Sodium was determined in the dried salt with the following results:

	Calculated for $C_{12}H_{10}O_2N_4Na_2$.	Found. I.	Found. II.
Na	15.97	15.75	15.80

HAVEMEYER LABORATORIES, COLUMBIA UNIVERSITY,
June, 1905.

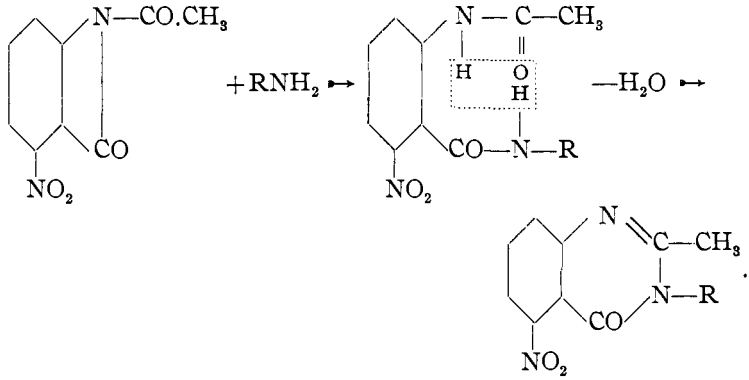
[CONTRIBUTIONS FROM THE HAVEMEYER LABORATORIES OF COLUMBIA UNIVERSITY, NO. 111.]

THE SYNTHESIS OF 2-METHYL-5-NITRO-4-KETODIHYDROQUINAZOLINES FROM 6-NITROACETANTHRANIL AND PRIMARY AMINES.[1]

BY MARSTON TAYLOR BOGERT AND HARVEY AMBROSE SEIL.

Received August 21, 1905.

IN a previous paper,[2] Bogert and Chambers have shown that quinazolines can be readily obtained from 6-nitroacetanthranil and primary amines, the reactions involved being as follows:



They carried out this synthesis only with ammonia and with aniline. The present paper records similar syntheses with the following primary amines—methyl, ethyl, normal and isopropyl, iso- and secondary butyl, isoamyl and allyl—thus demonstrating the general applicability of the reaction to primary aliphatic amines.

We are now engaged in extending the reaction to other primary amino compounds, including the amino acids, and have already

[1] Read at the Meeting of the New York Section of the American Chemical Society, May 5, 1905.

[2] This Journal, **27**, 649 (1905).

secured some very interesting results which will be communicated in the near future.

We have experimented with some of the other nitroacetanthranils and find that they exhibit a similar behavior with primary amines. Papers upon these are in preparation.

It will be seen, from the above exhibition of the reaction, how a primary amine condenses with the nitroacetanthranil to form a quinazoline, and that this condensation is entirely independent of the character of "R." Our experiments to date indicate that almost any primary amino group can thus be converted into a nitroquinazoline cycle. The interesting synthetic field thus opened is obvious. But it is not unlikely that the reaction may have analytical value also, by affording a means of changing an unstable or liquid primary amino compound into a stable crystalline nitroquinazoline which can be easily identified.

The condensation of acylanthranils and primary amines to quinazolines was discovered by Anschütz, Schmidt and Greiffenberg.[1] They used unsubstituted acylanthranils, which we think are not so easily prepared or so reactive as the nitro derivatives.

The intermediate products in the above synthesis, the nitroacylanthranilamides, have been isolated in several cases, and then in turn changed to quinazolines, thus demonstrating experimentally the course of the reaction.

EXPERIMENTAL.

Preparation of 6-Nitroacetanthranil.

The preparation of this compound was carried out in approximately the same way as already described by Bogert and Chambers[2] from 3-nitrophthalic acid, through the nitrophthalimide, nitrophthalamic acid, and nitroanthranilic acid.

In the preparation of the nitrophthalimide, some additional experiments were made which may be of value to other workers in the same field. The following methods of preparation were compared:

(1) The action of ammonia gas upon the fused anhydride.[3]

(2) Heating the acid ammonium salt.[4]

(3) Heating the neutral ammonium salt.

[1] *Ber.*, **35**, 3480 (1902).

[2] *Loc. cit.*

[3] Kahn: *Ber.*, **35**, 3866 (1902).

[4] Bogert and Chambers: *Loc. cit.*

(4) Adding excess of ammonia to the acid methyl ester, evaporating to dryness, and fusing the residue.

The first of these methods proved the least satisfactory, both as to yield and quality of product. The others all gave good yields and good products. The advantage of the third and fourth methods is that an excess of ammonia can be used and the preparation of a pure acid salt thus obviated. As the 3-nitrophthalic acid is frequently separated from the isomeric 4-nitro acid by conversion into its acid methyl ester, the application of the fourth method is evident.

The third and fourth methods are carried out in much the same way. The acid, or acid ester, is treated with an excess of ammonia and evaporated to dryness at 110°. The temperature is then raised to 170–180° until no more ammonia is evolved, and then to 210° until fusion occurs. When the fused mass has ceased to effervesce, the temperature is raised for a few minutes to 216°, and the melt is then allowed to cool. The crude imide from the acid methyl ester forms large, yellow lustrous needles, melting sharply at 216°, and is practically pure. That from the neutral ammonium salt melts at 210–216°, but is easily purified by crystallization from alcohol.

Preparation of Quinazolines from 6-Nitroacetanthranil.

The general method of procedure was as follows: Five grams of the nitroacetanthranil were placed in a flask with a slight excess of an aqueous (1 : 3) solution of the primary amine. Considerable heat was evolved (the reaction with the pure amine was generally too violent), and the solution became colored. This color varied from a yellow with methylamine, to a red with isoamylamine. When the first reaction was over, the flask was heated two or three minutes on a steam-bath, and then allowed to cool. Most of the quinazoline separated as a precipitate in the flask, contaminated with some of the intermediate amide. The mixture was made slightly acid with acetic acid and filtered. The precipitate of quinazoline was freed from amide by washing it with cold dilute caustic potash, and the alkaline washings were added to the mother-liquor. The combined mother-liquor and alkaline washings should be slightly alkaline (too strong alkali gives a deep red color). By boiling this alkaline solution, all amide was changed to quinazoline and precipitated at once. This precipitate was

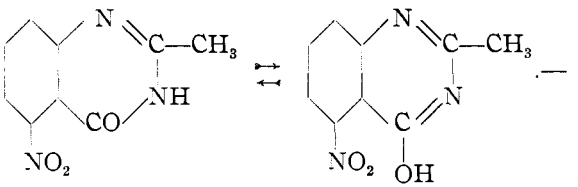
combined with the first crop of quinazoline, and the two purified together by crystallization from alcohol. The total yield in most cases was nearly quantitative.

The following method of converting the amide into quinazoline was also tried: After the completion of the reaction between the anthranil and the amine, the mixture was evaporated to dryness at 100°. The temperature was then raised to 150° and kept there until the cessation of all effervescence (about four hours), when it was allowed to cool. There resulted a brown cake, from which the pure quinazoline was obtained only after frequent recrystallizations from alcohol in the presence of boneblack. The yield also was poor.

Weddige[1] has shown that acylanthranilamides pass into quinazolines on boiling with water or with alkalies, or when fused.

These quinazolines are all white crystalline solids, of high melting-points. The allyl derivative is dimorphous. All, except the quinazoline obtained with ammonia, carry hydrocarbon radicals in positions 2 and 3, and are, therefore, insoluble in alkalies. In general, they are all insoluble, or difficultly soluble, in water, carbon tetrachloride, carbon disulphide, petroleum ether, cold benzene or cold ether; moderately soluble in the two latter solvents at the boiling-point, or in cold methyl, ethyl or amyl alcohols, or in cold acetone; easily soluble in the four latter solvents at the boiling-point, and in chloroform, or ethyl acetate. Beautiful crystals may be secured by dissolving the quinazoline in a slight excess of boiling strong alcohol, adding water carefully to the hot solution until it begins to cloud, and then allowing the solution to cool.

2-Methyl-5-nitro-4-ketodihydroquinazoline (*2-Methyl-5-nitro-4-oxyquinazoline*),



This was prepared from the nitroacetanthranil and ammonia, as already described by Bogert and Chambers.[2] As it contains a

[1] *J. prakt. Chem.* [2], **31**, 124 (1885); **36**, 141 (1887).

[2] *Loc. cit.*

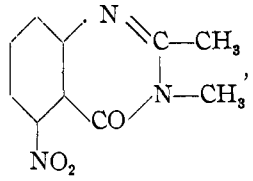
replaceable (enolic) hydrogen, it dissolves freely in alkalies. It is also moderately soluble in water. In these respects, it differs from the quinazolines which follow:

6-*Nitroacetanthranilamide*,

(6) $O_2N.C_6H_3\begin{cases}CO.NH_2\ (1)\\ NH.CO.CH_3\ (2)\end{cases}$.—

This is the intermediate product in the above condensation, and was isolated in one of the experiments. It is a white crystalline substance, melting at 218–219° (corr.), and dissolves in dilute alkalies. On heating its alkaline solution, it is changed to the quinazoline, which remains in solution as the alkaline salt and can be precipitated by passing in carbon dioxide.

2,3-*Dimethyl*-5-*nitro*-4-*ketodihydroquinazoline*,



from nitroacetanthranil and methylamine, melts at 203° (corr.). Found: C, 54.43, 54.51; H, 4.08, 4.16; N, 19.24, 19.31. Calculated for $C_{10}H_9O_3N_3$: C, 54.79; H, 4.11; N, 19.17.

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

$O_2N.C_6H_3\begin{cases}N=C-CH_3\\ CO-N-C_2H_5\end{cases}$, from nitroacetanthranil and ethylamine, melts at 208° (corr.). Nitrogen found, 17.87. Calculated for $C_{11}H_{11}O_3N_3$, 18.00.

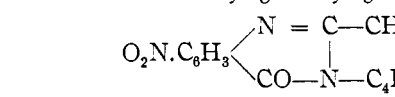
2-*Methyl*-3-*n-propyl*-5-*nitro*-4-*ketodihydroquinazoline*,

$O_2N.C_6H_3\begin{cases}N=C-CH_3\\ CO-N-C_3H_7(n)\end{cases}$, from nitroacetanthranil and normal propylamine, melts at 204–205° (corr.). Nitrogen found, 16.93. Calculated for $C_{12}H_{13}O_3N_3$, 17.00.

2-*Methyl*-3-*i-propyl*-5-*nitro*-4-*ketodihydroquinazoline*,

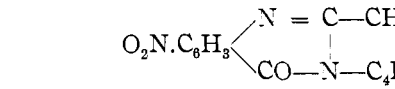
$O_2N.C_6H_3\begin{cases}N=C-CH_3\\ CO-N-C_3H_7(i)\end{cases}$, from nitroacetanthranil and isopropylamine, melts at 219–220° (corr.). Nitrogen found, 16.88. Calculated for $C_{12}H_{13}O_3N_3$, 17.00.

2-Methyl-3-i-butyl-5-nitro-4-ketodihydroquinazoline,



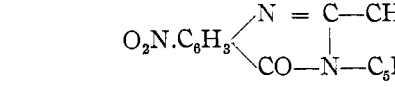
, from nitroacetanthranil and isobutylamine, melts at 202–203° (corr.). Nitrogen found, 16.08. Calculated for $C_{13}H_{15}O_3N_3$, 16.09.

2-Methyl-3-secondary butyl-5-nitro-4-ketodihydroquinazoline,



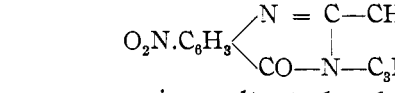
, from nitroacetanthranil and secondary butylamine, melts at 209–210° (corr.) Nitrogen found, 15.84. Calculated for $C_{13}H_{15}O_3N_3$, 16.09.

2-Methyl-3-i-amyl-5-nitro-4-ketodihydroquinazoline,



, from nitroacetanthranil and isoamylamine, melts at 213–214° (corr.). Found: C, 60.82, 60.74; H, 6.12, 6.41; N, 15.17, 15.35. Calculated for $C_{14}H_{17}O_3N_3$: C, 61.09; H, 6.18; N, 15.27.

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



, from nitroacetanthranil and allylamine, melts at 160–161° (corr.). It is dimorphous, crystallizing in rhombic plates or long needles. Nitrogen found, 16.95. Calculated for $C_{12}H_{11}O_3N_3$, 17.14.

HAVEMEYER LABORATORIES, COLUMBIA UNIVERSITY,
June, 1905.

[CONTRIBUTIONS FROM THE HAVEMEYER LABORATORIES OF COLUMBIA UNIVERSITY, No. 112.]

SOME EXPERIMENTS ON THE NITRO DERIVATIVES OF FLUORESCEIN.[1]

BY MARSTON TAYLOR BOGERT AND RALPH GARRIGUE WRIGHT.

Received August 3, 1905.

A STUDY of the nitro and amino derivatives of fluorescein has been undertaken, to determine the influence of these groups upon the fluorescence of this well-known substance, both as re-

[1] Read at the General Meeting of the American Chemical Society, June 22, 1905. The fluorescein for this investigation was generously supplied by the firm of Kuttroff, Pickhardt & Co., to whom we wish to express our thanks.