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THE SYNTHESIS OF ALKYL KETODIHYDROQUINAZOLINS
FROM ANTHRANILIC ACID.

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THEORY.

It has been shown in two previous papers¹ that the action of nitriles upon anthranilic acid, when heated together under pressure, results in the formation of ketodihydroquinazolins; and in the second paper the preparation of 2-methyl-4-ketodihydro-

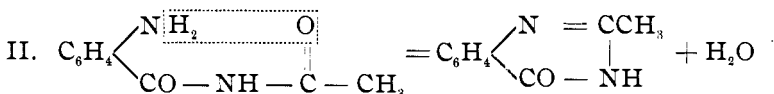
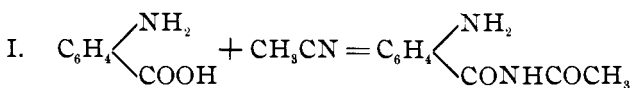
quinazolin (or α -methyl- β -quinazolone), C_8H_8 $\begin{matrix} \diagup N = CCH_3 \\ \diagdown CO - NH \end{matrix}$, was

discussed in detail, both theoretically and practically. The present paper treats of the application of this method to the synthesis of higher members of the series; *viz.*, the ethyl, normal and isopropyl-, isobutyl-, and isoamylquinazolons, the last two being new; and also the preparation of several of their derivatives.

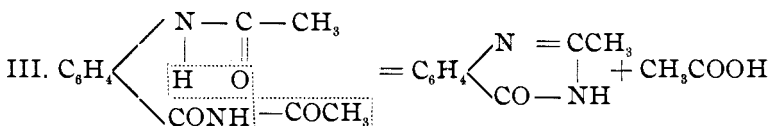
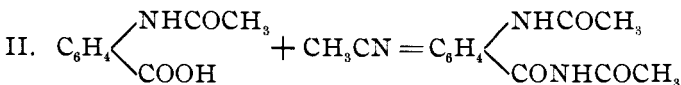
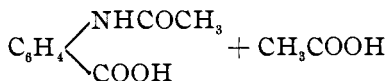
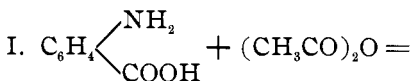
It has already been stated² that the addition of acetic anhydride was found very beneficial in the preparation of the methyl derivative and that the reactions thought most probable are as follows: Without anhydride:

¹ Bogert and Gotthelf: This Journal, **22**, 129 and 522.

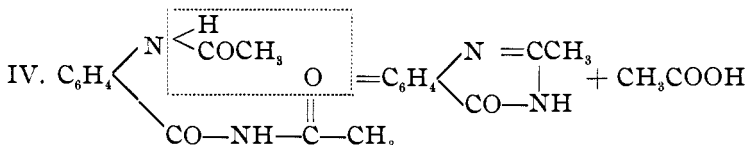
² This Journal, **22**, 530.



With anhydride:



or



In preparing the higher derivatives, various modifications of the process were tried in order to throw more light upon these reactions and to determine the conditions necessary for the best yield. These may be summed up as follows: Anthranilic acid was heated with:

- I. Nitrile alone.
 1. Propionitrile.
 2. *n*-Butyronitrile.
 3. Isovaleronitrile.
 4. Isocapronitrile.

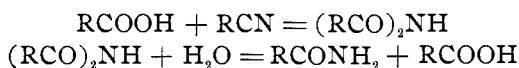
Nothing in confirmation of, or opposition to, the theory of this reaction as given above was discovered from these experiments. The yield varied, being very poor in some cases and good in others.

II. Nitrile and the corresponding acid anhydride.

1. Propionitrile and propionic anhydride.
2. *n*-Butyronitrile and *n*-butyric anhydride.
3. Isovaleronitrile and isovaleric anhydride.

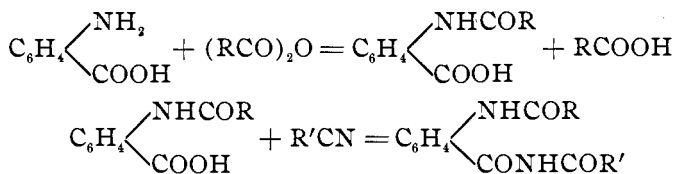
The addition of anhydride was found to greatly increase the yield in every instance. The reaction probably taking place under these conditions has already been shown. The rapid combination of the anhydride with the anthranilic acid was indicated in each case by the mixture becoming warm and solidifying almost immediately after mixing.

The by-products of the reaction are the anilide and amide of the fatty acid whose anhydride and nitrile are used. The former is found, however, only in those tubes which show considerable pressure on opening, and its formation is, therefore, probably due to the splitting off of carbon dioxide from the acylanthranilic acid. The presence of the amide can be explained by supposing a secondary amide to form in the tube by the interaction of the fatty acid and nitrile, which then, on heating with water in the after-treatment of the tube-contents, decomposes to the primary amide:

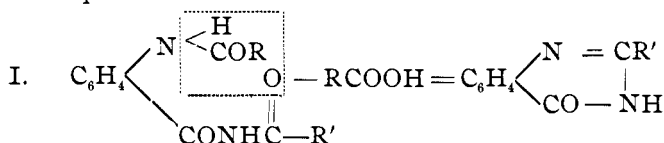


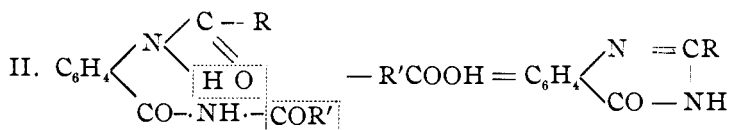
III. Nitrile and a different acid anhydride.

In the experiments thus far considered the formation of but one quinazolone was possible (excluding tautomeric forms), but when different anhydrides and nitriles are used, two may result, as shown by the following equations:



The reaction so far is the same as usual, but now, in forming the ring, either RCOOH or R'COOH may split off, resulting in different quinazolones:





The reactions tried were:

A. Nitrile and a higher acid anhydride.

1. Acetonitrile and propionic anhydride.
2. Acetonitrile and *n*-butyric anhydride.
3. Acetonitrile and isobutyric anhydride.
4. Propionitrile and isobutyric anhydride.

In these cases the reaction always followed equation (II); *i. e.*, the anhydride determined which quinazolon was formed: (1) giving ethyl; (2) normal propyl; and (3) and (4) isopropyl quinazolon.

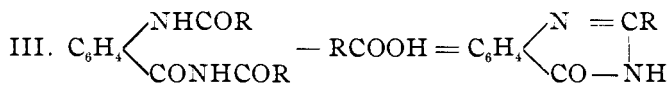
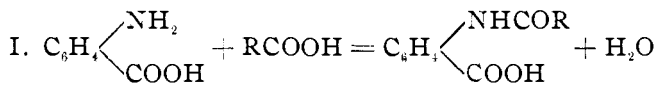
B. Nitrile and a lower acid anhydride.

1. Propionitrile and acetic anhydride.
2. Isocapronitrile and isobutyric anhydride.
3. Isocapronitrile and *n*-butyric anhydride.

Of these, (1) yielded pure methyl quinazolon and therefore reacted according to equation (II), while (2) and (3) yielded mixtures.

IV. Nitrile and the corresponding acid.

The reaction in this case, if it follows the same course as when anhydride is used, is as follows:



It does not seem likely, however, that, especially with the higher weaker acids, reaction (I) proceeds to any great extent, if at all, as it depends on the affinity between the fatty acid and the amino group of the anthranilic acid, an affinity which, among the higher acids, is practically zero. Experiments by the writer with normal butyric and isocaproic acids show that, under the

same conditions as to heat and pressure that existed in the tubes, these acids do not combine, to any appreciable extent, with anthranilic acid.

The nitriles and acids used were :

1. Acetonitrile and acetic acid.
2. Propionitrile and propionic acid.
3. *n*-Butyronitrile and *n*-butyric acid.
4. Isocapronitrile and isocaproic acid.

In these reactions the results were very similar to those of case (II), the yields being about the same and anilides and amides being found as by-products. The formation of the amide can be more simply explained in this case by the action of the liberated water on the nitrile. In order to allow for this saponification, two molecules of nitrile were used to one each of anthranilic acid and fatty acid. The anilides are doubtless due to the action of aniline, formed by the decomposition of anthranilic acid, on either the fatty acid or the amide.

V. Nitrile and a different acid.

As in the third case, so in this one, the formation of two quinazolons is possible. The reactions tried were :

A. Nitrile and a higher acid.

1. Acetonitrile and propionic acid.
2. *n*-Butyronitrile and capric acid.
3. Isocapronitrile and capric acid.

Of these, (2) and (3) gave pure quinazolons; the former, the normal propyl, and the latter, the isoamyl derivative. The capric acid appears, therefore, to have taken no part in the reaction, probably because it is too weak to form any acyl derivative whatever with the anthranilic acid. Reaction (1), on the contrary, gave a product which was evidently a mixture.

B. Nitrile and a lower acid.

1. Acetonitrile and formic acid.
2. Propionitrile and formic acid.
3. Isocapronitrile and formic acid.
4. Isocapronitrile and propionic acid.

Reaction (4) resulted in pure isoamyl quinazolone and (3) in isoamyl quinazolone with a trace of what appeared to be 4-ketodihydroquinazolin itself, while (1) and (2) gave, apparently, no phenmiazine derivative at all.

In considering those reactions in which anhydrides or acids not corresponding to the nitriles were used, it will be seen that their course appears to depend both on the ease with which the anhydride or acid reacts with anthranilic acid to form acylanthranilic acid, and on the molecular weights of the radicals introduced. Thus, under III, *A*, using nitrile and a higher anhydride, normal and isobutyric anhydrides were heated with acetic and propionic nitriles and in every case pure normal or isopropyl quinazolone resulted, while, under V, *A* (nitrile and a lower anhydride), the same anhydrides, when heated with isocapro-nitrile, yielded mixtures. Evidently, in the latter case, the superior weight of the isocaproyl radical has exerted its influence and forced out the lighter radical as indicated in equation (I).

That the product also depends upon the relative strength of the acids and anhydrides is shown by the fact that, when using anhydrides, pure quinazolones, whose formulas depended upon that of the anhydride, were obtained in five instances, while, when using acids, in every case either a mixture resulted or the quinazolone obtained depended wholly upon the nitrile used. This is clearly shown by comparing reactions III, *A*, 1 and V, *A*, 1, in which propionic anhydride and propionic acid were heated with acetonitrile and yielded, respectively, pure ethyl quinazolone and a mixture.

To roughly determine the ease with which the higher fatty acids and anhydrides combine with anthranilic acid, a few experiments were performed, a description of which will be found at the end of this paper.

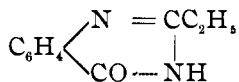
For purposes of comparison the melting-points of the quinazolones treated of in this paper are here tabulated. It will be noticed that they descend with the increase in molecular weight and that the isoderivatives melt much higher than the corresponding normal ones.

	Normal.	Iso.
Methyl	239°
Ethyl.....	234°
Propyl... ..	199°-200°	230°-232°
Butyl.....	194°-195°
Amyl.....	184°

EXPERIMENTAL PART.¹

In all the following work the proportions of material used, unless specially mentioned, were the same in corresponding reactions; *i. e.*, when nitrile alone was used, two molecules were heated with one molecule of anthranilic acid; when acid anhydride was added, the proportions were one molecule nitrile, one of anhydride, and one of anthranilic acid; when a fatty acid was substituted for the anhydride, one molecule of fatty acid, two of nitrile, and one of anthranilic acid were used.

2-ETHYL 4-KETODIHYDROQUINAZOLIN.

*Preparation.*

I. *Anthranilic Acid and Propionitrile.*—The tube was heated to 170°–180° for six hours and then to 200°–210° for another six hours. After the first period the pressure was considerable but after the second it was slight. The tube-contents were dark-colored, completely crystalline, and smelled of ammonia. They were treated with cold sodium carbonate solution and the undissolved portion filtered out. The latter was then ground in a mortar with cold dilute caustic potash solution, the mixture filtered, the residue washed, and the quinazolon precipitated from the filtrate by passing carbon dioxide. The yield, after crystallizing once from water, amounted to 22½ per cent. of the theoretical.

The residue from the caustic potash treatment was crystallized from water and found to be propionanilide, crystallizing in leaflets, melting at 104°–105°, and yielding aniline when boiled with caustic alkali. It was probably formed by the action of aniline on propionamide, resulting in ammonia and propionanilide; as mentioned above, ammonia was found in the tube.

II. *Anthranilic Acid, Propionitrile, and Propionic Anhydride.*—This tube was heated to 160°–170° and to 200°–210° for six hours each, opening after each period. There was considerable pressure after the first heating and very little after the second, the tube contents consisting of a light brown homogeneous mass of

¹ All melting-points given, unless stated to be uncorrected, were determined with Anschütz short-scale thermometers, the entire mercury column being immersed in the heating liquid.

crystalline material. This was treated with cold sodium carbonate solution, and the residue extracted with alcohol, in which practically all dissolved. The alcoholic solution, after being decolorized with bone-black, was evaporated and the residue crystallized from water. The impure ethyl quinazolon thus obtained was separated from the propionanilide mixed with it by the use of cold dilute caustic alkali as described under (I). The yield was $31\frac{1}{2}$ per cent.

With another tube the treatment with alcohol was omitted, the residue insoluble in sodium carbonate being warmed directly with dilute caustic potash for a short time. The solution was then cooled to permit the propionanilide to crystallize, filtered, and the quinazolon precipitated and purified as before. The yield in this case was 29 per cent.

The effect of an excess of anhydride and nitrile was also tried, a tube being prepared containing the substances in the proportion of $1\frac{1}{2}$ molecules of anhydride and 2 of nitrile to 1 molecule of anthranilic acid. It was heated to 160° – 170° for six hours and to 200° – 210° for a similar period and yielded 30 per cent. of quinazolon.

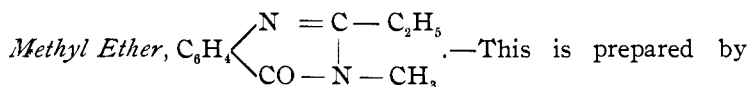
III. *Anthranilic Acid, Propionitrile, and Propionic Acid.*—A tube containing these was heated to 160° – 165° and to 200° – 210° for five hours each. There was strong pressure after the first heating but little after the second, and the contents were light-colored and crystalline. They were treated successively with sodium carbonate and caustic potash solutions in the manner already described and the yield was 36 per cent. of the theoretical. Propionanilide was again a by-product.

Another tube containing the same amounts of material was heated to 150° – 160° for five hours and to 175° – 180° for five hours. The contents, after treatment with soda solution, were crystallized directly from water and yielded 28 per cent. of quinazolon.

IV. *Anthranilic Acid, Acetonitrile, and Propionic Anhydride.*—The tube was heated successively to 180° – 190° , 220° – 230° , and 225° – 235° for five hours each. The pressure at any time was slight. After washing with soda solution the product was crystallized from water and a yield of about 17 per cent. of ethyl quinazolon obtained. No methyl quinazolon could be found although the experiment was repeated several times and the by-products carefully examined.

Properties.

The ethyl quinazolon obtained by the above methods agreed in all its properties with those observed by Bischler and Lang¹ and by Niementowski.² It crystallizes from water in long fine needles which are moderately soluble in hot water, slightly in cold, easily in alcohol and benzene. Its melting-point is given by Bischler and Lang as 227°–228° and by Niementowski as 225°. The writer found 227°–228° to be the uncorrected melting-point and 234° the corrected.

Derivatives.

heating the quinazolon with caustic alkali and methyl iodide in alcoholic solution, for a few hours, with a return condenser, evaporating the alcohol and treating the residue with water. Sometimes the addition of a little more caustic alkali is necessary at this point to cause the complete separation of the ether, which is then filtered out and crystallized from water. It forms long colorless needles melting at 121°.

Hydrochloride.—This salt results from the action of hydrochloric acid on the quinazolon. It crystallizes in needles which sublime without melting.

Nitrate.—The nitrate crystallizes from a hot solution of the base in nitric acid (1 : 4) in the form of coarse yellow needles which melt with decomposition at 173°–174°.

Sulphate.—This salt is obtained by saturating cold dilute sulphuric acid with quinazolon, filtering and concentrating the filtrate. It forms coarse needles which gradually darken on heating and melt at 240°–241°.

Chromate.—The chromate crystallizes from a hot concentrated aqueous solution of quinazolon and chromic acid, in the form of light brown needles which decompose at about 155°.

Picrate.—This is prepared in the same way as the chromate but is less soluble in cold water. It crystallizes in thin plates of a light yellow color and melts at 191°–192°.

¹ *Ber. d. chem. Ges.*, **28**, 280.

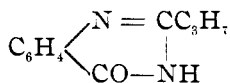
² *J. prakt. Chem.*, (2), **51**, 564.

Oxalate.—This is also prepared as is the chromate and forms long needles melting at 180–181°.

*Chlorplatinat*e.—The quinazolone is dissolved in hot hydrochloric acid and an excess of platinic chloride added; on cooling, the double salt separates as a red crystalline powder. It was analyzed for platinum with the following results :

	Calculated for (C ₁₀ H ₁₀ N ₂ O.HCl) ₂ PtCl ₄ .	I.	Found. II.
Platinum.....	25.63	25.66	25.63

2·*n*·PROPYL 4·KETODIHYDROQUINAZOLIN.



Preparation.

I. *Anthranilic Acid and n-Butyronitrile*.—The tube was heated to 120°–125° for four and one-half hours, 200°–210° for six hours, and 210°–220° for six hours, opening after each period. The pressure was considerable only after the second period and the product was crystalline. After the usual sodium carbonate treatment the residue was crystallized from water. The quinazolone thus obtained was dissolved in cold caustic alkali to separate it from *n*-butyranilide but none of the latter was found. The base was then precipitated with carbon dioxide as usual and crystallized from water. The yield was about 17 per cent.

The sodium carbonate solution used in the first treatment was evaporated, the residue extracted with ether, and the extract crystallized from benzene. Leaflets were obtained melting at 112°–113°, very soluble in water, and evolving ammonia when boiled with caustic alkali. Hofmann¹ states that *n*-butyramide melts at 115°.

II. *Anthranilic Acid, n-Butyronitrile, and n-Butyric Anhydride*.—A tube containing these substances was heated to 180°–190° for four hours and to 190°–200° for five hours. The yield was 30 per cent. Another tube heated to 180°–190° for five and one-half hours and to 210°–220° for six hours gave 39 per cent.

There was practically no pressure in either case and the contents were very light-colored. Both products were treated in the same way; first washed with sodium carbonate solution and then twice crystallized from water, decolorizing with bone-black.

¹ *Ber. d. chem. Ges.*, 15, 952.

The soda solutions were found to contain *n*-butyramide as in the last case.

No butyranilide was found and none was expected from the fact that the slight pressure in the tubes showed that practically no anthranilic acid had decomposed.

III. *Anthranilic Acid, Acetonitrile, and n-Butyric Anhydride*.—The tube was heated to 180°–190° for five hours and to 210°–220° for six hours. There was no pressure. The contents were treated as in (II). The quinazolon obtained agreed in all its properties with *n*-propylquinazolon. The yield was about 28 per cent.

By evaporating the soda solution, extracting the residue with ether, and crystallizing the extract from benzene, a very small amount of material was obtained which softened at 93°, but was not entirely melted at 130°. It dissolved completely in cold dilute caustic potash and was reobtained by passing carbon dioxide and concentrating the solution. On crystallizing from benzene it now melted at 232°–233° (uncorrected), and was probably methyl quinazolon.

IV. *Anthranilic Acid, n-Butyronitrile, and n-Butyric Acid*.—The tube was heated for three periods of six hours each to 155°–175°, 210°–215°, and 230°–240°. After each of the first two periods there was considerable pressure, but after the third, there was none. The product was treated successively with soda solution and dilute caustic alkali, and the quinazolon precipitated from the latter solution as usual by passing carbon dioxide. It was purified by crystallization from water.

The part insoluble in the caustic alkali was found, on recrystallizing from dilute alcohol, to be *n*-butyranilide. It melted at 93°–94° and yielded aniline when boiled with concentrated alkali. Gerhardt¹ gives the melting-point of *n*-butyranilide as 90° but the writer found that anilide prepared by boiling *n*-butyric acid with aniline for a few hours, pouring the product into water, and crystallizing the precipitate from dilute alcohol, melted at 93°–94°, and otherwise agreed with that obtained from the tube.

The soda solution, as usual, contained *n*-butyramide.

Properties.

Normal propyl quinazolon has been prepared by Bischler and Lang,² who found the melting-point to be 205°. While in all

¹ *Ann. Chem.* (Liebig), **87**, 166.

² *Ber. d. chem. Ges.*, **28**, 286.

other properties the quinazolone obtained by the writer agrees with that of these authors, its melting point is 199° – 200° .

Derivatives.

The salts and ethers of this and the following quinazolones were almost all prepared in exactly the same way as were those of ethyl quinazolone and therefore only their properties are given.

Methyl ether, $C_6H_4 \left\{ \begin{array}{l} N = C - C_3H_7 \\ | \\ CO - N - CH_3 \end{array} \right.$, crystallizes from water in

long colorless needles melting at 77° – 78° .

Hydrochloride.—Thin plates which sublime without melting.

Nitrate.—Coarse flat needles melting with decomposition at 159° – 160° .

Sulphate.—Long coarse needles melting at 227° – 228° .

Chromate.—Yellow crystalline powder. On heating, it gradually darkens, commencing at about 150° .

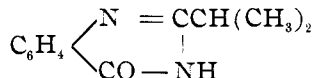
Picrate.—Light yellow needles with serrated edges, melting at 183° – 184° .

Oxalate.—White needles melting at 193° – 194° .

Chlorplatinate.—Coarse red crystals. The platinum was determined by ignition.

	Calculated for ($C_{11}H_{12}N_2O.HCl$) $_2PtCl_4$.	I.	Found.	II.
Platinum.....	24.71	24.79		24.82

2-ISOPROPYL 4-KETODIHYDROQUINAZOLIN.



No isobutyric nitrile being conveniently at hand, its action alone on anthranilic acid could not be studied. It was found, however, that, for the production of isopropyl quinazolone, the use of isobutyric nitrile was unnecessary, and that the combined action of isobutyric anhydride and a lower nitrile, acetic or propionic, on anthranilic acid resulted in its formation, the yield, especially with propionitrile, being very good.

I. *Anthranilic Acid, Isobutyric Anhydride, and Propionitrile*.—The tube was heated to 180° – 190° for five hours, 210° – 220° for five hours, and 230° – 240° for twelve hours. The pressure at any time was very slight. After preliminary treatment with sodium

carbonate solution the product was crystallized from alcohol and decolorized with bone-black. The yield of quinazolone was about 40 per cent.

Another tube was heated to 180°–190° for six hours and to 210° for six hours and yielded 32 per cent.

No trace of ethyl quinazolone was found in either of these tubes.

II. *Anthranilic Acid, Isobutyric Anhydride, and Acetonitrile.*—This tube was heated to 180°–190° for five hours and 210°–220° for six hours and yielded 15½ per cent. of isopropyl quinazolone, the process of purification being the same as when using propionitrile.

Properties.

Bischler and Lang¹ and Niementowski² have prepared isopropyl quinazolone but differ as to its melting-point, the former giving it as 195°–196° and the latter as 224°. Niementowski³ has suggested that this difference may be due to a difference in constitution in the sense of tautomerism.

The quinazolone obtained by the writer melts at 225°–226° uncorrected or at 231°–232° corrected; it therefore agrees quite well with Niementowski's product. Its other properties are the same as those recorded by these authors.

A peculiarity in the solubility of this base was observed by the writer, which possibly indicates that it consists of a mixture of the two forms, keto and hydroxy? While all the other quinazolones, when in a fluffy crystalline condition, dissolved instantly in cold dilute caustic alkali, it was found that the isopropyl showed a difference in the rapidity of solution. Only a portion dissolved instantly; the rest remained undissolved for a short time, though it ultimately also went into solution. In one case the slower dissolving portion was filtered out, washed, and dried. Its melting-point was found to be 223°, while the portion which had dissolved, when precipitated with carbon dioxide and crystallized from alcohol, melted at 231°–232°, the ordinary melting-point of the quinazolone. No further work has, at present, been done on this subject.

¹ *Ber. d. chem. Ges.*, **28**, 287.

² *J. prakt. Chem.* (2), **51**, 569.

³ *Ber. d. chem. Ges.*, **27**, R., 516.

Derivatives.

Methyl Ether, $C_6H_4 \left\{ \begin{array}{l} N = C - C_3H_7 \\ | \\ CO - N - CH_3 \end{array} \right.$.—Long silky needles melting at $78^\circ - 79^\circ$.

Hydrochloride.—Rectangular plates.

Sulphate.—Coarse needles melting at $219^\circ - 220^\circ$.

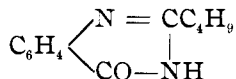
Chromate.—Transparent coarse brown needles which decompose on heating.

Pierate.—Light yellow crystalline powder melting at $213^\circ - 214^\circ$.

*Chlorplatinat*e.—Coarse red crystals. The platinum was determined by ignition.

	Calculated for		Found.	
	$(C_{11}H_{12}N_2O.HCl)_2PtCl_4$.		I.	II.
Platinum.....	24.71		24.85	24.69

2·ISOBUTYL, 4·KETODIHYDROQUINAZOLIN.

*Preparation.*

I. *Anthranilic Acid and Isovaleronitrile*.—The tube was heated to $160^\circ - 165^\circ$ for five hours and to $200^\circ - 210^\circ$ for five hours. Moderate pressure was found on opening, and the contents were dark-colored but crystalline. They were heated with dilute caustic potash solution for a short time, the solution cooled, filtered, and carbon dioxide passed into the filtrate. The precipitated quinazolon was then crystallized from water. The yield was only 5 per cent. of the theoretical.

II. *Anthranilic Acid, Isovaleronitrile, and Isovaleric Anhydride*.—The mixture was heated successively to $180^\circ - 190^\circ$ for five hours, $210^\circ - 220^\circ$ for five hours, and $230^\circ - 240^\circ$ for twelve hours. The pressure in the tube was very slight and the contents were light-colored and entirely crystalline. They were treated with soda solution and then crystallized from dilute alcohol. To separate the quinazolon from isovaleranilide the treatment with cold dilute caustic alkali was applied to this product. The anilide was crystallized from dilute alcohol and obtained in the form of colorless needles melting at $112^\circ - 113^\circ$, and yielding aniline when boiled with concentrated alkali. The quinazolon, after precipita-

tion with carbon dioxide, was crystallized from water and amounted to 35 per cent. of the theoretical yield.

The soda solution with which the tube-contents were first treated was evaporated and the residue extracted with ether. The extract was crystallized from benzene and found to be isovaleramide melting at 131° , and evolving ammonia when boiled with alkali.

Another tube containing the same materials and heated to 190° – 200° for three hours and to 225° for six hours yielded 26 per cent.

Properties.

Isobutyl quinazolone crystallizes from water in small needles melting at 194° – 195° . It is moderately soluble in hot water, very slightly in cold, somewhat in ether, and easily soluble in alcohol and hot benzene.

Derivatives.

Methyl Ether, C_6H_4 $\left\{ \begin{array}{l} N = C - C_4H_7 \\ | \\ CO - N - CH_3 \end{array} \right.$.—Colorless needles melt-

ing at 68° – 69° .

Hydrochloride.—Coarse needles.

Nitrate.—Yellow plates decomposing at 171° – 172° .

Sulphate.—Needles arranged in bunches and melting at 228° – 229° .

Chromate.—Yellow crystalline powder which decomposes at 154° .

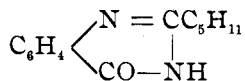
Picrate.—Light yellow needles melting at 192° .

Oxalate.—White felted needles melting at 204° – 205° .

Chlorplatinate.—Transparent coarse brown needles. It was analyzed for platinum.

	Calculated for ($C_{12}H_{14}N_2O \cdot HCl$) ₂ PtCl ₄ .	Found.
		I. II.
Platinum.....	23.86	23.93 24.00

2-ISOAMYL 4-KETODIHYDROQUINAZOLIN.



Preparation.

I. *Anthranilic Acid and Isocapronitrile*.—The tube was heated to 180 – 185° for five hours, to 220 – 225° for six hours, and to 240° –

250° for six hours. Moderate pressure was found after the first period but none after the second and third. The quinazolon was extracted and purified exactly as was isobutyl quinazolon (I). The yield was 18 per cent.

II. *Anthranilic Acid, Isocapronitrile, and Isocaproic Acid.*—This tube was heated successively to 185°–190°, 210°–215°, and 230°–240° for six hours each. Considerable pressure was found only after the first heating. The product was treated in exactly the same way as was that of the isobutyl tubes (II). The yield of quinazolon was 37 per cent.

An anilide was found as usual. It crystallized from dilute alcohol in long needles melting at 110°–111°, and yielding aniline when boiled with alkali.

0.1533 gram gave 9.9 cc. nitrogen (20°, 761 mm.).

	Calculated for $C_{12}H_{17}NO.$	Found.
Nitrogen.....	7.33	7.39

It is therefore, as was expected, isocaproanilide. As the properties of this anilide have apparently not been recorded, some was prepared by boiling isocaproic acid with aniline for a short time, pouring the product into water, and crystallizing the precipitate from dilute alcohol. Its properties were found identical with those of the anilide obtained from the tube.

0.1814 gram gave 11.9 cc. nitrogen (21°, 762 mm.).

	Calculated for $C_{12}H_{17}NO.$	Found.
Nitrogen.....	7.33	7.49

Another by-product found in this tube was isocaproamide, extracted from the sodium carbonate solution by the usual method. It melted at 119°–120° and evolved ammonia when boiled with alkali.

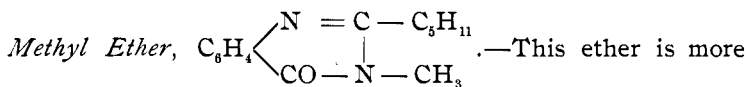
Properties.

Isoamyl quinazolon crystallizes from water in very small felted needles melting at 184°. It is soluble in ether, alcohol, and benzene, moderately in boiling water and almost insoluble in cold. The nitrogen was determined with the following results:

I. 0.1563 gram gave 18.3 cc. nitrogen (23°, 752 mm.).

II. 0.1494 gram gave 17.3 cc. nitrogen (22°, 753 mm.).

	Calculated for $C_{13}H_{16}N_2O.$	I.	II.
Nitrogen.....	12.96	13.05	13.02

Derivatives.

difficult to obtain crystalline than is that of any of the other quinazolons. It was prepared in the usual way by heating the quinazolone with methyl iodide and caustic alkali in alcoholic solution. The alcohol was evaporated, the residue taken up with water, and extracted with ether. The ether solution was evaporated and the methyl ether obtained in the form of an oil, which solidified only after long standing in a desiccator. To obtain it in crystals various solvents were tried, but without success. The method finally used was to form the hydrochloric acid salt, dissolve it in water, add a slight excess of sodium carbonate, while cooling with ice, and finally inoculating the milky solution with some of the solid ether obtained in the desiccator. On standing, crystals finally appeared in the form of small needles melting at $40^\circ-41^\circ$, and practically insoluble in water.

Hydrochloride.—Fine needles.

Nitrate.—Thin plates decomposing at $160^\circ-161^\circ$.

Chromate.—Attempts to prepare this salt were unsuccessful. The methods used were the action of chromic acid on the base and double decomposition between the hydrochloride of the base, and potassium chromate. In neither case was any crystalline product obtained, the base apparently decomposing.

Picrate.—Yellow leaflets melting at $164^\circ-165^\circ$.

Chlorplatinate.—This salt could not be obtained, the affinity between the hydrochloride of the base and platinic chloride seeming to be very weak.

In general it appears that the salts of the higher quinazolons are weaker and more easily dissociated than are those of the lower.

MISCELLANEOUS REACTIONS.¹*Nitrile and a Lower Acid Anhydride.*

I. *Anthranilic Acid, Propionitrile, and Acetic Anhydride*.—The tube was heated to $140^\circ-150^\circ$ for three hours, $180^\circ-190^\circ$ for five hours, and $200^\circ-205^\circ$ for six hours. There was practically no

¹ The order and numbering of these reactions are the same as in the first part of the paper.

pressure at any time and the contents were completely crystalline. After washing with sodium carbonate solution, the product was extracted with boiling water. From this solution, on cooling, methyl quinazolon separated in considerable quantity. The residue, after the water extraction, was a brown amorphous powder from which nothing crystalline could be obtained.

The methyl quinazolon was identified by its melting-point, physical properties, and by the melting-point of its methyl ether.

No ethyl quinazolon was found.

II. *Anthranilic Acid, Isocapronitrile, and Isobutyric Anhydride.*

—The mixture was heated to 210° – 220° for five and one-half hours. The pressure, on opening, was slight and the contents were light-colored and crystalline. After preliminary treatment with sodium carbonate, the caustic alkali method of extraction was applied to the residue.

The quinazolon so obtained melted gradually from 200° – 205° , and, when sublimed, these limits were increased to 180° – 210° , while the melting-points of the two possible products, isopropyl and isoamyl quinazolons are, respectively, 225° – 226° and 179° – 180° (uncorrected). Recrystallization three times from water did not appreciably change this point. Three crystallizations from alcohol were necessary to obtain pure isopropyl quinazolon melting at 226° – 227° (uncorrected). A system of fractional crystallization was applied to the mother-liquor but no product was obtained melting wholly below 205° , although several began to melt around 190° .

That this product and those obtained from some of the reactions still to be described are mixtures seems certain when it is considered that in all other cases the quinazolons were obtained pure after the caustic alkali treatment and one crystallization, and that, as the reactions proceeded just as smoothly, it is unlikely that any exceptional impurities were formed. The difficulty in separating the mixtures is due to the great similarity in the properties of their constituents; the successful identification of isopropyl quinazolon in the reaction just described is due to its slightly smaller solubility in alcohol as compared with isoamyl quinazolon; it was also undoubtedly present in the larger quantity.

III. *Anthranilic Acid, Isocapronitrile, and n-Butyric Anhydride.*

—Heated to 180° – 185° for five hours, 220° – 225° for six hours, and

240°–250° for six hours. The pressure was very slight at any time and the contents crystalline. The soda and caustic alkali method of purification was used. The quinazolon obtained melted at 187°–188°, and, on recrystallization, at 184°–187°. The two quinazolons which it was possible to have formed in this reaction, the normal propyl and the isoamyl, melt respectively at 194°–195° and 179°–180° (uncorrected).

As the methyl ether of the normal propyl quinazolon is quite soluble in hot water while that of the isoamyl is almost insoluble, it was thought that this might prove a method of separation. Only the ether of normal propyl quinazolon could, however, be identified; but, on account of the small amount of material available and the difficulty experienced in getting isoamyl quinazolon methyl ether crystalline, as already mentioned, this can hardly be considered a proof that none of that base was present.

Nitrile and a Higher Acid.

I. *Anthranilic Acid, Acetonitrile, and Propionic Acid.*—The tube was heated to 170°–180° for five hours. On opening, a moderate pressure was observed. The contents were treated exactly as in the last reaction. The quinazolon obtained melted at 213°–214° (uncorrected), and this point remained constant on sublimation. Recrystallization from water raised it to 218°–220°, and this also did not change on sublimation. Methyl and ethyl quinazolons melt, respectively, at 232° and 227°–228° (uncorrected), while their methylethers melt at 110°–111° and 121°–122° (uncorrected). The methyl ether obtained from the supposed mixture melted indefinitely at from 90°–105°.

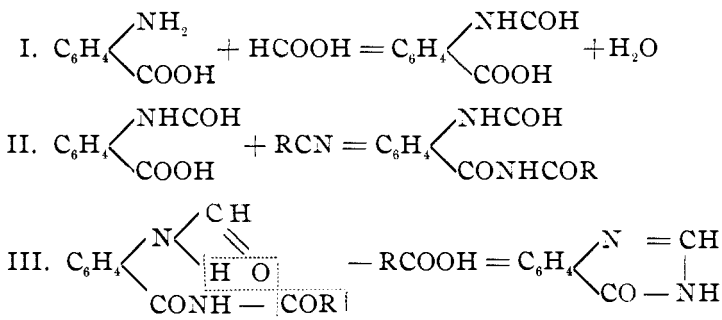
II. *Anthranilic Acid, n-Butyronitrile, and Capric Acid.*—The mixture was heated to 185° for six hours and to 200°–210° for five and one-half hours. The pressure was moderate and the tube-contents light in color and crystalline. The quinazolon was separated and purified as in the last case and was found to be the pure normal propyl derivative melting at 190°.

III. *Anthranilic Acid, Isocaproitrile, and Capric Acid.*—The tube was heated exactly as was No. 2. After the first period the pressure was moderate and the contents consisted almost entirely of a dark red liquid with a very small amount of solid matter; after the second period, however, they were wholly crystalline. By following the same method of separation as in No. 2 and crys-

tallizing the product from dilute alcohol, pure isoamyl quinazolone, melting at 184° , was obtained.

Nitrile and a Lower Acid.

The following experiments of heating anthranilic acid with formic acid and various nitriles were performed in the hope of obtaining 4-ketodihydroquinazolin itself, as follows :



In the other experiments on the action of acids and nitriles on anthranilic acid it was found that, apparently, the question as to whether a single or a mixture of quinazolons will form depends on the ease with which the fatty acid combines with the anthranilic acid to form an acylanthranilic acid; it was thought, therefore, that, as formic and anthranilic acids react with the greatest ease, the above reaction was a very likely one. On trial, however, it was found that while formylanthranilic acid is quickly formed it apparently does not react with nitriles at temperatures at which it is stable; according to Meyer and Bellmann,¹ formylanthranilic acid, when heated with water, decomposes at 130° – 140° into formic acid, carbon dioxide, and aniline.

I. *Anthranilic Acid, Formic Acid, and Acetonitrile.*—One tube containing these was heated to 100° – 110° for twelve hours. There was no pressure and the contents were completely crystalline. On adding sodium carbonate solution the entire product dissolved, showing that no quinazolone was present. The addition of hydrochloric acid to the solution caused a precipitate, which, washed and crystallized from water, was found to be formylanthranilic acid, melting at 165° – 166° .

Another tube was heated to 100° , 140° – 150° , and 190° – 200° for six hours each. After the first period there was no pressure and

¹ *J. prakt. Chem.*, (2), 33, 25.

the contents were crystalline and much as in the first tube; after the second, the pressure was moderate and the contents were entirely liquid; after the third, there was again moderate pressure and the contents consisted of about half crystals and half liquid. The treatment with sodium carbonate followed by dilute caustic alkali was applied, but, on passing carbon dioxide into the alkali solution, the precipitate obtained was so slight that nothing further was done with it.

II. *Anthranilic Acid, Formic Acid, and Propionitrile*.—The results from this reaction were as unsatisfactory as those just detailed.

III. *Anthranilic Acid, Formic Acid, and Isocapronitrile*.—This tube was heated to 120° – 125° for five hours, 160° – 170° for six hours, and 210° – 220° for six hours. There was considerable pressure and the product consisted of a sirupy liquid and a small amount of crystalline material. The same treatment as in the previous tubes was used and a small amount of isoamyl quinazolon obtained.

The sodium carbonate solution was evaporated, the residue extracted with ether, and the extract crystallized from benzene. Two kinds of crystals were obtained and these were separated by treatment with warm benzene, which dissolved one faster than the other. The more soluble substance was found to be isocaproamide, melting at 119° – 120° , while the less soluble one, melting at 190° – 195° , and, on sublimation, at 211° (uncorrected), was probably 4-ketodihydroquinazolin. The melting-point of this quinazolon is stated by Knape¹ to be 211° – 212° and by Bischler and Burkart² to be 209° .

As it has been shown that the best yields of quinazolon were obtained when using the nitrile and the corresponding acid or anhydride, the correct nitrile to use with formic acid, for the production of 4-ketodihydroquinazolin, is formic nitrile or hydrocyanic acid. No anhydrous hydrocyanic acid being available, a few experiments were tried aiming to produce the acid in the tube as the reaction proceeded, but no encouraging results were obtained.

IV. *Anthranilic Acid, Isocapronitrile, and Propionic Acid*.—The mixture was heated to 170° – 180° for five hours and then to 200° –

¹ *J. prakt. Chem.*, (2), **43**, 214.

² *Ber. d. chem. Ges.*, **26**, 1349.

210° for six hours. There was considerable pressure after the first period but none after the second. The contents were almost wholly crystalline. The quinazolone was extracted and purified by the same method as followed above, and proved to be the isoamyl derivative. Its melting-point was 183°–184°.

Action of Fatty Acids and Anhydrides on Anthranilic Acid.

These experiments were performed for the purpose already stated on page 614. Anthranilic acid was heated with normal butyric and isocaproic acids respectively, both in sealed tubes and open, at temperatures varying from but slightly above 100° to the boiling-point of the fatty acid, without any action being discernible. In contradistinction to this it was found that both normal butyric and isovaleric anhydrides reacted quite smoothly to form the corresponding acylanthranilic acids. Merely heating the acid and anhydride together on the water-bath for three to four hours was sufficient to give a yield of about 30 per cent.

Only the isovalerylanthranilic acid was closely examined. It crystallizes from water in needles melting at 110°–111°.

I. 0.1816 gram gave 10.6 cc. nitrogen (26°, 755 mm.).

II. 0.2016 gram gave 11.7 cc. nitrogen (23°, 754 mm.).

	Calculated for	Found.	
	$C_{12}H_{15}NO_3$	I.	II.
Nitrogen.....	6.33	6.43	6.49

This work is being continued and extended, and other papers will appear shortly.

ORGANIC LABORATORY, HAVEMEYER HALL,
COLUMBIA UNIVERSITY, June 1, 1901.

ON THE ESTIMATION OF UREA IN URINE.

By J. H. LONG.

Received July 23, 1901.

INASMUCH as about 90 per cent. of the total assimilated nitrogen leaving the human body is excreted in the form of urea the accurate determination of this substance in the urine must remain among the most important of physiological-chemical problems. The interest attaching to the question is fully shown by the great number of contributions to the subject appearing in the chemical literature, yet, notwithstanding all that has been written, the problem is still far from satisfactory solution. In the older text-books of urine analysis the Liebig method by use of mercuric