ordinary methanol was used the reduction failed completely.

After the reduction, the catalyst was filtered off and the clear solution was stripped of its solvent at reduced pressure and below 30°. A higher temperature at this stage greatly reduced

the yield. Then the volume was reduced to about 15 ml., about 80 ml. water was added, and the solution was made strongly alkaline with sodium-hydroxide. The solution was extracted five times with 30 ml. ether. The extracts were dried over sodium sulfate and ether stripped off below 25°.

The solid residue was recrystallized from benzene. The yield was 4.1 grams, m.p. 126 - 127°.

It was interesting to note that, in the reduction on the 4-chlorquinazoline, even in the presence of the carbonate, the hydrogen chloride that was formed gave the hydrochloride of the base. When the solution after the reduction was stripped of its solvent, the hydrochloride of 3, 4-dihydroquinazoline was isolated. It was crystallized from methanol, and melted between 234 and 236° with decomposition.

Preparation of 3-acetyl-3, 4-dihydroquinazoline:

Five grams of 3, 4-dihydroquinazoline was added to 50 ml. of benzene and 10 ml. of acetic anhydride were added. The mixture was refluxed for two hours. The solvent was stripped off at reduced pressure below 70°. The solid residue was recrystallized from benzene-ligroin mixture (3:1). The yield was 4.5 grams, m.p. 131 - 132°.

Oxidation with aqueous potassium permanganate:

3-acetyl-3, 4-dihydroquinazoline, 350 mg., was dissolved in 7 ml. normal sulfuric acid. Twenty milliter potassium permanganate

solution, 0.426N, (5% excess), was gradually added in 10 minutes. Immediate oxidation took place. The oxidized solution was left at room temperature for two hours. It was then neutralized with sodium-hydroxide and extracted with chloroform. Total extracts amounted to 160 ml. The extracts were dried over magnesium sulfate and evaporated to dryness. The solid residue obtained was recrystallized from acetonitrile. The yield was 98 mg., m.p. 215 - 216°. A mixed melting point with 4-quinazolone showed no depression.

Oxidation using anhydrous hydrogen peroxide:

Recrystallized 3-acetyl-3, 4-dihydroquinazoline, 800 mg., was dissolved in 2 ml. anhydrous acetic acid, and 1.5 ml. acetic anhydride was added (30% excess). Twenty-six milliters of 0.706 N solution of hydrogen peroxide, (equivalent amount) was gradually added in an hours time. The solution was transferred to a crystallizing dish and was left in a desiceator over sodium-hydroxide under vacuum. Evaporation was very slow. In seven days the mass got to a pasty condition, and hardened more in the next two days. Attempts to crystallize the mass were not successful. It was too soluble in benzene, acetonitrile, and dioxane. From ethyl acetate butyl acetate and amyl acetate, it came out in a gluey form, despite repeated efforts to crystallize. Mixtures of ligroin and other solvents in which it was too soluble were tried, but it did not improve the situation. A solution of the substance in benzene-ligroin mixture was left in

the desiccator for over three months, and attempts were made from time to time to induce crystallization by scratching without any success.

Oxidation using chromic anhydride solution in acetic acid:

One gram 3-acetyl-3, 4-dihydroquinazoline was dissolved in freshly distilled acetic acid. Six milliters redistilled acetic anhydride (21% excess) was added. Twenty-five milliters of 0.926N chromic anhydride solution in acetic acid (1% excess) were added gradually in an hours time. Immediate oxidation was noticed. After the addition of the oxidizing agent, the solution was transferred to a crystallizing dish and was left in a desiccator over sodium hydroxide under vacuum. The acetic acid was evaporated in eight hours, and left a dry residue. The residue was finely powdered and extracted with dry benzene. The extracts on evaporation gave a solid residue, m.p. 215 - 216°. A mixed melting point with 4-quinazolone showed no depression. Total yield was 400 mg.

The residue was further extracted with ethyl acetate, alcohol, and dioxane, but no more organic matter was extracted.

A DISCUSSION ON THE EXPERIMENTAL RESULTS:

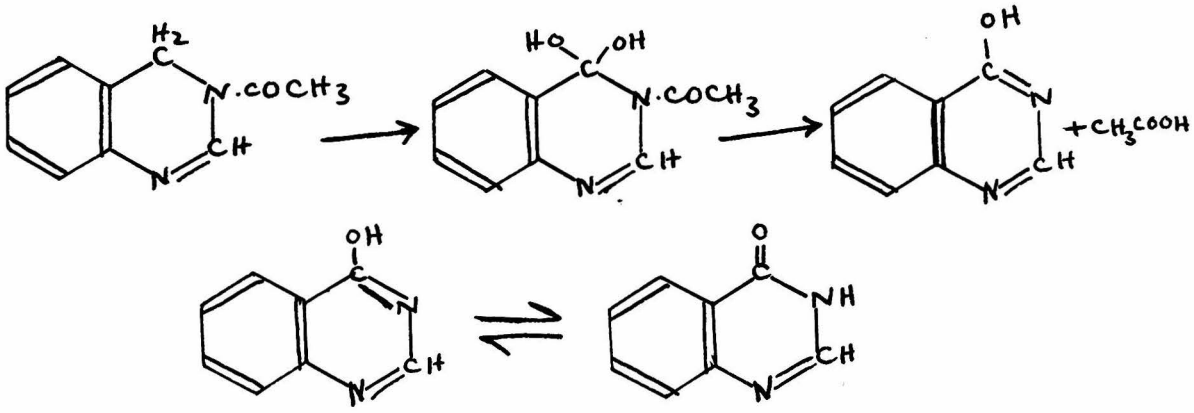
Although the above experiments are not sufficiently clear cut so as to reveal the structure of the new compound directly, the evidence obtained and the data from the other sources can be put together to give a reasonable picture of the situation.

The first two experiments, which consist in the acetylation of 4-quinazolone using acetyl chloride and acetic anhydride respectively, should be expected to give N-acetyl-4-quinazolone under normal conditions. It is a well known fact in quinazolone chemistry that the reaction of alkyl halide with 4-quinazolone in alkaline medium gives the three substituted derivatives. In a similar way, one would expect the acetylation with acetyl chloride to give the three substituted derivative.

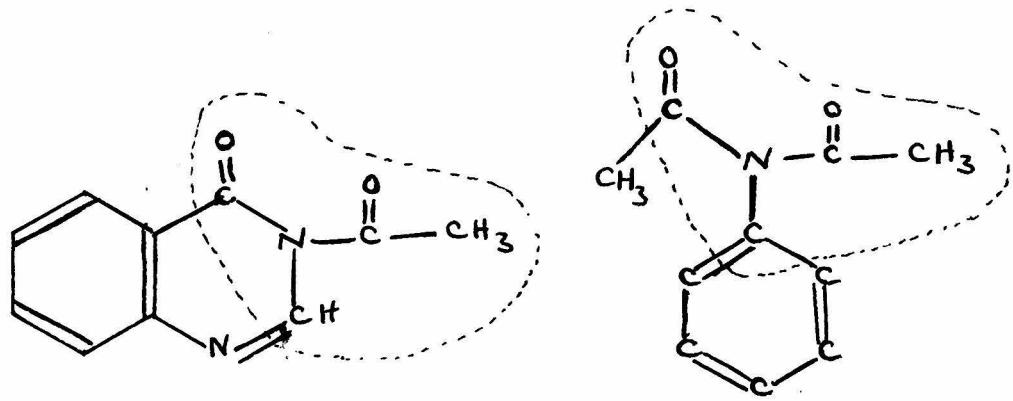
The third experiment, which consists in refluxing 4-quinazoline with silver acetate, makes this picture rather blurred. Under normal conditions, one would expect the reaction to give the 4-acetoxy compound. However, the compound formed is the same as that obtained in the above two experiments. In this connection, it is interesting to note that the migration of the acetyl group has been reported in the literature[2]. It is known that diacetanilide on heating alone or in presence of zinc and hydrochloric acid gives p-acetaminoacetophenone. The conditions under which 4-chlorquinazoline reacts with silver acetate being vigorous enough, the migration of the acetyl group is quite possible.

The dilemma of the above three experiments would have been solved if the oxidation of the 3-acetyl-3, 4-dihydroquinazoline had let to isolation of the same or some other compound. The failure to do so did not make it possible to throw light directly on the matter. However, the results throw much light indirectly on the subject.

The fact, that the oxidation of the acetyl derivative gave quinazolone both in aqueous and non-aqueous medium, gives a clear indication that the acetyl group is split off from the nucleus in some way during the oxidation. The removal of the acetyl group can perhaps be attributed to two things. Either the acetyl group is split off in an intermediate step involved in the oxidation of the methylene group to the carbonyl group; or the presence of the carbonyl group next to the N-acetyl group makes the system unstable, and thus hydrolyses off the acetyl group. The first possibility can be pictured as follows:



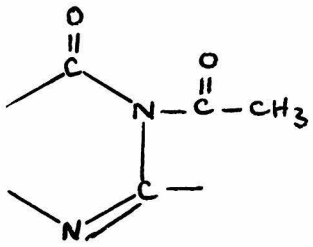
The second possibility is well supported by the properties of the substances that have the essentials of the N-acetyl-4-quinazolone. An interesting compound in this connection is diacetanilide. The structure of diacetanilide and that of 3-acetyl-4-quinazolone are written below to show the close similarity that exists between them.



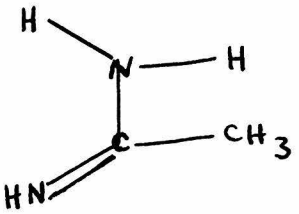
A correlation exists between diacetanilide and acetanilide on the one hand, and the new compound and 4-quinazolone on the other. Acetanilide is barely soluble in benzene and petroleum ether, whereas the diacetanilide shows solobility in both. A similar situation exists between 4-quinazolone and the isolated compound. Again the melting points of acetanilide and diacetanilide are 114° and 37° respectively; 4-quinazolone melts at 216° and the isolated compound melts at 86°. The easy hydrolysis of the first acetyl group in diacetanilide is again noteworthy. Whereas the first acetyl group is removed even by hundreth normal base[2], the second is known to require quite drastic conditions for its removal. The ease with which the acetyl group is hydrolysed from the new compound has already been mentioned. The comparatively greater ease of hydrolysis in this case, is perhaps because of the additional structural features of the 4-quinazolone molecule.

A search in the literature was made to find more compounds which have the structural features, shown below, so that the study

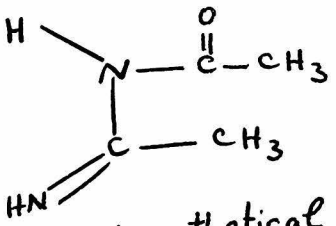
of their properties might give a deeper insight into the matter. The amidines seem to have some of the features. A comparasion is made below between acetamidine and the typical structural feature mentioned above.



Typical structure



Acetamidine



Hypothetical Acetyl acetamidine

Perhaps a closer analogy would exist if the acetyl derivative of acetamidine was represented. But no reference to the acetyl derivative of the acetamidine could be found, maybe because of the fact that the acetyl derivative of acetamidine is too unstable to exist, which further goes to illustrate the instability of the system represented above.

The above data, when summed up, gives a good indication that the compound isolated is 3-acetyl-4-quinazolone.

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PART III.

ATTEMPTS TO SYNTHESIZE SOME 3-SUBSTITUTED-4-QUINAZOLONES AS POTENTIAL ANTIMALARIALS

INTRODUCTION

The synthesis of 3-substituted-4-quinazolones as potential antimalarials presented an interesting proposition because of two reasons. Firstly, the quinazoline derivatives in general have been reported to be much less toxic than the quinoline derivatives [1,2]; secondly, the recent isolation of the alkaloid febrifugine, which has shown a very high antimalarial activity, has been shown to be a three substituted 4-quinazolone[3]. Since three substituted derivatives with the alkylaminoalkyl side chains have not been reported, attempts were made to prepare compounds of this type.

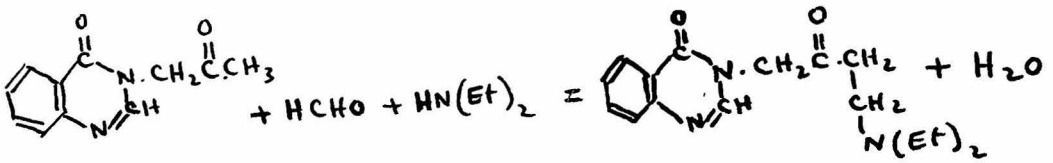
The work done in this field can be divided into two parts. The first part concerns the attempts to increase the side chain of the 3-acetonyl-4-quinazolone by undertaking the Mannich reaction. The second part concerns the attempts to introduce some well known antimalarial side chains in the 4-quinazolone nucleus.

PART IIIa.

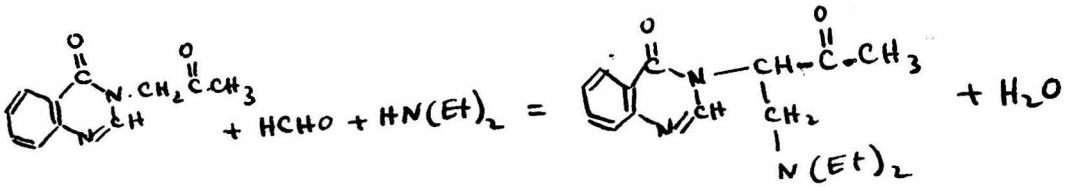
MANNICH REACTIONS WITH 3-ACETONYL-4-QUINAZOLONE

INTRODUCTION

Attempts were made to increase the side chain of 3-acetonyl-4-quinazolone by the Mannich reaction. The reaction was studied with diethylamine. It was thought that the reaction would go in the following way:



or



When the reaction was tested experimentally, it gave a colorless crystalline compound. However, the elementary analysis of this compound did not agree with the values expected for the compound shown above. The mode of formation of this compound and its properties are noted in the following pages.

Mode of Formation and Properties:

On adding diethylamine to a solution of 3-acetonyl-4-quinazolone in water-alcohol mixture, in presence of formaldehyde, there was an immediate reaction, with the evolution of heat. On keeping the solution at room temperature, a thick white precipitate came out in ten to thirty minutes. The reaction was allowed to proceed at room temperature for different lengths of time, and the amount of substance produced was noted. The amount of substance obtained by allowing the reaction to proceed for an hour corresponded to about 20% of the weight of the acetonyl compound, taken initially. In six hours time, the yield was about 60% while an interval of seven days increased the yield to 80%. A yield of 60% was obtained by conducting the reaction at 60° for an hour. However, when the reaction was refluxed, instead of the crystalline product, a yellow amorphous substance was produced.

When alcohol was used instead of water-alcohol solution, the reaction went slowly. The reaction in water-alcohol mixture went very fast, and a 50/50 mixture of the two was the one that was used in most of the experiments.

The reaction was studied by varying the amounts of the three components. First, the amount of formaldehyde was varied. The amount that was used was from 100% excess to 600% excess, while the amount of the amine was 10% more than that necessary for one mole of the acetonyl compound. There was no change in the nature or the amount of the product.

The reaction was then studied by increasing the amount of the amine. To one mole of the acetonyl compound, two moles of the amine and four moles of formaldehyde were added. The reaction gave the same product. Increasing the amine to three moles and the formaldehyde to six moles again made no difference.

When the reaction was done, using the amine hydrochloride instead of the free amine, there was no reaction under the conditions which normally gave the new compound.

The compound obtained in the above experiments was a colorless crystalline substance, m.p. 234 - 235° (uncor). The insolubility this compound showed in organic solvents made its crystallization a difficult task. It was insoluble in alcohol, water, dioxane, chloroform, acetonitrile, nitromethane, methyl cellosolve, esters, and all other organic solvents ordinarily used in crystallizing substances. It was soluble only in nitrobenzene. Even in nitrobenzene the solubility up to 100° is not much. A sharp increase in the solubility is noticed above 150°. When the substance was crystallized from nitrobenzene, it was found convenient to remove the nitrobenzene by washing it with methanol before drying.

Contrary to expectations, the compound proved insoluble in dilute hydrochloric acid. It was soluble only in acid whose strength was greater than normal.

As both the analysis and the properties of the compound were against what one expected for the normal reaction, attempts

were made to get a deeper insight into the matter by conducting the reaction in the absence of one of the three components. First a series of experiments were set up in which different amounts of the acetonyl compound were refluxed with formaldehyde. There was no reaction, and the acetonyl compound was quantitatively recovered. Similarly, it was confirmed that acetonyl compound does not react with diethylamine in absence of formaldehyde. Diethylamine and formaldehyde too did not give any solid product when they were refluxed in absence of 3-acetonyl-4-quinazolone.

The above experiments made it clear that, for the reaction to go to give the new compound, the presence of the diethylamine, formaldehyde, and the 3-acetonyl-4-quinazolone was essential, although the product formed was not what one would expect for a normal Mannich reaction.

PART IIIb.

This part concerns the attempts to introduce the following three chains in the 4-quinazolone nucleus:

a. $ClCH_2CH_2N(Et)_2 \cdot HCl$

b. $ClCH_2CH_2CH_2CH_2CHNHCH(CH_3)_2 \cdot HCl$

c. $CH_3CHBrCH_2CH_2CHNHCH(CH_3)_2 \cdot HBr$

The first chain, called the Novalid salt, differs from the other two in being a tertiary amine. It was possible to attach the Novalid side chain to 4-quinazolone and to obtain the resulting compound in a crystalline form as the dihydrobromide. Similar methods did not work with the other two. In all the experiments the chains, instead of reacting with 4-quinazolone, underwent self condensation. The experiments done in this direction are recorded in the following pages.

EXPERIMENTAL:

a. The Novalid Chain:

The Novalid salt, obtained in a crude state, was purified by crystallization from absolute alcohol. Two crystallizations were necessary to give a colorless compound, m.p. 207 - 208°. The Novalid salt could be crystallized equally well from acetonitrile.

Twenty grams of the above purified Novalid salt (0.1165 moles) was added to 17 grams 4-quinazolone (0.1165 moles), dissolved

in 157 ml. 1.485N alcoholic sodium-hydroxide (0.233 moles). The solution was made to 250 ml. with absolute alcohol and refluxed in an oil bath for ten hours. The sodium chloride was filtered off and the solvent was stripped at reduced pressure below 70°. A thick viscous liquid was obtained which could not be crystallized. It was converted to the dihydrobromide by the addition of 50 ml. of 48% hydrobromic acid. The solvent was removed at reduced pressure and the dry solid residue was crystallized from 200 ml. 95% alcohol. Colorless chunky crystals, m.p. 238 - 239° (uncor.) were obtained. The yield was 34.5 grams (73%).

Anal. Found: C, 41.25; H, 5.26; N, 10.25; Br, 39.11

Calc. for $C_{14}H_{21}ON_3Br$. C, 41.29; H, 5.19; N, 10.23; Br, 39.25

The dihydrochloride and the dihydroiodide of the base were also prepared. The dihydrochloride proved very hygroscopic. The dihydroiodide was not hygroscopic, but showed a broad decomposition temperature, from 204 - 214°.

b. 1-Chloro-5-isopropylaminopentane hydrochloride:

The above side chain was prepared from the corresponding alcohol by the method given by Drake[4]. The alcohol was obtained from the Sharples Chemical, Inc.

5-Isopropylamino-1-pentanol, 3.75 grams, was dissolved in anhydrous ether, and dry hydrogen chloride was passed until the solution became acidic to litmus. The hydrochloride was removed and dried under vacuum. It weighed 4.6 grams.

The hydrochloride obtained above was suspended in 25 ml. petroleum ether (60 - 70°), and 2.1 ml. redistilled thionyl chloride was added. The mixture was kept at 50° for half an hour with constant stirring, and was then refluxed for seven hours. A dark solid was obtained. The solvent was decanted off and the residue was washed three times with petroleum ether. It was recrystallized twice from 10% ether solution in acetone. Crystals came out in the form of plates, m.p. 123 - 124°. The yield was 3.7 grams (73%).

The above hydrochloride, 3.7 g. (0.0185 moles) was added to a solution of 2.8 grams of 4-quinazolone (0.0192 moles) dissolved in 21.0 ml. 1.82N alcoholic potassium hydroxide (0.0382 moles). Absolute alcohol, 20 ml., was then added and the mixture was refluxed for 24 hours. The potassium chloride was removed by filtration and was found to have a dry weight of 2.6 grams. The solvent was stripped off at reduced pressure below 70°. The solid residue was dissolved in sodium hydroxide and the solution was made strongly alkaline. It was extracted with chloroform five times (total extracts were 200 ml.). The extracts were dried over sodium sulfate and evaporated to dryness. An oil was obtained which did not give a solid hydrochloride, hydrobromide, or hydroiodide.

The alkaline solution after the chloroform extraction was neutralized by passing in carbon dioxide. A thick white precipitate was obtained. It was removed by filtration, and the solution was extracted with 200 ml. chloroform in five batches. The extracts

were dried and the solvent was stripped off. The solid residue was combined with the one obtained by the filtration, and was crystallized, from acetinitrile. The solid weighed 2.7 grams, m.p. 215 - 216°. A mixed melting point determination with 4-quinazolone showed no depression.

The above experiment was repeated using sodium ethoxide instead of the alcoholic potassium hydroxide solution. The same results were obtained. The use of anhydrous sodium acetate too did not prevent the self condensation of the side chain.

c. 2-Bromo-5-isopropylaminopentane hydrobromide:

The above side chain was prepared from the corresponding alcohol. The alcohol was obtained from the Sharples Chemical, Inc.

5-isopropylamino-2-pentanol, 1.6 grams (0.011 moles), was refluxed with 10 ml. 48% hydrobromic acid (0.059 moles) for four hours. The solvent was removed at reduced pressure. The solid residue was recrystallized from acetone ether mixture (1:1). Four crystallizations were necessary to give a colorless crystalline compound, m.p. 154 - 156°. The yield was 1.1 grams (36%).

One gram of the above hydrobromide (0.00345 moles) was added to 520 mg. of 4-quinazolone (equivalent amount), dissolved in 7.1 ml. 1.086N sodium ethoxide solution. The solution was made up to 15 ml. with absolute alcohol, and was refluxed for twenty-four hours. The sodium chloride was filtered off and the solvent was stripped off at reduced pressure below 70°. The solid residue was

dissolved in 10 ml. of 10% sodium hydroxide and was extracted with chloroform five times. The total extracts (200 ml.) were dried over sodium sulfate and evaporated to dryness. An oil was obtained which could not be converted to a solid hydrochloride or hydrobromide.

The solution, after extraction, was neutralized with carbon dioxide gas. A white solid came out and was removed by filtration. The filtrate was extracted with 150 ml. of chloroform. The extracts were dried over sodium-sulfate and evaporated. The residue was crystallized from acetonitrile. The crystalline mass weighed 490 mg., m.p. 215 - 216°. A mixed melting point determination with 4-quinazolone showed no depression.

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