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THE PROGRESSIVE STUDY OF 4-QUINAZOLONES AND THEIR ACTIVE METHYLENE COMPOUNDS FOLLOWED BY SYNTHESIS OF 3-AMINO-2-BENZYL-3,4-DI- HYDRO-4-OXO-QUINAZOLINE.

Chemistry

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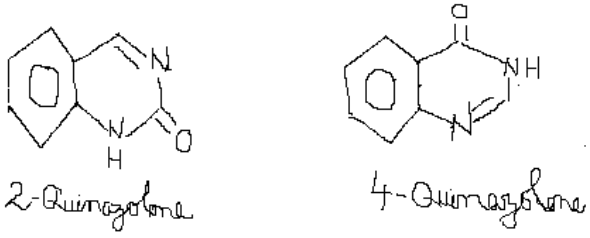
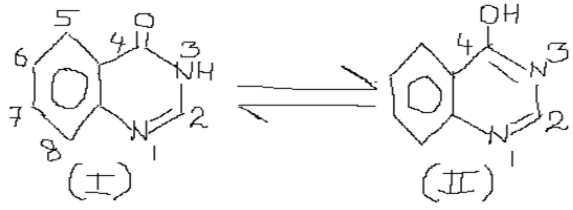
KEYWORDS

INTRODUCTION :

Quinazolone is a heterocyclic chemical compound. There are two structural isomers of 'Quinazolones' i.e 2- Quinazolone and 4-quinazolone. Out of the two isomers 4-quinazolone (isomer) is more common.



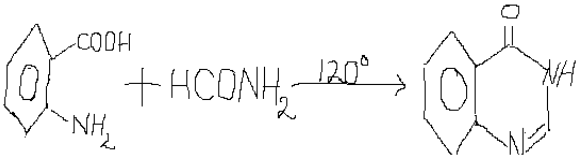
The '4-Quinazolone' is also known as 3,4-di hydro-4-oxo quinazoline (I) which is a tautomer of 4-Hydroxy quinazoline (II).



In this tautomeric form the equilibrium rests mainly with (II).

Due to this aforesaid tautomerism the 2- or 4- oxo- di hydro quinazoline differ in their properties with that of other quinazolines. The 4-Hydroxy derivative acquire exceptional stability due to their tautomerism which causes depletion of full complement of 6π electrons in the pyrimidine ring. This becomes quite evident when we compare the properties of quinazolines and 2- or 4-oxo-di hydro quinazolines.

Methods of preparation of quinazoline are however limited but a variety of procedure is available for synthesis of 3,4-di hydro-4-oxo-quinazoline. One of the earliest method for the preparation of 3,4-di hydro-4-oxo-quinazoline (I) is due to v. Niementowski. He heated anthranilic acid with formamide at 120° in an open container and obtained results with almost quantitative yield.

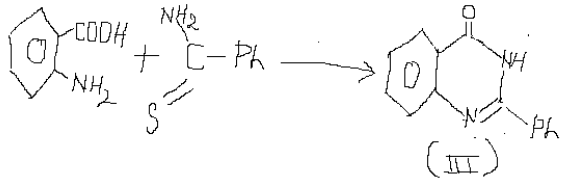


v.Niementowski also prepared anumber of 2-alkyl-3,4-dihydro-4-oxo quinazolines by simply replacing formamide with other aliphatic acid amide.

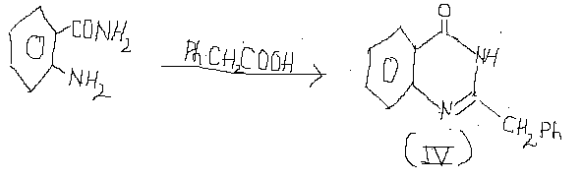
DISCUSSION :-

The v.Niementowski reaction proved to be of general application but unsatisfactory results were obtained by benzamide and other acid amides, Better yields of 4-oxo-quinazolines were obtained by replacing amides with thio amides e.g: thio- benzamide (or ethyl imido benzoate)

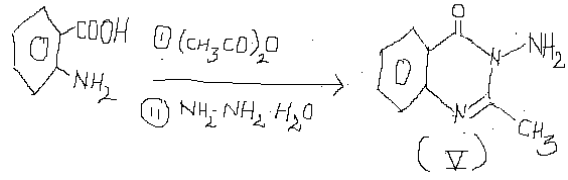
Gave good yield of 2-phenyl -3,4-di hydro-4-oxo- quinazolines[9].



On the basis of v.Niementowski reaction, when o-amino benzamide was heated with phenyl acetic acid, 2-benzyl-3,4-di hydro-4-oxo-quinazoline (IV)[10] was obtained.



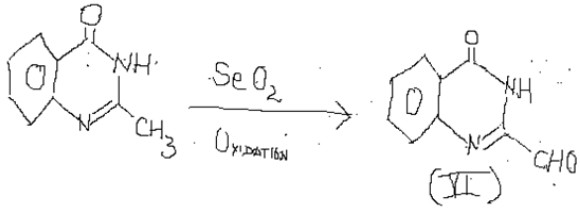
A one pot synthesis of 3-amino-2-methyl-3,4-dihydro-4-oxo quinazoline (V)directly from anthranilic acid is reported by Klosa11. He first heated anthranilic acid with acetic anhydride and after distilling off the excess of acetic anhydride partly treated the residue with methanolic hydrazine hydrate



In the above reaction the methyl group at position- 2 comes from acetic anhydride because of acetylation of anthranilic acid by the reagent.

In quinazolines and more particularly in 3,4-di hydro-4-oxo –quinazolines, substituents in the heterocyclic ring are found to be very reactive. Also. a methyl group at position -2 is found to be more reactive than at position-4[12].This reactivity of methyl group is typical of alkyl group placed ortho- or para- to the N-atom in a heterocyclic ring.

The greater reactivity of methyl group placed ortho to the heterocyclic N-atom was also observed in oxidation reaction. Monti[13] oxidized 2-methyl-3,4-dihydro-4-oxo quinazoline by selenium di oxide to give 3,4- di hydro2-formyl-4-oxo-quinazoline (VI) in good yield.

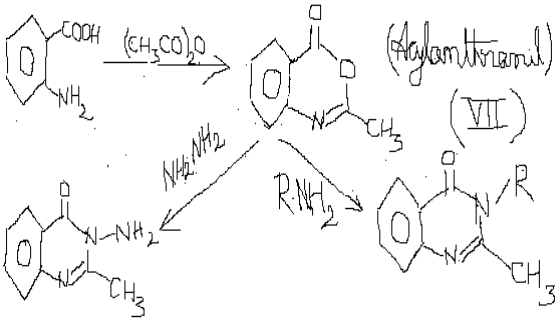


In 3-amino-2-methyl-3,4-di hydro-4-oxo-quinazoline, the amino group is yet another site which is reactive and can undergo a large number of reactions but is rather less investigated.

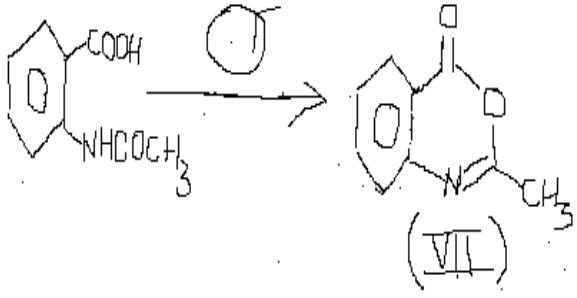
Methodology for the preparation of 3-amino-2-benzyl-3,4-di hydro-4-oxo-quinazoline:--

For the projected study of the reactivity of amino and the methylene groups at position -2 and position-3 in 3-amino-2-benzyl-3,4-di hydro-4-oxo-quinazoline and other similar compounds, it was necessary to evolve a precise method for their preparation in quantity in a routine way.

One of the general method fpr obtaining N-substituted 3,4-di hydro-4-oxo-quinazoline, begins with anthranilic acid. Anthranilic acid is converted into 3,4-di hydro-4-oxo-quinazoline through intermediate acyl- anthranil (VII),which may or may not be isolated. Treatment of acyl-anthranil with amine yields 3-alkyl (or aryl) substituted 3,4-di hydro-4-oxo-quinazoline. An amino or alkyl (or aryl)amino function can be introduced at N—(3) by taking hydrazine or an appropriate hydrazine derivative.



Errede has reported the preparation of a large number of acyl-anthranils in pure white crystalline state with yield higher than 50%[14-15].His method is distinctly an improvement over Bogert's process. He heated N-acyl- anthranilic acidwith acetic anhydride or thionyl chloride to effect ring closure and then isolated the acyl anthranil by distilling the crude product in vaccum. The method appeared to be particularly suitable in our case where the acid anhydride i.e phenyl acetic anhydride (m.pt.72^{0}C) is neither a liquid nor is easily availale.



On the basis of the above study, it was found that in almost all the different methods for the preparation of 2,3-di- substituted 4-quinazolines, anthranilic acid was first converted into a suitable derivative which was subsequently transformed into the quinazolines.

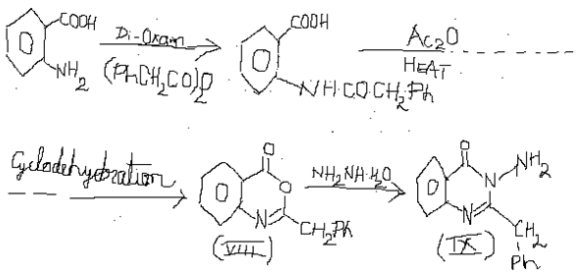
The working method for the synthesis of 3-amino-2-benzyl-3,4-di hydro 4-oxo- quinazoline is developed on the basis of above experimental methods.

Experimental procedure :-

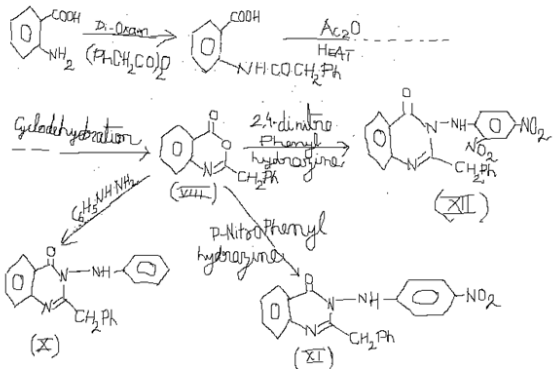
Anthranilic acid in di-oxan was refluxed with phenyl acetic anhydride and the reaction mixture was diluted with cold water. Upon cooling, the analide was obtained as a dark red solid. This compound, after necessary purification, was subjected to cyclodehydration with rigorously dried acetic anhydride under reflux condition. After cooling and distilling off a major bulk of acetic anhydride, the remainder was removed by distillation under reduced pressure.

The anthranil was not purified any further and it was directly subjected to the methanolic solution of hydrazine hydrate. The resulting compound was isolated by diluting the reaction mixture and alkalising with aqueous ammonia.

Crystallization furnish the pure product with sharp melting point. The compound gave correct analysis for carbon, hydrogen and nitrogen. It also showed characteristic I.R.absorption at 1670 c.m $^{-1}$ (quinazolone carbonyl) 3330c.m^{-1} and 3230c.m^{-1} (N-H primary and bonded). The data were consistent with it's structure.



The hydrazine derivative, phenyl hydrazine, p-nitro phenyl hydrazine, 2,4-di nitro phenyl hydrazine were also used in place of hydrazine itself. They were made to react with the acyl- anthranil in glacial acetic acid solution to give the N-substituted derivative (X), (XI) , (XII).



CONCLUSION :-

There was no suitable readymade process available for the preparation of our main compound 3-amino 2-benzyl- 3,4- dihydro 4-oxo-quinazoline. The corresponding 2-methyl analogue was prepared by Josef Klosa[11].He heated anthranilic acid with excess of acetic anhydride, removed about half of the acetic anhydride by distillation and treated the reaction mixture with a methanolic solution of hydrazine hydrate at 50-60^{0}C. The product was deposited after keeping the reaction mixture for some time.

This method of Josef Klosa was considered suitable but with modifications. In Klosa's method acetic anhydride used has three functions. It worked as acylating agent, the cyclodehydrating agent and provided a medium for the reaction. Further the excess of it was easily removable by distillation.

In our case, phenyl acetic anhydride, being a solid could only work as an acylating agent. Hence ,here Josef Klosa's method could be partially followed. The method of Errede [14-15] was also examined who worked with different acylating agent in which some of them were solid too.His process of isolating the acylated derivative was followed but purification of anthranil was dispensed to it.

A proper combination of the two methods was followed but with some modifications for better yield and purer product.

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