[CONTRIBUTIONS FROM THE HAVEMEYER LABORATORIES OF COLUMBIA UNIVERSITY, NO. 123.]

RESEARCHES ON QUINAZOLINES (FIFTEENTH PAPER[1]). ON A 3-AMINOQUINAZOLINE, AND THE CORRESPONDING 3,3'-DIQUINAZOLYL, FROM 6-NITROACETANTHRANIL AND HYDRAZINE HYDRATE.[2]

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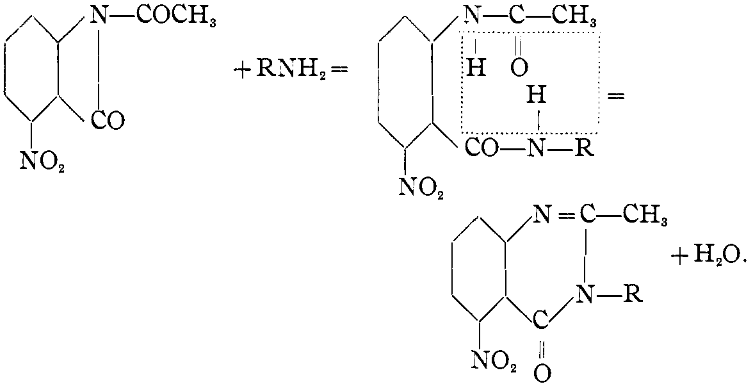
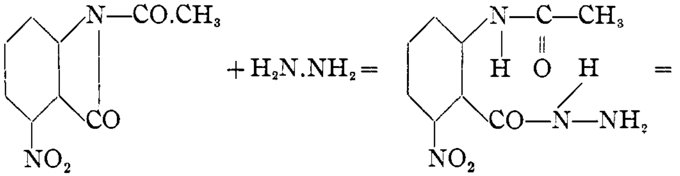
Received May 5, 1906.

THE preparation of quinazolines from 6-nitroacetanthranil and primary monamines has been reported from this laboratory in previous papers,[3] the reactions involved being as follows:



From an examination of these reactions it will appear that a similar condensation should occur with hydrazine, giving rise to aminoquinazolines and diquinazolyls:



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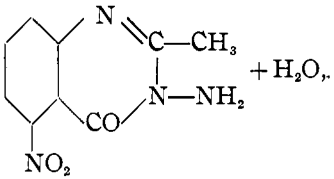
[1] The previous papers have appeared in this Journal, under various headings as follows: 22, 129, 522 (1900); 23, 611 (1901); 24, 1031 (1902); 25, 372, 935 (1903); 27, 649, 1127, 1293, 1302, 1305, 1327 (1905); 28, 94, 207 (1906).

[2] Read at the meeting of the New York Section of the American Chemical Society, April 6, 1906.

[3] Bogert and Chambers: This Journal, 27, 649; Bogert and Seil: Ibid., 27, 1305 (1905).



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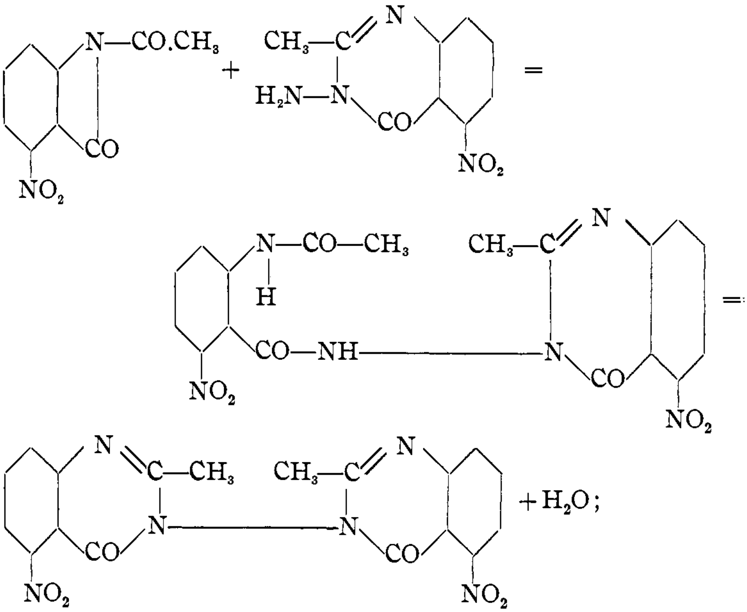

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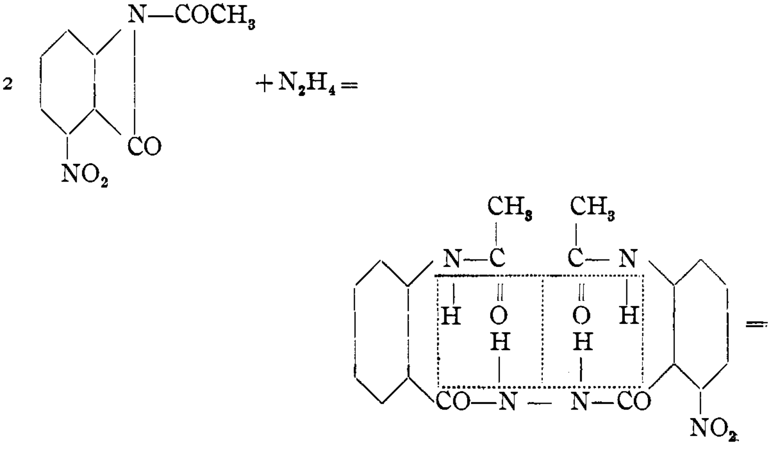
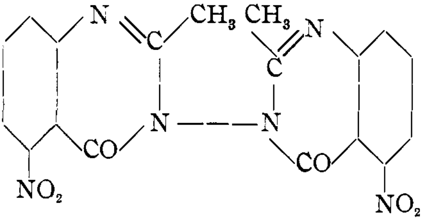




On testing this experimentally, such was found to be the case, as both the aminoquinazoline and the diquinazolyl were obtained.

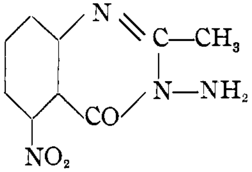
When equal molecules of the anthranil and hydrazine were used, the former being added gradually to the latter, the aminoquinazoline was the chief product. With two molecules of the anthranil to one of the hydrazine, adding the latter gradually to the former, the chief product was the diquinazolyl. The diquinazolyl was also produced by condensing the aminoquinazoline with a second molecule of the anthranil, but the yield by this method was poor.

The aminoquinazoline is easily separated from the diquinazolyl by its solubility in dilute alcohol. Its hydrochloride, chlorplatinate, diacetyl derivative, bromdiacetyl derivative, phenylhydrazinophenylhydrazone and uramino derivative were prepared and studied, as well as its behavior with potassium hydroxide, with chloroform and potassium hydroxide, and with benzaldehyde. The action of nitrous acid upon it is now being investigated, and the results will be reported later.

The diquinazolyl is difficultly soluble in most of the ordinary solvents, is not easily attacked by either acid or alkali, and forms no bromine derivative. With excess of acetic anhydride, addition apparently occurs on one nucleus only.

EXPERIMENTAL.

2-*Methyl*-3-*amino*-5-*nitro*-4-*ketodihydroquinazoline*,



—This was prepared by adding 6-nitroacetanthranil to the calculated quantity of hydrazine hydrate in 33 per cent. aqueous solution. Reaction took place immediately, as was shown by the heat developed and the change in color from yellow to white. After boiling for a few minutes, to convert any amide to quinazoline, the solution was evaporated almost to dryness and filtered. The crude aminoquinazoline, yellow in color, was washed with dilute acetic acid, to remove any excess of base, and then extracted several times with water and finally with a mixture of alcohol and water. In this way it was separated from the diquinazolyl present. On evaporating the combined extracts to small bulk and allowing the solution to stand, beautiful, long, pink prisms of the aminoquinazoline were obtained, which, when treated with bone-black and recrystallized from dilute alcohol, appeared in long, colorless prisms. The aminoquinazoline is moderately soluble in water, alcohol or acetone; slightly soluble in chloroform or benzene; and almost insoluble in ether. It melts at 152–153° (corr.).

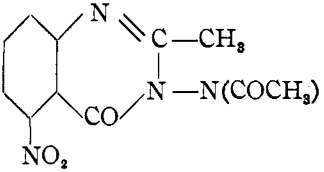
Calculated for $C_9H_8O_3N_4$: C, 49.09; H, 3.63; N, 25.45. Found: C, 48.91 and 48.86; H, 3.60 and 3.51; N, 25.46 and 25.43.

Hydrochloride.—Hydrochloric acid was added to a saturated aqueous solution of the aminoquinazoline. Small crystals separated at once, which gradually grew into flat, glistening plates.

The hydrochloride is insoluble in water, but soluble in dilute hydrochloric acid, from which it can be recrystallized. It is not hydrolyzed by boiling water, and melts at 253–254° (corr.).

Chlorplatinate.—The aminoquinazoline forms a chlorplatinate when chlorplatinic acid is added to an alcoholic solution acid with hydrochloric acid. Some reduction always occurs, and the yellow crystals of the chlorplatinate are thereby contaminated with metallic platinum. A pure sample for analysis could not be prepared.

2-*Methyl*-3-*diacetylamino*-5-*nitro*-4-*ketodihydroquinazoline*,

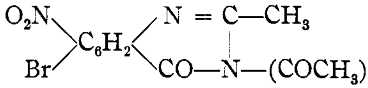


—The aminoquinazoline was dissolved in an excess of acetic anhydride, solution taking place gradually. The excess of anhydride was evaporated and the residual heavy syrup allowed to crystallize. It was then dissolved in alcohol and allowed to cool slowly. Long, fine, white needles separated, melting at 233° (corr.).

The diacetyl derivative is insoluble in water, moderately soluble in hot alcohol, but practically insoluble in cold alcohol.

Calculated for $C_{13}H_{12}O_5N_4$: N, 18.42. Found: N, 18.74.

Brom-2-methyl-3-diacetylamino-5-nitro-4-ketodihydroquinazoline,



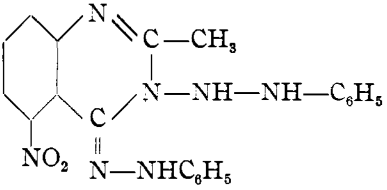
$$\begin{matrix}O_2N\\ Br\end{matrix}\!\!>C_6H_2<\!\!\begin{matrix}N=C-CH_3\\ \quad\quad | \\ CO-N-(COCH_3)_2\end{matrix}$$

—Attempts to brominate the aminoquinazoline in aqueous solution gave negative results. A dark brown gummy mass was obtained, from which no pure substance could be isolated. Bromination of the diacetyl derivative, however, proceeded smoothly.

The aminoquinazoline was dissolved in acetic anhydride, and bromine dissolved in acetic anhydride was added to the warm solution until on gentle warming the color was no longer discharged. The bromine derivative precipitated as a white compact powder. The solution was allowed to cool, the precipitate filtered out and crystallized from dilute alcohol. Small yellow crystals resulted, which softened at 105° and melted at 110° (corr.).

Calculated for $C_{13}H_{11}O_5N_4Br$: N, 14.62; Br, 20.88. Found: N, 14.93; Br, 20.60.

Phenylhydrazone of 2-methyl-3-phenylhydrazino-5-nitro-4-ketodihydroquinazoline,



—This derivative was prepared by two methods: (1) by boiling the aminoquinazoline directly with phenylhydrazine; and (2) by dissolving the aminoquinazoline in acetic acid, adding an acetic acid solution of phenylhydrazine, and boiling the solution for an hour.

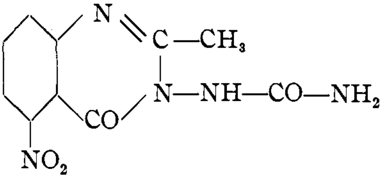
(1) The aminoquinazoline was warmed gently with an excess of phenylhydrazine. When boiling commenced the flame was

removed, the heat of reaction sufficing to maintain the boiling for several minutes. The reaction was completed by a further boiling over the flame for a few minutes. Ammonia was evolved during the reaction. The solution was acidified with dilute acetic acid, evaporated to small bulk, the residue taken up with alcohol, and the solution treated with bone-black. On standing, large, white, lustrous plates separated, melting at 124–125° (corr.).

(2) The aminoquinazoline was dissolved in acetic acid, alcohol and an excess of phenylhydrazine in acetic acid were poured in, and the mixture heated on the water-bath for an hour. Sufficient alcohol was added to yield a clear solution, and the whole set aside to crystallize. The crystals which separated corresponded entirely with those obtained by the first process.

Calculated for $C_{21}H_{19}O_2N_7$: N, 24.43. Found: N, 24.75.

2-Methyl-3-uramino-5-nitro-4-ketodihydroquinazoline,



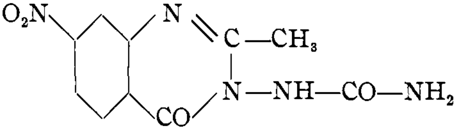
—An acid solution of the aminoquinazoline was treated with potassium cyanate, but no reaction occurred, and the aminoquinazoline was recovered unaltered.

The uramino compound was obtained, however, by condensing the nitroacetanthranil with semicarbazide, the reaction being entirely analogous to that between hydrazine and the acetanthranil by which the aminoquinazoline is formed. The crude product melted at 263–264° (uncorr.).

Calculated for $C_{10}H_9O_4N_5$: N, 26.61. Found: N, 26.48.

Not enough of the material was prepared to purify it further, as we were running short of our 5-nitroacetanthranil. The experiment, was therefore, continued with 4-nitroacetanthranil.

2-Methyl-3-uramino-7-nitro-4-ketodihydroquinazoline,



—Like the 5-nitro compound, the 7-nitro-3-amino-2-methyl-4-ketodihydroquinazoline (this compound will be described more fully in a subsequent paper) gave no uramino derivative when treated in acid solution with potassium cyanate, the aminoquinazoline being recovered unaltered.

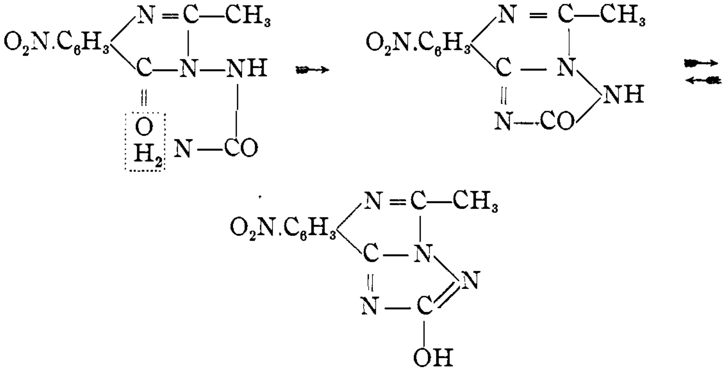
The 4-nitroacetanthranil was then treated with an aqueous solution of semicarbazide in slight excess. At first no change was noted, but on heating vigorous reaction commenced and the whole mass finally solidified. After removing the water by filtration, the residue was washed with dilute acetic acid and crystallized from boiling water. Masses of fine, white, silky crystals separated in clusters, melting at 266° (corr.).

Calculated for $C_{10}H_9O_4N_5$: N, 26.61. Found: N, 26.24.

An aqueous solution of the substance gave a white flocculent precipitate when treated with bromine water.

The condensation of the nitroaminoquinazolines with thiosemicarbazide gave dark colored products, from which we were unable to separate any pure substance.

By the condensation of the uramino side chain in the above compounds with the adjacent keto group, a new triazine ring should be formed:



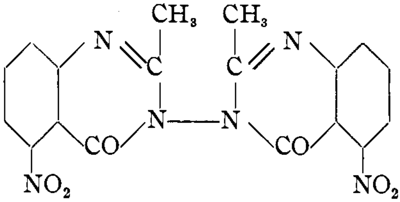
So far, our efforts to accomplish this condensation have been futile. The uramino compound was boiled with 20 per cent. hydrochloric acid, with phosphorus oxychloride (alone, and in nitrobenzene solution), with a mixture of phosphorus oxychloride and pentachloride, and with acetic anhydride in excess. Long boiling with the hydrochloric acid ruptured the miazine cycle, and hydrolyzed the compound completely to the nitroanthranilic acid. The results of boiling with the phosphorus halides were likewise disappointing, charring taking place in every case. When the uramino-7-nitro compound was boiled with excess of acetic anhydride for half an hour, solution occurred slowly. When a clear solution was obtained, it was allowed to cool, and the anhydride hydrolyzed by water. This acetic acid solution was then nearly neutralized with caustic alkali and allowed to stand for some time. White crystals of *2-methyl-3-diacetyluramino-7-nitro-4-ketodihydroquinazoline* were deposited, melting at 229–230° (corr.).

Calculated for $C_{14}H_{13}O_6N_5$: N, 20.17. Found: N, 20.08.

OTHER REACTIONS OF 2-METHYL-3-AMINO-5-NITRO-4-KETODIHYDROQUINAZOLINE.

In addition to the above, the aminoquinazoline exhibited other characteristic aniline reactions. With chloroform and potassium hydroxide solution, an isonitrile odor was obtained. With benzaldehyde, condensation occurred, apparently with formation of the benzylidene derivative, but the product was not analyzed. The aminoquinazoline was not affected by cold potassium hydroxide solution, but on warming it slowly dissolved in the alkali with a purple-red color and without liberation of ammonia. On neutralizing the alkaline solution with acetic acid, a light yellowish green fluorescent color appeared, and brownish crystals slowly separated from the solution. These were soluble in water, contained nitrogen, and melted at 259–260° (uncorr.), but were not obtained in sufficient amount to identify.

2,2′-Dimethyl-5,5′-dinitro-4,4′-diketotetrahydrodiquinazolyl,



—In preparing the aminoquinazoline from 6-nitroacetanthranil and hydrazine hydrate, the anthranil was added to the hydrazine solution in order to keep the latter always in excess, and thus insure a monomolecular condensation. In preparing the diquinazolyl, on the other hand, the hydrazine hydrate was added to the anthranil, so that the anthranil might always be in excess and a dimolecular reaction secured.

The hydrazine hydrate was added to the finely powdered anthranil with constant stirring, and the solution was gently heated. The product of the reaction formed a compact yellow mass at the bottom of the beaker. This was filtered, and the residue boiled with dilute alcohol to remove any aminoquinazoline, and finally washed with dilute potassium hydroxide solution to remove any 6-nitroacetanthranilic acid which might have been formed from the excess of anthranil. The residual diquinazolyl was crystallized from a mixture of alcohol and acetone.

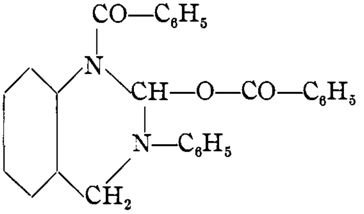
It forms small, granular crystals, which melt at 306°. It is not affected by acids or alkalies, and apparently forms no bromine derivative.

Calculated for $C_{18}H_{12}O_6N_6$: C, 52.74; H, 2.94; N, 20.58. Found: C, 52.32 and 52.21; H, 2.89 and 2.73; N, 20.35 and 20.15.

This same diquinazolyl was obtained by condensing the aminoquinazoline with another molecule of the acetanthranil, but the yield by this process was very poor.

Acetic Anhydride Addition Product of the Diquinazolyl.—When the foregoing diquinazolyl was boiled with excess of acetic anhydride, it was slowly dissolved. On cooling, cubical crystals separated, which softened at 223° and melted at 228° (corr.).

This may be a substance analogous to that obtained by Heller[1] on treating orexine with benzoic anhydride, and to which he ascribed the following formula:



Great difficulty was experienced in analyzing both the diquinazolyl and its acetic anhydride addition product. In both cases the carbon turned graphitic. The acetic anhydride addition product exploded unless the heating was very carefully con-

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[1] Ber. 37, 3114 (1904).

ducted, and even then no satisfactory analysis could be secured, the results, however, indicating quite clearly that only one molecule of acetic anhydride had been added to the diquinazolyl.

HAVEMEYER LABORATORIES,
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A REVIEW OF RECENT PROGRESS IN PHYSICAL CHEMISTRY.

BY GILBERT N. LEWIS.

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IT IS becoming more difficult year by year to make a satisfactory survey of any given field of scientific investigation. In the last year 1644 articles were classed as physico-chemical and abstracted in the Physikalisch-chemisches Centralblatt. To attempt anything like a summary of this enormous mass of literature would be absurd. I shall only try in a fragmentary way to touch upon some of the larger problems of general chemistry and a few of the more noteworthy contributions toward their solution. As is customary in these reviews I shall consider only the work done in foreign lands, and I shall further restrict the field by omitting any reference to the modern developments in radioactivity and the theory of electrons, for I fear that if I should embark upon this fascinating subject little space would be left for the older problems of our science.

In no other line of physico-chemical research during the past year has there been more satisfactory progress than in the determination of the so-called free energy of chemical reactions, nor is there any work of greater importance than this to be done. Complete tables for free energy such as we now have for the heat of chemical reactions would permit the technical chemist to calculate at once the maximum amount of work which he could hope to obtain from a given reaction or the minimum amount of work necessary to effect it. It would enable the student of pure chemistry to predict under given circumstances just what reactions could occur and how nearly they would run to an end. It would be the first step towards a fuller knowledge of chemical affinity.

Since mechanical power is now the most valuable of all commodities, the great technical problem of the day is to obtain from the combustion of coal the largest possible amount of available work. Many attempts have been made to construct a galvanic cell which will consume at one electrode the oxygen of the air, at the other some kind of fuel. Several of these attempts such as the carbon monoxide cell of Borchers and the coke cell of Jacques have at first appeared successful, but in every case it has been