

oxysulphonic acid. There is, however, no experimental evidence to prove this.

CHICAGO VARNISH CO.,
CHICAGO, June, 1903.

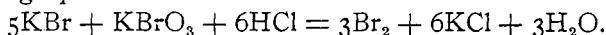
[CONTRIBUTION FROM THE HAVEMEYER LABORATORIES OF COLUMBIA UNIVERSITY, No. 86.]

3,5-BIBROM-2-AMINO BENZOIC ACID : ITS NITRILE AND THE SYNTHESIS OF QUINAZOLINES FROM THE LATTER.¹

BY MARSTON TAYLOR BOGERT AND WILLIAM FLOWERS HAND.

Received July 25, 1903.

ATTEMPTS to brominate nitrites have usually resulted unsuccessfully, and the bromination of anthranilic acid has given only tribromaniline. By the use of the calculated amount of nascent bromine, however, we have succeeded in introducing two atoms of bromine, not only into the molecule of anthranilic acid, but also into that of its nitrile, the brominating agent being an aqueous solution of potassium bromide and bromate, in the proportion of five molecules of the former to one of the latter, which, upon acidifying, liberates exactly 3 molecules of bromine, according to the following equation:



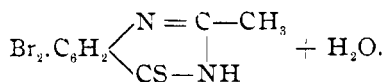
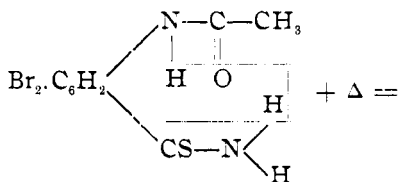
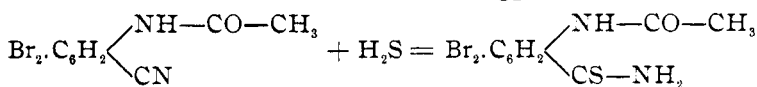
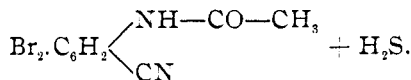
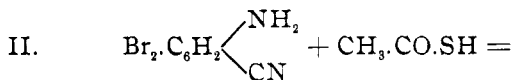
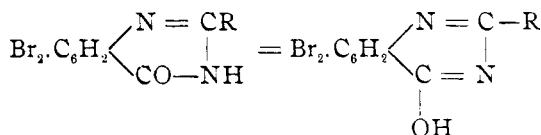
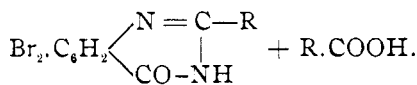
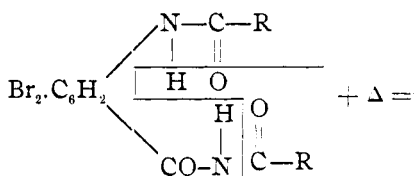
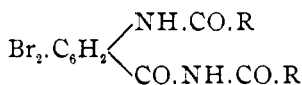
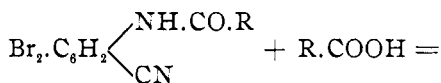
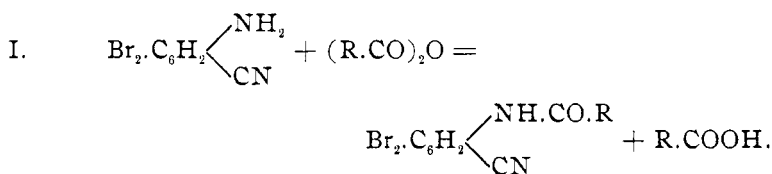
A standard solution of bromide and bromate, 1 cc. of which, upon being acidified, liberated 0.0800 gram of bromine, gave very satisfactory results.

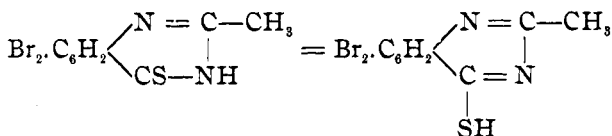
With both anthranilic acid and its nitrile, the bromine entered in the ortho-para positions with reference to the amino group, giving 3,5-bibrom-2-aminobenzoic acid and its nitrile, from which, by elimination of the amino group, 3,5-bibrombenzoic acid and its nitrile were obtained. This elimination of the amino group was accomplished with the greatest difficulty, the yield of the bibrombenzoic compound being small.

The bibromanthranilic nitrile we have converted into quinazolines and thioquinazolines by the use of the methods previously reported by us,² the equations being as follows:

¹ Read at the Cleveland meeting of the American Chemical Society, June 30, 1903.

² This Journal, **24**, 1031; **25**, 372.





By these reactions, 6,8-bibrom-2-alkyl-4-ketodihydroquinazolines the corresponding methyl thioquinazoline, and certain of their derivatives have been prepared.

EXPERIMENTAL PART.

BROMINATION OF ANTHRANILIC NITRILE. 3,5-BIBROM-2-AMINO-BENZONITRILE.

The anthranilic nitrile used in these experiments was prepared by the method described in our previous paper.¹

Bromination in Carbon Tetrachloride, Benzene, or Aqueous Solution.—On adding a carbon tetrachloride solution of bromine to a similar one of anthranilic nitrile, a white, amorphous precipitate immediately separates, which melts at (roughly) about 195°-200°. By a single crystallization of this product from alcohol, colorless needles of considerable length are obtained, melting quite sharply at 95.5° (corr.). Bromination in benzene or in aqueous solutions appears to yield similar results. This product has not as yet been further investigated.

Bromination with Hypobromite, and with Nascent Bromine.—Three grams of anthranilic nitrile were dissolved in dilute alcohol, dilute hydrochloric acid added, and then sufficient alkaline potassium hypobromite solution gradually stirred in to form a bibrom-derivative. Small, white, feathery needles separated, which melted sharply at 156°-156.5° (corr.) after several recrystallizations from 95 per cent. alcohol. A portion was sublimed, and the sublimate showed exactly the same melting-point.

	Found.	Calculated for C ₇ H ₄ N ₂ Br ₂ .
Nitrogen	10.38	10.15
Bromine	57.73	58.00

A solution of bromide and bromate of potassium was prepared as already described. The anthranilic nitrile was dissolved in about ten parts of strong alcohol, acidified with hydrochloric acid,

¹ This Journal, 24, 1035.

and the calculated amount of the brominating solution poured in. At first we used a large excess of dilute hydrochloric acid and cooled with ice, but later found both these precautions unnecessary. The brownish substitution product separates at once. It is washed thoroughly, dissolved in the smallest possible amount of 95 per cent. alcohol on the water-bath, hot water added until the cloud formed redissolves but slowly, and the solution is then allowed to cool. The bibromanthranilic nitrile separates very completely, in needles, the yield being nearly theoretical, and the product quite pure. A single recrystallization will usually remove the last traces of color from the crystals, the substance being identical in all respects with that obtained by the action of the hypobromite.

This bibrom nitrile forms no salt when hydrochloric acid gas is passed through its dry ethereal solution; nor is it acetylated by long boiling with acetic anhydride, the amino group remaining unaffected. To determine the position of the bromine atoms in the molecule, the saponification of the nitrile was undertaken.

SAPONIFICATION OF 3,5-BIBROM-2-AMINO BENZONITRILE.

Potassium Hydroxide.—The bibrom nitrile was boiled for some time with caustic potash of various strengths, with but little effect. A small amount was dissolved, and a few white needles separated on cooling. Very strong alkali appeared not to dissolve it at all, while fusion with potassium hydroxide gave only a yellow decomposition product.

Hydrochloric Acid.—The nitrile was unchanged by several hours' boiling with concentrated hydrochloric acid. When they were heated together in sealed tubes at 180° for several hours, partial saponification was secured, accompanied by some decomposition.

Sulphuric Acid.—Concentrated sulphuric acid charred the nitrile, but dissolved it completely on gentle warming. Acid of 75 per cent. to 85 per cent. strength gave a fairly good saponification, but the product was always brown, even after solution in caustic soda and reprecipitation with hydrochloric acid. In a sealed tube at 180° , however, 80 per cent. sulphuric acid gave a satisfactory saponification. Above 185° , rapid decomposition sets in. It is advisable to use as short a sealed tube as possible and to turn the same in the furnace from time to time, as the nitrile sublimes out of the sulphuric acid into the upper end of the tube and is thus liable to escape complete saponification. The contents

of the tube are poured into water, and the precipitate filtered out, washed and crystallized from alcohol, when white needles are obtained melting at 235.5° - 236° (corr.). A portion sublimed showed exactly the same melting-point.

3,5-BIBROM-2-AMINO BENZOIC ACID.

The melting-point of the acid obtained by us, by saponification of the bibromanthranilic nitrile, does not coincide with that of any of the bibromanthranilic acids so far reported.

Hübner¹ gives the melting-point of the 3,5-bibrom-2-amino-benzoic acid as 225° , and exactly the same figure (225°) for the melting-point of the 3,4-bibrom-2-aminobenzoic acid, while Dorsch² found the melting-point of the 3,4-bibrom acid to be 226° - 228° , and states that his acid is identical with that of Smith.³

We, therefore, decided to attempt the bromination of anthranilic acid itself in the same manner as its nitrile, in the hope of obtaining the same bibromanthranilic acid, and in this we were quite successful.

The anthranilic acid was dissolved in a very large volume of dilute hydrochloric acid and the bromide-bromate solution stirred in. The mixture turns blue and a precipitate slowly separates. After standing for half an hour, the precipitate is filtered out, washed thoroughly to remove unchanged anthranilic acid, etc., and then separated from any tribromaniline by solution in cold, dilute caustic soda and reprecipitation with hydrochloric acid.

By using rather less than the calculated amount of the brominating solution, very little tribromaniline is formed; any excess of bromine, however, above 2 molecules, increases the yield of tribromaniline and correspondingly diminishes that of the bibromanthranilic acid. With 3 molecules of bromine to 1 of anthranilic acid, only a trace of the bibromanthranilic acid was found, the product being nearly pure tribromaniline.

The precipitated bibromanthranilic acid is washed and treated with boneblack. The light amber solution thus obtained, on cooling, separates small needles nearly white. These needles are suspended in boiling water, baryta water is added to alkaline reaction, and the excess of baryta then removed by saturating the boiling solution with carbon dioxide. The barium carbonate and

¹ *Ann. Chem.* (Liebig), **222**, 175.

² *J. prakt. Chem.* (2), **33**, 36.

³ *Ber. d. chem. Ges.*, **10**, 1706.

a small amount of material insoluble in baryta water are filtered out, and the filtrate evaporated to crystals. On cooling, the barium salt of the bibromanthranilic acid separates in small, white prisms, which are recrystallized from water, and then decomposed by hydrochloric acid. The bibrom acid thus liberated is crystallized from benzene and from alcohol, then appearing in needles of a faint yellowish cast, melting at 235° - 235.5° (corr.), and identical in other respects with the acid obtained by the saponification of the bibromanthranilic nitrile. Both the acid and its barium salt are rather troublesome to purify, their solutions rapidly darkening when heated, and this may account for the low melting-point reported by Hübner.¹ Well-formed crystals can be obtained only by very slow cooling.

The pure 3,5-bibrom-2-aminobenzoic acid, as thus prepared, is easily soluble in alcohol (absolute), ether or acetone; moderately, in 95 per cent. alcohol, boiling benzene, or boiling toluene, but only sparingly in the latter two when cold; insoluble in ligroin; almost insoluble in water, cold or hot. It is decomposed, with loss of bromine, when gently heated with slaked lime. Heated alone in a sealed tube, at 260° - 270° it decomposes with liberation of hydrobromic acid. By elimination of its amino-group, 3,5-bibrombenzoic acid is formed. By the action of dry hydrochloric acid gas upon its dry ethereal solution, the hydrochloride separates as a white powder, which, when washed with dry ether and dried, gives off hydrochloric acid very rapidly.

SALTS OF 3,5-BIBROM-2-AMINOBENZOIC ACID.

Alkaline Salts.—By evaporating concentrated aqueous solutions of the sodium or potassium salts over sulphuric acid *in vacuo*, these salts separate in needles of considerable length. On account of their great solubility in both water and alcohol, it is very difficult to purify them.

Barium Salt.—The preparation of this salt we have already outlined. It crystallizes in small needles, moderately soluble in boiling water, but only sparingly soluble in cold. The crystals carry 3.5 molecules of water, of which 1.5 molecules are removed by drying over sulphuric acid *in vacuo*. According to Hübner¹ the crystals contain $4\text{H}_2\text{O}$.

Some of the crystals, dried five hours at 100° , lost 7.89 per

¹ *Loc. cit.*

cent. in weight; $(C_6H_2Br_2(NH_2)COO)_2Ba.3\frac{1}{2}H_2O$ contains 7.99 per cent. water. A determination of the water in the crystals dried over sulphuric acid, *in vacuo*, gave 4.78 per cent. and 5.05 per cent.; $(C_6H_2Br_2(NH_2)COO)_2Ba.2H_2O$ contains 4.73 per cent. H_2O .

This latter product, containing $2H_2O$, was further analyzed for barium and nitrogen, with the following results:

	Found.	Calculated for $(C_6H_2Br_2(NH_2)COO)_2Ba.2H_2O$.
Barium	17.76	17.83
Nitrogen	4.90	4.74

When heated in an open tube, this barium salt takes fire and burns. By careful manipulation, however, a sublimate was obtained, melting at 74° - 75° (corr.), which has not been further examined.

ELIMINATION OF THE AMINO-GROUP FROM 3,5-BIBROM-2-AMINO-BENZONITRILE.

The bibrom nitrile was suspended in water, hydrochloric acid added, and potassium nitrite solution gradually dripped in. No diazotizing whatever occurred, the nitrile being recovered unchanged.

The nitrile was then dissolved in 95 per cent. alcohol, and oxides of nitrogen (from nitric acid and arsenious oxide) passed through the boiling solution. On concentrating the alcohol solution, groups of small needles separated which were dried and carefully sublimed, the sublimate melting sharply at 96.5° - 97° (corr.) The yield is very small, and subliming at 98° - 100° in a gentle current of air is the only method by which we have been able to get a product with a sharp melting-point.

The action of ethyl nitrite upon the nitrile was puzzling and unsatisfactory. A boiling 15 per cent. solution of the nitrite was used in large excess, with a few drops of hydrochloric acid. The solution was evaporated to dryness on the water-bath, and the residue crystallized from dilute alcohol, but no pure product could be obtained. On subliming the crude crystals on the water-bath in a gentle current of air, beautiful, white needles were obtained, the melting-point of which rose steadily with the progress of the sublimation. One crop melted at 59° - 59.5° (corr.), another at 67.5° - 68° (corr.), and a third at 87° - 88° (corr.). Saponification of the last lot gave an acid, melting poorly at about 205° , and presumably impure 3,5-bibrombenzoic acid.

The yield in all these reactions was so small that not enough material was secured for an analysis. Conversion of the products, however, to 3,5-bibrombenzoic acid points clearly to the presence of its nitrile. The action of nitrous vapors upon the amino nitrile always gives the same product, melting sharply at 96.5° - 97° (corr.), though in small yield, and we are of the opinion that this is the pure 3,5-bibrombenzonitrile, although Claus and Weil¹ report its uncorrected melting-point as 89° .

Some of this product, melting at 96.5° - 97° (corr.), was saponified by heating it in a sealed tube for three hours at 170° with 75 per cent. sulphuric acid. Like its amino derivative, the bibrom nitrile tends to sublime out of the sulphuric acid and thus escape complete saponification. A short, sealed tube should, therefore, be used, as suggested. From the sealed tube, on cooling, large, glassy crystals separated which were contaminated with unsaponified nitrile. The crude bibrom acid was purified by solution in dilute caustic alkali and reprecipitation with hydrochloric acid. Crystallized from alcohol, the bibrombenzoic acid was obtained in small, glassy needles, softening slightly at 215° and melting at 218.5° (corr.). The crystals sublime quite easily. If the first crude acid is very dark in color, it may, with advantage, be recrystallized from concentrated sulphuric acid, in which it dissolves on warming and separates out unchanged on cooling.

ELIMINATION OF THE AMINO GROUP FROM 3,5-BIBROM-2-AMINO-BENZOIC ACID.

The bibromanthranilic acid was dissolved in absolute alcohol, the solution heated to boiling, and saturated with nitrous gases (from nitric acid and arsenious oxide), causing the solution to assume a deep reddish brown color. The boiling solution was poured into twice its volume of water, and the light yellow precipitate filtered out and thoroughly washed with water. The crude acid thus obtained was converted into its difficultly soluble barium salt, which was purified by repeated crystallizations from water and then decomposed with hydrochloric acid. The purified bibrombenzoic acid was crystallized from benzene, and separated in radiating masses of long, white needles (m. p. 219.5° - 220.5° (corr.)), similar in all its properties to the acid obtained by saponification of the bibrombenzonitrile, and evidently the 3,5-bibrombenzoic acid. The complete purification of this acid is very tedious.

¹ *Ann. Chem.* (Liebig), **269**, 223.

ous, small amounts of impurities lowering the melting-point considerably.

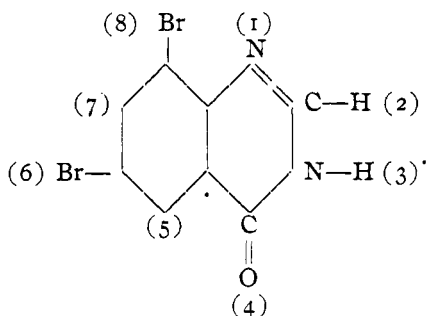
Barium Salt of 3,5-Bibrombenzoic Acid.—This was prepared by the action of baryta water upon the purified acid. It can be purified by crystallization from water, in which it is less soluble than the barium salt of the bibrom amino acid. It separates in needles of a faint yellow color. The air-dried salt was analyzed with the following results:

	Found.	Calculated for (C ₇ H ₃ Br ₂ O ₂) ₂ Ba. 3 $\frac{1}{2}$ H ₂ O.
Water	8.58	8.31
Barium	18.03	18.07

Angerstein¹ gives the melting-point of 3,5-bibrombenzoic acid as 223°-227°; Hübner,² as 213°-214°; Claus and Weil,³ as 209° (uncorr.). Hübner and Claus and Weil assign to the Ba salt 4 molecules H₂O; Angerstein dried the salt over H₂SO₄ and then found 2H₂O.

SYNTHESIS OF QUINAZOLINES FROM 3,5-BIBROM-2-AMINO BENZO-NITRILE.

6,8-Bibrom-4-Ketodihydroquinazoline,



Three grams bibromanthranilic nitrile were heated in a sealed tube with 3 cc. glacial formic acid for five hours at 225°-235°. This temperature was much higher than necessary, as the tube was under heavy pressure when opened and the contents were black. By solution in dilute caustic soda and saturation of the alkaline liquid with carbon dioxide, a yellow precipitate separated in small amount.

¹ *Ann. Chem.* (Liebig), **158**, 10.

² *Ibid.*, **222**, 171.

³ *Ibid.*, **269**, 224.

A second tube, containing 3 grams of the nitrile and 3.5 cc. glacial formic acid, was heated for sixty-nine consecutive hours at 200° - 209° , and the contents worked up in the same manner. A beautiful, white crystalline substance was obtained which, after recrystallization from aniline, formed small, clear needles. The yield of pure substance was about 50 per cent. of the theoretical. It does not melt, but decomposes above 300° . On analysis, the substance gave 9 per cent. nitrogen, while the above formula requires 9.21 per cent. nitrogen.

Ethyl Ether of 6,8-Bibrom-4-Ketodihydroquinazoline.—One-half gram of the quinazoline was heated for two and a half hours in a sealed tube with slight excess of alcoholic sodium hydroxide and excess of ethyl iodide, at 100° - 104° . The beautiful, crystalline product was washed with water and with alcohol, and then formed a snow-white mass of small, clear needles, melting sharply at 229° - 230° (corr.). On analysis, 8.70 per cent. nitrogen was found; required for $C_{10}H_8ON_2Br_2$, 8.43 per cent.

6,8-Bibrom-2-Methyl-4-Ketodihydroquinazoline.—Two grams of the nitrile and 2 cc. of acetic anhydride were heated together for about six hours in a sealed tube at 220° - 230° . By solution of the tube's contents in dilute caustic soda, filtering and saturating the filtrate with carbon dioxide, a snow-white product was obtained, which was recrystallized from aniline. By very careful heating, in a current of carbon dioxide, it may be partly sublimed in beautiful needles. It does not melt, but decomposes slowly when heated above 300° . It shows about the same solubilities as the methyl thioquinazoline (see beyond), except that it is rather more soluble in glacial acetic acid.

	Found.	Calculated for $C_{10}H_8ON_2Br_2$.
Nitrogen	9.14	8.81
Bromine	50.03	50.31

We have run a number of sealed tubes for the preparation of this quinazoline, varying the temperature and the duration of the heating, but in every case so far the yield has been very poor.

Ethyl Ether of 6,8-Bibrom-2-Methyl-4-Ketodihydroquinazoline.—One-half gram of the quinazoline was heated for two and a half hours at 100° - 105° in a sealed tube with slight excess of alcoholic sodium hydroxide and excess of ethyl iodide. No crystals separated on cooling. The alcoholic solution was evaporated to a small

volume; the brown needles which crystallized out were recrystallized from alcohol, but still retained a slight brownish color. They began to decompose very slowly at about 170° , but did not melt at 290° .

6,8-Bibrom-2-Ethyl-4-Ketodihydroquinazoline.—Three grams nitrile and 3 cc. propionic anhydride were heated together in a sealed tube for ten and a half hours at 200° , followed by five hours longer at 210° . On treating the tube's contents with sodium hydroxide and carbon dioxide, as already described, the ethyl quinazoline was obtained as a white precipitate. Crystallized from moderately dilute alcohol, it separates in long, white, silky needles (m. p. 278° - 280° (corr.)). The yield was poor.

0.2148 gram substance gave 8.10 per cent. nitrogen; required, 8.43 per cent.

6,8-Bibrom-2-Normalpropyl-4-Ketodihydroquinazoline.—Three grams nitrile and 3 cc. normal butyric anhydride were heated together in a sealed tube for ten and a half hours at 200° , followed by five hours and a half at 210° . Treatment of the tube's contents in the usual manner resulted in the separation of the N-propylquinazoline as a white, voluminous precipitate. It crystallizes from dilute alcohol in colorless, microscopic needles (m. p. 238° - 240° (corr.)). The yield is only fair.

0.2351 gram substance gave 8.07 per cent. nitrogen; required, 8.09 per cent.

6,8-Bibrom-2-Isopropyl-4-Ketodihydroquinazoline. — Three grams of the nitrile and 3 cc. of isobutyric anhydride were heated together in a sealed tube for ten and a half hours at 200° , followed by five and a half hours at 210° , and then two hours longer at 220° . The tube's contents were worked up as the others were. The isopropyl quinazoline thus produced appears to the unaided eye as a white, amorphous powder, but is really a felted mass of white, microscopic, hairy crystals, which melt at 259° - 260° (corr.). The yield was only fair.

0.2228 gram substance gave 7.92 per cent. nitrogen; required, 8.09 per cent.

6,8-Bibrom-2-Isobutyl-4-Ketodihydroquinazoline.—Three grams of the nitrile and 3 cc. of isovaleric anhydride were heated together in a sealed tube for ten and a half hours at 200° , five and a half hours at 210° , and two hours at 215° - 220° . The tube's contents were

worked up in the usual manner, and the isobutyl quinazoline separated as a precipitate. The recrystallized substance forms colorless, microscopic needles (m.p. 230° - 231.5° (corr.)). 0.1999 gram substance gave 7.82 per cent. nitrogen; required, 7.77 per cent.

Most of these brominated quinazolines decompose wholly or partly on melting. It is interesting to note that with increase in molecular weight the melting-point steadily sinks, iso compounds showing a higher melting-point than those with normal side-chains. We have already called attention to the same condition of affairs in the case of the unbrominated alkyl quinazolines and the acylated anthranilic nitriles.

These brominated quinazolines dissolve very readily in caustic alkali, but do not appear to form salts with the mineral acids.

6,8-Bibrom-2-Methyl-4-Thioketodihydroquinazoline.—Two grams of the bibromanthranilic nitrile and the calculated amount of thiactic acid were heated together in a sealed tube for about six hours at 220° - 230° . On opening the tube, slight pressure, due to hydrogen sulphide, was observed. The contents of the tube were boiled with dilute alkali, the solution cooled, filtered, and carbon dioxide passed through the filtrate, whereby a yellow, amorphous precipitate separated. Crystallized from aniline, this precipitate changed to beautiful, yellow needles. The substance does not melt at 290° , but decomposes slowly when heated. By very careful heating in a gentle current of carbon dioxide, it may be partially sublimed. It is nearly insoluble in alcohol, benzene or 50 per cent. acetic acid, slightly soluble in glacial acetic acid, and soluble in boiling aniline. It is only moderately soluble in caustic alkalies; when enough alkali is used to dissolve the quinazoline completely and a few drops of acetic acid are then added, the quinazoline is partly reprecipitated, although the solution remains strongly alkaline to litmus.

The temperature used in the first experiment (220° - 230°) was unnecessarily high, as partial decomposition had occurred, and the yield of thioquinazoline was poor. Another tube, heated sixty-nine hours at 200° - 209° , likewise showed too much decomposition. A third tube, heated forty-two hours at 180° , was much more satisfactory in appearance; but little decomposition had occurred, and a yield of 2.1 grams of the pure thioquinazoline was obtained from 3 grams of the bibromnitrile.

Analysis of 6,8-Bibrom-2-Methyl-4-Thioketodihydroquinazoline.—The determination of carbon and hydrogen in this bibrom-thioquinazoline proved exceedingly troublesome, on account of the high percentage of bromine (nearly 48 per cent.) and the presence of sulphur.

The de Roode mixture of red lead and lead chromate was used as the oxidizing agent, and it was found to be much more efficient with freshly prepared lead chromate than with the commercial fused article. Freshly precipitated and thoroughly washed lead chromate was mixed with red lead and made into little balls. These were dried, ignited in an open dish, and then thoroughly burned out in a stream of dry oxygen. As thus prepared, they did not melt or disintegrate.

A long combustion tube was used, in which were placed an oxidized copper gauze, then a long porcelain boat containing the thioquinazoline mixed with ignited red lead and covered with the same, then a short, silver spiral, followed by the oxidizing mixture, a long, silver spiral, and a bright copper gauze. The combustion was conducted very slowly at a moderate temperature. Unless the temperature of the exit end of the tube was kept well down, bromine could be detected in the gases passing into the absorption train.

	Found.	Calculated for $C_9H_6N_2SBr_2$.
Carbon.....	32.94-32.76	32.33
Hydrogen.....	2.01-2.03	1.80
Nitrogen.....	8.70-8.52	8.38
Sulphur.....	9.64	9.58
Bromine.....	47.79	47.91

Ethyl Ether of 6,8-Bibrom-2-Methyl-4-Thioketodihydroquinazoline.—This was prepared by the method already described for the corresponding oxygen compound. The product crystallized out of the sealed tube on cooling. Washed with water and with alcohol, it appeared in beautiful, light yellow needles, which began to decompose at about 305° , but did not melt completely at 360° .