[CONTRIBUTIONS FROM THE HAVEMEYER LABORATORIES, COLUMBIA UNIVERSITY, NO. 76].

THE SYNTHESIS OF ALKYLTHIOKETODIHYDROQUINAZOLINES FROM ANTHRANILICNITRILE.

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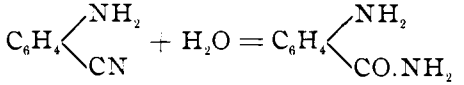
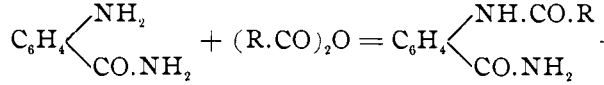
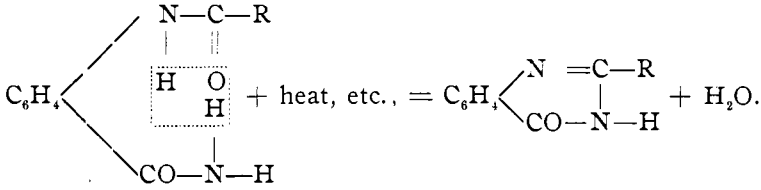
THEORETICAL PART.

The methods for the production of alkylketodihydroquinazolines from anthranilicnitrile all depend upon the intermediate formation of acyl derivatives of anthranilamide, which then condense to the quinazoline by loss of water. In brief, these methods are as follows:

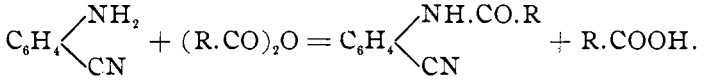
(1) Preparation of anthranilamide from the nitrile, conversion to an acyl derivative, and condensation of the latter by the action of heat, acids or alkalies, as worked out by Weddige and his students, by Niementowski and others:[1]

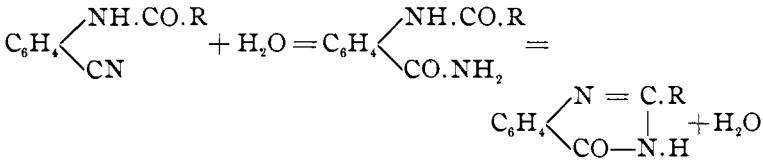






(2) By the action of warm alkaline hydrogen peroxide solution upon acylanthranilicnitriles:[2]

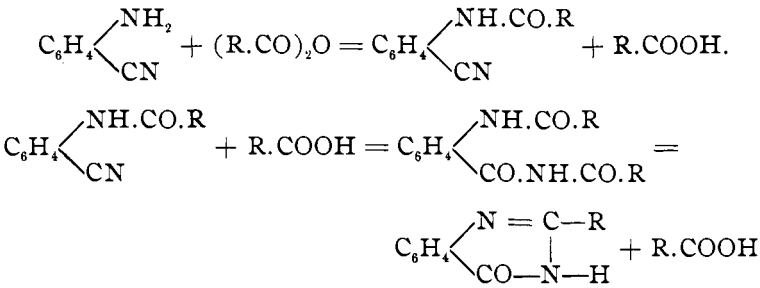




[1] Weddige: *J. prakt. Chem.* [2], **31**, 124 (1885); **36**, 141 (1887); Körner: *Ibid.*, **36**, 155 (1887); Niementowski: *Ber. d. chem. Ges.*, **21**, 1534 (1888), and *J. prakt. Chem.* [2], **40**, 1 (1889); Knape: *J. prakt. Chem.* [2], **43**, 209 (1891); etc.

[2] Bogert and Hand: this Journal, **24**, 1031 (1902).

(3) By heating anthranilicnitrile in sealed tubes with acid anhydrides:[1]



In (1) the amide is first formed and then acylated, in (2) the acyl group is introduced first and the nitrile then changed to the amide, while in (3) both reactions are accomplished in one operation, the amino group being the first point of attack.

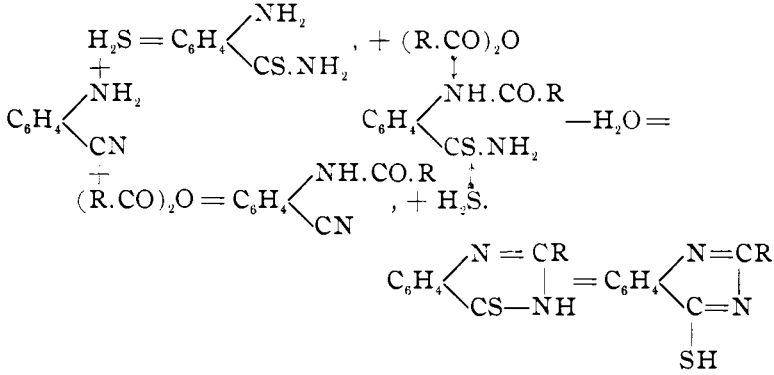
An examination of the reactions involved in methods (1) and (2) will immediately suggest to the reader, as it did to us, the possibility of preparing the corresponding thio derivatives by a similar series of reactions, in which the thiamide should be the intermediate product, instead of the oxygen amide. As the result of the practical testing in the laboratory of this idea, we are able to report the following new methods for the preparation of thioquinazoline derivatives:

(4) Anthranilic nitrile is converted to the thiamide by the direct addition of hydrogen sulphide, the thiamide acylated, and the acyl derivative then immediately condenses to the thioquinazoline by loss of water, the reactions involved being similar to those given under (1).

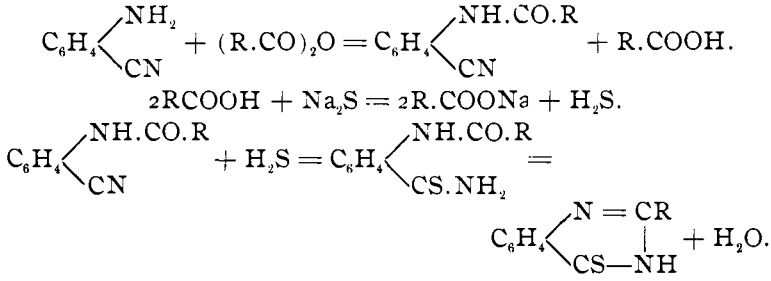
(5) The nitrile is first acylated, hydrogen sulphide then added to the cyanogen group, and the resulting acylthiamide condenses to the thioquinazoline as just noted, the reactions being similar to those given under (2).

The relation of methods (4) and (5) to one another appears clearly in the following diagram:

[1] Bogert and Hand: *Loc. cit.*

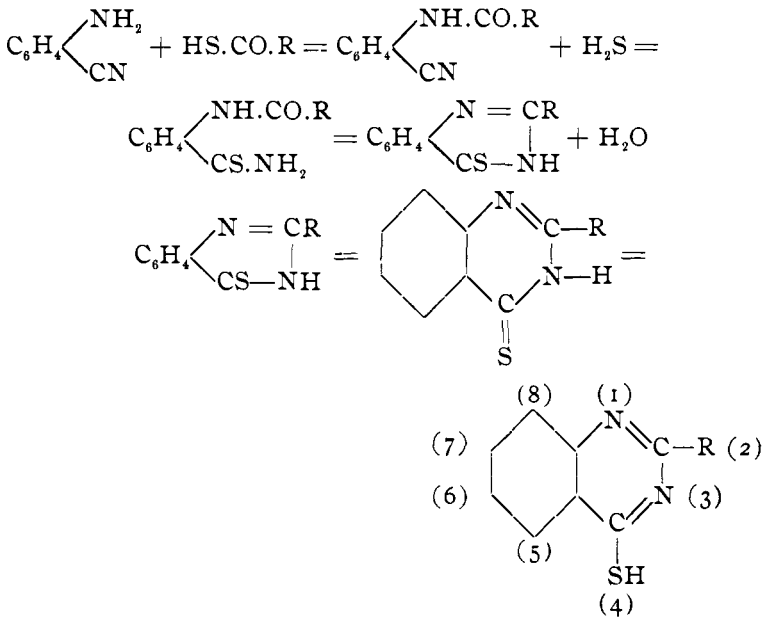


(6) The reactions involved in method (5) may be carried out practically simultaneously by treating the aminonitrile with an acid anhydride and sodium sulphide. The anhydride first acylates the amino group, the organic acid thus separated as the by-product liberates hydrogen sulphide from the sodium sulphide, this hydrogen sulphide attaches itself to the cyanogen, and the acyl thiamide thus produced condenses as usual to the thioquinazoline, the entire series of reactions being completed in one operation:

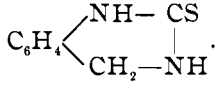


The sodium salt formed probably assists in some cases in the elimination of the water for the final condensation. This synthesis may be carried out in open flasks or in sealed tubes. So far, our results have been rather better with sealed tubes, and we have found it advantageous to use an excess of the sulphide.

(7) By the use of thio acids, in sealed tubes, the same results may be secured, likewise, in a single operation. The thio acid first acylates the amino group with liberation of hydrogen sulphide, and as this hydrogen sulphide cannot escape from the tube it attaches itself to the cyanogen, and the condensation already described then takes place:



The thioquinazolines obtained by these reactions belong to a different type from any hitherto recorded, in that they carry the sulphur atom upon the carbon adjacent to the benzene nucleus (*i. e.*, at position 4), while in those already known the sulphur is attached to the carbon between the two nitrogens (*i e.*, at position 2), as in the following compound:[1]



In the preparation of the methyl, ethyl, normal and isopropyl derivatives by these methods, the condensation product invariably separated in beautiful golden yellow crystals which were quite easily purified, and the yield in several cases was nearly quantitative.

EXPERIMENTAL PART.

o-Aminobenzthiamide, $H_2NC_6H_4CSNH_2$.—This was prepared by placing anthranilicnitrile in a strong glass tube, adding alcohol which had been previously saturated at 0° with dry ammonia and

[1] Compare Stewart: *J. prakt. Chem.*, [2], **44**, 415 (1891); Busch: *Ber. d. chem. Ges.*, **25**, 2853 (1892); Paal and Commerell: *Ibid.*, **27**, 1866, 2427 (1894); Paal and Vanvolxem: *Ibid.*, **27**, 2413 (1894); Busch and Brunner: *J. prakt. Chem.*, [2], **52**, 373 (1895); etc.

dry hydrogen sulphide, sealing the tube and heating at 100° for several hours. Generally, the thiamide crystallized out as the tube cooled. The crystals thus obtained, if washed with ether, to remove unchanged nitrile, and recrystallized from alcohol, were quite pure. Where no crystals separated in the tube, evaporation of the alcoholic solution gave large yellowish cubical crystals of the thiamide, which melted quite sharply at 120°, and yet which contained considerable free sulphur, as shown by check analyses. These crystals, when dried, carefully washed with carbon bisulphide (in which the thiamide is also partly soluble) and recrystallized from water, melted at 121°-122°. The thiamide may be precipitated from its concentrated alcoholic solution by the addition of chloroform; or, by adding water, the thiamide and nitrile may be precipitated together and the nitrile removed from the dried precipitate by washing with chloroform, the residue being purified by recrystallization from water.

The pure thiamide crystallizes in beautiful, light yellow flakes or plates, or occasionally in cubical crystals, melting-point 121°-122°. It is difficultly soluble in water, ether or chloroform in the cold, moderately soluble in the same solvents when boiling, and soluble in alcohol or carbon bisulphide. The substance softens under boiling water. Some of the purified product was analyzed, with the following results:

	Calculated for $C_7H_8N_2S$.	Found.				
		I.	II.	III.	IV.	V.
Carbon.....	55.260	55.36	....	....	....	....
Hydrogen.....	5.263	5.31	....	....	....	....
Nitrogen.....	18.425	...	18.65	18.55	...	....
Sulphur.....	21.052	...	....	....	20.81	20.76

Analysis (I) was made with crystals which had been precipitated from alcoholic solution by chloroform and subsequently purified; analyses (II), (III), (IV) and (V) were made with crystals which separated in the tube and were purified by washing with ether and recrystallizing.

The thiamide can also be prepared at ordinary pressure, but we have not found the yield so good as when the reaction is carried out in sealed tubes.

2-Methyl-4-thioketodihydroquinazoline, $C_6H_4\begin{cases} N=C-CH_3 \\ \quad\quad | \\ CS-NH \end{cases}$

From o-Aminobenzthiamide and Acetic Anhydride.—The thiamide was boiled gently for some time with acetic anhydride, and the thioquinazoline produced purified by crystallization from dilute alcohol. The yield was not very good.

From Acetylanthranilicnitrile and Hydrogen Sulphide.—The nitrile was heated in sealed tubes at 100° with alcohol saturated at 0° with hydrogen sulphide and containing a little ammonia. The thioquinazoline crystallized out in the tubes, on cooling, and was purified by crystallization from 20 per cent. alcohol. The yield was good. The same synthesis was accomplished by heating in an open flask, but the yield was less satisfactory.

From Anthranilicnitrile, Acetic Anhydride and Sodium Sulphide.—By heating these substances together in sealed tubes for an hour and a half at 100°-110°, the condensation product was obtained in beautiful crystals and in good yield. The contents of the tube were dissolved in dilute sodium hydroxide solution, the thioquinazoline precipitated by a current of carbon dioxide, and the precipitate purified by recrystallization from dilute alcohol. The tubes should not be heated much above 110°, or decomposition is likely to set in. This condensation was also carried out in an open flask. On mixing the substances, heat was developed, but very little hydrogen sulphide escaped. After heating for an hour and a half, the mixture in the flask set to a mass of yellow crystals. These were washed with cold water and purified as before.

From Anthranilicnitrile and Thiacetic Acid.—When these substances were heated together in sealed tubes the yield of thioquinazoline was rarely less than 80 per cent. of the theoretical and frequently approached quantitative results. The condensation product separated in the tubes in crystals which were practically pure.

Properties of 2-Methyl-4-thioketodihydroquinazoline.—The product obtained from the above reactions crystallizes from dilute alcohol in beautiful, long, yellowish needles or prisms, melting at about 218°-219° with decomposition; by careful heating, it may be sublimed, and then shows a slightly higher melting-point. It dissolves readily in alkalies or in hot alcohol, and is slightly soluble in water, ether, chloroform or benzene, when hot. Some of the purified product from the action of hydrogen sulphide upon acetylanthranilicnitrile was analyzed, with the following results:

	Calculated for $C_9H_8SN_2$.	Found.		
		I.	II.	III.
Carbon	61.364	61.29	....	....
Hydrogen	4.546	4.71	....	....
Nitrogen	15.909	....	15.93	15.96
Sulphur	18.181	....	....	....

The *picrate* forms large, light yellow needles, melting at 198.5°-199.5°, and is moderately soluble in cold water, more readily in hot water or in dilute alcohol, easily soluble in 95 per cent. alcohol.

2-Ethyl-4-thioketodihydroquinazoline.

From o-Aminobenzthiamide and Propionic Anhydride.—The thiamide was placed in a strong, glass tube and treated with a slight excess of propionic anhydride. Considerable heat was developed, and as the temperature rose the amide was thereby completely dissolved. On cooling down, the product separated upon the sides of the tube in small rose-like masses, the contents soon entirely solidifying. The tube was then heated for an hour and a half at 110°-115°, when light yellow, cubical crystals separated upon cooling, which were washed with dilute alcohol and dried, and then appeared to be the pure thioquinazoline.

From Propionylanthranilicnitrile and Hydrogen Sulphide.—The nitrile was dissolved in alcohol, the solution saturated with dry hydrogen sulphide and dry ammonia, and heated at 156° for sixteen hours. The contents of the tube were then dissolved in warm dilute sodium hydroxide solution, the thioquinazoline precipitated by a current of carbon dioxide and purified by crystallization from dilute alcohol.

From Anthranilicnitrile, Propionic Anhydride and Sodium Sulphide.—By heating these substances together in sealed tubes for seven hours at 165°-170°, the thioquinazoline is produced and crystallizes out upon cooling. It was purified as described above. The same condensation can be secured by heating the mixture in an open flask at 100°-125°, the cake of crude crystals thus obtained being purified in the usual manner. A rather higher temperature and longer heating is necessary than in the case of the methyl derivative.

Properties of the 2-Ethyl-4-thioketodihydroquinazoline.—The ethyl derivative forms yellowish needles, melting at about 203°-

204° with decomposition. By careful heating, it may be sublimed in needles, which show a somewhat lower melting-point (200.5°-201.5°). It is apparently insoluble in cold water, moderately soluble in dilute alcohol or in carbon tetrachloride, soluble in alcohol, aniline, benzene, or in caustic alkalies. The purified substance from the sodium sulphide method was analyzed, with the following results:

	Calculated for $C_{10}H_{10}SN_2$.	Found. I.	II.	III.	IV.
Carbon	63.158	63.79	....	....	....
Hydrogen	5.263	5.34	....	....	....
Nitrogen	14.737	....	14.93	14.90	....
Sulphur	16.842	....	....	....	17.50

The material used in (IV) consisted of crystals taken direct from one of the tubes, washed and dried, but not further purified. It shows, as expected, slight contamination with free sulphur.

The *picrate* crystallizes in coarse needles.

2-Isopropyl-4-thioketodihydroquinazoline.

Anthranilicnitrile, isobutyric anhydride and sodium sulphide, were heated together in sealed tubes for from three to six hours at 170°-175°, and the product purified by dissolving in sodium hydroxide solution, precipitating with carbon dioxide and crystallizing the precipitate from alcohol. Long warming with dilute alkali appears to induce partial decomposition with separation of gummy substances, so that the alkaline solution should be precipitated by the carbon dioxide without undue delay. The pure substance crystallizes from alcohol in long, light yellow needles, melting-point 203°-204°. It will be observed that this melting-point is identical with the melting-point of the ethyl derivative.

2-Normal Propyl-4-thioketodihydroquinazoline.

Anthranilicnitrile, *n*-butyric anhydride and sodium sulphide were heated together in sealed tubes for eight hours at 182°, and the condensation product purified as described for the isopropyl derivative. It forms beautiful, light yellow needles, melting at 182°-183°, which can be sublimed by careful heating.

It is rather interesting to note that the melting-point of these thioquinazolines steadily sinks with increasing molecular weight, the iso-compounds melting higher than those with normal structure. We have already called attention in previous papers to a

similar condition of affairs in the case of the corresponding oxygen alkylketodihydroquinazolines and in the acylanthranilic-nitriles. The solubility, however, diminishes with increasing molecular weight.

All melting-points recorded in this paper were determined with Anschütz short-scale thermometers, standardized by the Reichs-Anstalt, the entire mercury column being immersed in the heating medium.

The work is being continued.

ORGANIC LABORATORY, HAVEMEYER HALL,
COLUMBIA UNIVERSITY, January 31, 1903.

ACTION OF METALLIC MAGNESIUM UPON AQUEOUS SOLUTIONS[1].

BY LOUIS KAHLENBERG.

Received January 31, 1903.

IT has long been known that metallic magnesium acts extremely slowly upon distilled water, and that it practically does not act at all upon solutions of the caustic alkalies. In 1899 Tommasi[2] made qualitative investigations of the action of magnesium on aqueous solutions of the following salts: KCl, NH_4Cl, $CaCl_2$, $MgCl_2$, NaCl, LiCl, $BaCl_2$, $SrCl_2$, $CuCl_2$, $CdCl_2$, $PbCl_2$, $HgCl_2$, $FeCl_3$, $CrCl_3$, $PtCl_4$, $AuCl_3$, $CuSO_4$, $ZnSO_4$, $FeSO_4$, $MnSO_4$. He found that from solutions of sodium, potassium and lithium chloride, magnesium liberates hydrogen more rapidly than from pure water, magnesium hydroxide being formed. Solutions of the chlorides of barium, strontium, and calcium were acted upon but feebly by magnesium, but ammonium chloride solution was attacked at a lively rate. From solutions of the salts of the heavy metals mentioned above, hydrogen was liberated by magnesium, the chloride or sulphate of that metal being formed, and a basic salt or hydroxide of the heavy metal, or the latter in the metallic state, precipitated. No theoretical explanations were attempted. In the same year G. Lemoine[3] called particular attention to the action of magnesium upon aqueous solutions of magnesium salts. He used solutions of the nitrate, chloride, sulphate and acetate of magnesium, but worked especially with the last three salts. From

[1] Read at the Washington meeting of the American Chemical Society, and at the meeting of the Wisconsin Academy of Sciences, Arts and Letters at Madison, December 26, 1902.

[2] *Bull. Soc. Chim.*, (3) **21**, 885-887 (1899).

[3] *Compt. Rend.*, **29**, 291 (1899).