

THE JOURNAL

OF THE

AMERICAN CHEMICAL SOCIETY.

[CONTRIBUTION FROM THE HAVEMEYER LABORATORIES, COLUMBIA UNIVERSITY, NO. 70.]

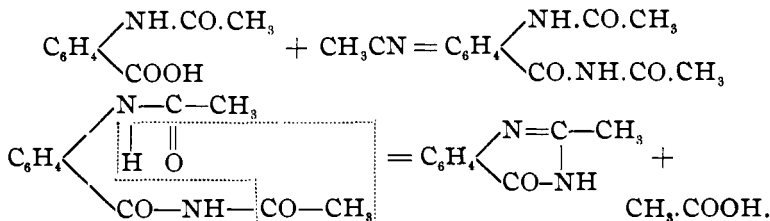
THE SYNTHESIS OF ALKYLKETODIHYDROQUINAZOLINES FROM ANTHRANILIC NITRILE.¹

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Received July 31, 1902.

THEORETICAL PART.

BOGERT AND GOTTHELF have already shown² that ketodihydroquinazolines may be prepared by heating together in sealed tubes anthranilic acid, or its acyl derivatives, with a nitrile, and the reactions there suggested in explanation of this synthesis, taking the case where an acylantranilic acid was the starting-point, were as follows:

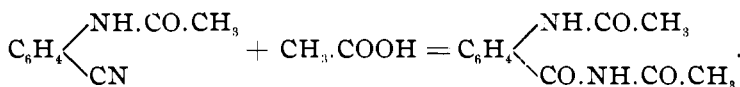


It will be seen upon examining the structure of the hypo-

¹ Read before the New York Section of the American Chemical Society, at its meeting January 24, 1902.

² This Journal, **22**, 129 and 522; **23**, 611.

thetical intermediate product, the secondary amide, that the —CO—NH—CO—group being symmetrical should be formed equally well from $\text{RCN} + \text{R'.COOH}$ as from $\text{R'CN} + \text{R.COOH}$; in other words, as the condensation takes place solely between the CN and COOH it is immaterial which radical carries the CN and which the COOH. This same secondary amide should therefore result when acetylanthranilic nitrile is heated with acetic acid, as follows:



At higher temperatures then, acetic acid would split off, as indicated, with production of the quinazoline body, and we have in this manner prepared a number of the quinazolines in question, the products being in every case identical with the compounds obtained from anthranilic acid already described in the articles referred to.

The alkylketodihydroquinazolines may therefore be prepared either from anthranilic acid or from the corresponding nitrile. In cases where the *o*-amino acid is best obtained by saponification of the nitrile, it is convenient to be able to pass directly to the quinazoline from the nitrile without having to prepare the acid at all, thereby saving one step in the synthesis. We have thus prepared quinazolines from homoanthranilic nitrile.

The starting-point for our work was *o*-nitraniline, from which *o*-nitrobenzotrile was prepared by the Sandmeyer reaction, the yield being excellent. The nitronitrile can be entirely freed from precipitated mineral cyanides by crystallizing from boiling carbon tetrachloride in which the latter are insoluble. This method of purification had been worked out by one of us before the article by Friedländer¹ came to our attention. The latter uses benzene as the means of separating the nitronitrile from the mineral cyanides, but we do not consider this so good a solvent as carbon tetrachloride, since the nitronitrile is much less soluble in cold carbon tetrachloride than in cold benzene, and where the latter is used much more of the compound is left the mother-liquors. The old process of purification by distillation

¹ *Monatsh. Chem.*, 19, 627 (1898).

in a current of superheated steam may therefore be abandoned.¹

The reduction of the nitronitrile is very readily accomplished by the use of stannous chloride and hydrochloric acid, with proper regulation of the temperature; the chloride of the aminonitrile then being precipitated by adding an excess of concentrated hydrochloric acid,² the tedious precipitation of the tin by hydrogen sulphide being thus wholly avoided. The free base may be recovered from its chloride by treatment with ice-cold alkali, collecting the base in ether; or, by adding an excess of strong ammonia water to the aqueous solution of the chloride the free base is immediately precipitated, and when washed well with cold water is practically pure. By this process, we have obtained yields of nearly 90 per cent. of that theoretically obtainable from the nitronitrile, and without a sign of saponification, no amide being found in any case, contrary to the experience of Pinnow and Müller,³ Pinnow and Saemann,⁴ and Friedländer.⁵

The anthranilic nitrile thus obtained was heated in sealed tubes with glacial formic acid, and with the anhydrides of acetic, propionic, normal butyric, isobutyric and isovaleric acid. With formic acid no satisfactory results were obtained. In all the other cases the quinazoline was obtained as expected, although the yields are not so good as from anthranilic acid. By using the acid anhydrides, the first products of the reaction are the acyl-anthranilic nitriles and the fatty acids, which then react at higher temperatures with production of the quinazolines. The presence of any water in the tubes is thus avoided and but little tar is produced.

Some of the acylanthranilic nitriles were isolated in the pure state and further investigated. Like the quinazolines obtainable from them, their melting-points decrease with increasing molecular weight, the iso-compounds melting higher than those with normal structure. As it was possible that the formation of the quinazolines was due to a rearrangement of the isomeric acyl-anthranilic nitriles as follows:

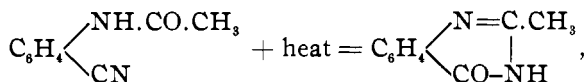
¹ Pinnow and Müller: *Ber. d. chem. Ges.*, **28**, 149 (1895); Pinnow and Saemann: *Ibid.*, **29**, 623 (1896).

² As recommended by Friedländer, *loc. cit.*

³ *Loc. cit.*

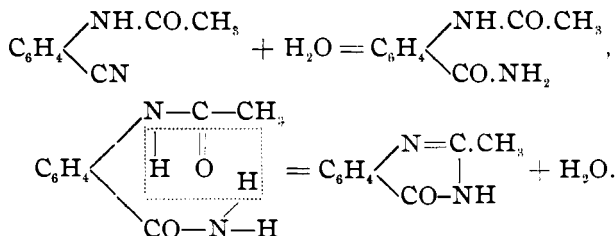
⁴ *Loc. cit.*

⁵ *Loc. cit.*



the acetylanthranilic nitrile, was heated for some time above its melting-point, and it was also heated in sealed tubes in toluene solution; but in neither case was any rearrangement noted. Nevertheless, some of these acylanthranilic nitriles, notably the higher ones, when in aqueous or alcoholic solution, show a decided tendency to pass over into the quinazoline, probably by addition and splitting off of the elements of water somewhat in the manner outlined in the reaction below.

Weddige¹ has already shown that acylanthranilamides can be readily condensed to quinazolines by the action of heat, acids or alkalis. As the acyl groups in these acylanthranilic nitriles are not readily split off, it seemed possible that we might pass direct from these latter substances to the quinazolines without separation of the intermediate amide and without the use of sealed tubes; and by the action of a warm alkaline hydrogen dioxide solution this change was accomplished with ease and rapidity, the yield of quinazoline usually being very large, and the only purification necessary being a single crystallization from water or dilute alcohol. Alkali alone, or hydrogen dioxide alone, we did not find to be nearly so efficient as the combination of the two. The reactions which occur in this synthesis are probably as follows:



The ease with which anthranilic nitrile may be converted into a quinazoline by the action of acetic anhydride suggests the possibility of obtaining a similar condensation by the action of acetic anhydride upon *o*-aminobenzaldoximes, the excess of anhydride changing the oxime to the nitrile when the other reactions out-

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

lined will take place with production of the quinazoline. We shall test this experimentally and communicate our results in a later article.

In conclusion, our experiments herein recorded indicate that alkylketodihydroquinazolines may be prepared:

(1) By heating anthranilic nitrile in sealed tubes with aliphatic acid anhydrides.

(2) By warming acylanthranilic nitriles with alkaline hydrogen dioxide solution.

EXPERIMENTAL PART.

o-Nitrobenzonitrile.

For the preparation of *o*-nitrobenzonitrile, the following process was found to give the best results:

13.8 grams finely pulverized *o*-nitraniline are treated with 17.5 cc. concentrated hydrochloric acid (sp. gr. 1.187) and the mass stirred until all is changed to the white chloride, taking care to crush up all lumps of *o*-nitraniline in order that the conversion to the chloride may be complete. 500 cc. of water are then added all at once and the mixture stirred thoroughly, causing the dissociation of the chloride and the separation of the free base in fine flocks which diazotize much more rapidly than the finely pulverized nitraniline. The suspended nitraniline is then diazotized by adding a solution of 7 grams sodium nitrite dissolved in 40 cc. water, stirring constantly with a turbine. No external cooling is necessary during the operation as the diazo-body is remarkably stable at ordinary temperatures, no appreciable decomposition occurring even on standing forty-eight hours at laboratory temperature, and cooling only retards the diazotizing and diminishes the yield of nitronitrile. At least one hour should be occupied in adding the sodium nitrite solution, and the mass should then be stirred for another hour, when all the orange nitraniline should be changed to the light-colored flocculent diazo-compound and starch iodide paper should still show the presence of an excess of nitrous acid. If the vessel then be allowed to stand for a few moments, any undiazotized nitraniline will collect on the bottom, and by careful decantation the suspended diazo-body may be poured off from the heavier nitraniline. Although with careful manipulation but little nitraniline escapes diazotizing, yet it is

advisable to decant from it at this point, as otherwise it follows the nitronitrile and must be separated from it later.

The suspended diazo-body is then poured very slowly into a cuprous potassium cyanide solution, prepared from 25 grams crystallized copper sulphate, 150 cc. water and 28 grams 96 per cent. potassium cyanide (carried out under a hood, on account of the cyanogen evolved). The cuprous potassium cyanide should be maintained at about 90° and stirred constantly during the addition of the diazo solution. The yield of nitronitrile depends largely upon this part of the operation. If the diazo solution is added very slowly with vigorous stirring, and the temperature kept at 90° - 100° , the yield will be large; rapid addition of the diazo mixture, or allowing the temperature of the cyanide solution to sink much below 90° , diminishes the yield considerably. When all the diazo solution has been added, the mixture is boiled for a few minutes over the open flame and filtered through a hot-water funnel. On cooling, the nitronitrile crystallizes from the filtrate in long yellow needles mixed with considerable cuprous potassium cyanide. A large amount of the nitrile remains behind in what appears to be tar. By extracting this with boiling water so long as crystals separate from the filtrate, on cooling, the rest of the nitrile may be recovered. The crystals obtained by extracting the tar are practically pure and free from mineral cyanides. The actual amount of insoluble tar remaining after these extractions is very small.

The crude crystals are washed well with cold water, dried and pulverized. By extracting this dry material with boiling carbon tetrachloride, the nitronitrile is readily dissolved while the mineral cyanides remain behind absolutely insoluble. From the carbon tetrachloride filtrate, on cooling, the nitronitrile crystallizes out, almost completely, in beautiful golden yellow scales, carrying any unseparated nitraniline, and the amount of the latter substance present may be roughly judged by the depth of color of the crystals and the extent of the orange-colored ring upon the filter-paper above them when they are filtered out. By recrystallization from boiling moderately dilute acetic acid, the nitraniline is removed and the nitronitrile obtained in nearly colorless crystals (m. p. 109°). By further crystallization from dilute acetic acid, or from water, the melting-point may be raised to 109.5° at which

point it remains constant (all melting-points recorded in this article were determined with standardized short-scale Anschütz thermometers, the entire mercury column being immersed in the heating medium).

The authors have repeatedly obtained 12 grams of the crude nitronitrile from 13.8 grams of the nitraniline, a yield of 87 per cent. of the weight of the nitraniline used, and the yield is equally good when working with five to ten times the above charges. The yield of pure nitronitrile (m. p. 109.5°) amounts to about 70 per cent. of the weight of the nitraniline used. As to the amount of mineral cyanide carried down with the nitronitrile—of 285 grams crude nitrile obtained in one experiment, 28 grams consisted of mineral matter insoluble in boiling carbon tetrachloride.

The process outlined above is based upon that of Sandmeyer,¹ with certain improvements suggested by Pinnow and Müller² and by Friedländer,³ together with some modifications of our own. Pinnow and Müller⁴ recommend the use of much more concentrated solutions, but their process was far less satisfactory in the hands of the writers than the one given above. So little water is used in their method that the diazo solution forms a stiff paste which it is difficult to stir properly, and the yield of crude nitrile is smaller, besides being richer in mineral cyanides.

Pure *o*-nitrobenzonitrile crystallizes from dilute acetic acid or from water in feathery bunches of fine colorless needles, occasionally united in transparent films with comb-like edges; from carbon tetrachloride it crystallizes in a web of colorless dazzling tinsel-like filaments of iridescent luster, so firmly interwoven that, after pouring out the carbon tetrachloride, it may be removed from the beaker in a single mass which is not easily torn apart. It is very readily soluble in chloroform, acetone, ethyl acetate; easily in methyl alcohol, ethyl alcohol, ethyl nitrate, absolute ether, glacial acetic acid, benzene and nitrobenzene.; slowly soluble in cold isoamyl alcohol, dissolving rapidly when heated; difficultly soluble in cold water, moderately soluble on boiling; very slightly soluble in cold carbon tetrachloride, quite readily in hot; difficultly soluble in cold oil of turpentine, easily in hot; difficultly soluble in

¹ *Ber. d. chem. Ges.*, 18, 1492 (1885).

² *Loc. cit.*

³ *Loc. cit.*

⁴ *Loc. cit.*

boiling carbon bisulphide, petroleum ether or benzine. It dissolves very slowly in cold concentrated hydrochloric acid and can be reprecipitated unchanged (m. p. 109.5°) by diluting with water.

o-Aminobenzonitrile (*Anthranilic Nitrile*).

According to our experience, the reduction of the nitronitrile can be accomplished more satisfactorily with stannous chloride and hydrochloric acid than with tin and hydrochloric acid.

The following process, based upon the method of Pinnow and Saemann¹ and embodying certain suggestions due to Friedländer², has given excellent results.

500 grams stannous chloride are dissolved in 425 cc. concentrated hydrochloric acid diluted with 7.5 cc. of water, and the solution is stirred vigorously with a turbine while 100 grams of the nitronitrile are gradually added at such a rate that the temperature of the solution remains at 20° - 30° , occasional cooling with ice being necessary. Below 20° the reduction proceeds very slowly. As the action progresses the nitronitrile gradually dissolves, and the reduction should be complete in a few hours. If the chloride of the aminonitrile begins to separate before the completion of the reduction it can be brought into solution again by careful addition of water. When all the nitronitrile has been reduced a large volume of concentrated hydrochloric acid is added and the mixture is left for twelve to eighteen hours at 0° . Nearly all of the aminonitrile will thus be precipitated as the chloride, in fine white granular crystals which can be filtered out through asbestos. The amount of this chloride remaining in the acid mother-liquor is usually very small and not sufficient to pay for the time and trouble necessary to recover it. Of course, if the reducing solution be too greatly diluted with water, the precipitation with hydrochloric acid will be much less complete, and it may then be advisable to work over the mother-liquor. In one of our experiments there was precipitated by the hydrochloric acid an amount of aminonitrile chloride equivalent to a yield of 80 per cent. of that theoretically obtainable from the nitronitrile, while from the acid mother-

¹ *Loc. cit.*

² *Loc. cit.*

liquor there was recovered but 5 per cent. more, making the total yield 85 per cent. of the theoretical. The precipitated chloride is washed free from tin with concentrated hydrochloric acid, sucked as dry as possible, and the free base liberated by either of the following methods:

(1) The chloride is added to a mixture of ice and ether contained in a separatory funnel. Sodium hydroxide solution is poured in to alkaline reaction, the mixture well shaken and the ether poured off, the residual aqueous solution being extracted three or four times more with ether. The ethereal extracts are combined, dried with calcium chloride, the ether distilled off, and the brown liquid residue placed *in vacuo* over concentrated sulphuric acid where it soon solidifies in a light brown crystalline cake melting at 49° C.

(2) The chloride may be added direct to an excess of moderately dilute ammonia water, the precipitated base washed with water till free from ammonium chloride, dried and crystallized from carbon bisulphide. The yield of pure aminonitrile by this process is usually at least 85 per cent. of the theoretical. We have not observed in any case the formation of nitro- or amino-amide, the crystals which separated during reduction being invariably only the chloride of the amino-nitrile, the free base obtained from them being always instantly and completely soluble in cold benzene (in which the *o*-nitro- and *o*-aminobenzamides are difficultly soluble).

The melting-point of the crude aminonitrile is 49°; on recrystallization this may be raised to 49.5° at which point it remains constant. Friedländer¹ gives the melting-point as 50°-51°.

Pure anthranilic nitrile crystallizes in colorless glassy monoclinic prisms. By slow cooling of a carbon bisulphide solution, we have obtained some superb prisms of light yellow cast, two inches long by a quarter of an inch thick and perfectly formed. It is very easily soluble in chloroform, methyl alcohol, ethyl alcohol, ethyl nitrate, absolute ether, acetone, ethyl acetate, carbon bisulphide, benzene, nitrobenzene and pyridine; easily soluble in carbon tetrachloride and amyl alcohol; moderately soluble in cold oil of turpentine, very easily on boiling; difficultly soluble in cold water, moderately soluble at boiling-point; insoluble in cold con-

¹ *Loc. cit.*

concentrated ammonia water, moderately soluble boiling; insoluble in cold petroleum ether or benzine, slightly soluble boiling. From boiling water the substance often separates as an oil which only slowly solidifies on standing. Occasionally, glassy blades may be obtained from water, but if these are left in the solution for a few days they become white and opaque and then show a lower melting-point (46° - 47°). The carbon bisulphide solution is very sensitive to changes of temperature; from a solution prepared at the ordinary temperature the nitrile may be crystallized out almost completely by cooling slowly in a freezing-mixture; and large crystals which have separated by slow evaporation of the solvent at the ordinary temperature may all be redissolved quite rapidly by a slight rise in the temperature of the laboratory.

Hydrochloride of Anthranilic Nitrile.

To prepare this chloride, the nitrile was dissolved in dry ether and a stream of dry hydrochloric acid gas passed in. The chloride precipitated immediately, and was filtered out, washed with dry ether, and recrystallized from glacial acetic acid. These crystals decompose when heated slowly, but can be melted if heated quickly. They are instantly dissociated by water and give off hydrochloric acid even in the air. They dissolve quite easily in absolute alcohol, are sparingly soluble in boiling toluene, moderately soluble in glacial acetic acid (with partial dissociation), and are apparently insoluble in chloroform, carbon tetrachloride, benzene, absolute ether, ligroin or acetone.

Pinnow and Müller¹ state that this chloride crystallizes in beautiful tablets which are quite stable, although they also admit that they tend to dissociate in aqueous solution, while Pinnow and Saemann² attempted to separate anthranilic nitrile from the corresponding amide by crystallizing their chlorides from water. Our experience concerning the stability in aqueous solution of the chloride of anthranilic nitrile is quite at variance with these statements. In concentrated hydrochloric acid the chloride appears to be quite stable, however.

¹ *Loc. cit.*

² *Loc. cit.*

The Preparation of 2-Alkyl-4-ketodihydroquinazolines by Heating Anthranilic Nitrile in Sealed Tubes with Aliphatic Acids or Their Anhydrides.

(1) *Anthranilic Nitrile and Glacial Formic Acid.*—These two substances were heated together in sealed tubes for eight hours at 270° - 284° , but no quinazoline could be found in the reaction product.

(2) *Anthranilic Nitrile and Acetic Anhydride.* Tube 1.—Four grams of the nitrile and 3 cc. of acetic anhydride were heated in a sealed tube for six hours at 175° , and then for five hours at 200° . There was no pressure in the tube when cold, and the contents consisted of a yellow crystalline mass of fine felted needles. This crystalline mass was repeatedly washed with ether, the residue crystallized from nitrobenzene, the crystals obtained, washed with naphtha, then with petroleum ether, dried, and recrystallized from boiling water, containing some bone-black. From the filtrate, on cooling, there separated short glassy needles of the 2-methyl-4-ketodihydroquinazoline, melting sharply at 239° and identical in all respects with that obtained by the action of acetic anhydride and acetonitrile upon anthranilic acid. A mixture of the products obtained from these two sources showed the same sharp melting-point as when the two were melted separately.

The crystals are very easily soluble in glacial acetic acid or in concentrated potassium hydroxide solution; they are difficultly soluble in petroleum ether, naphtha, carbon tetrachloride, ethyl nitrate, ether, acetic anhydride, carbon bisulphide, benzene, xylene, cymene, or concentrated hydrochloric acid; difficultly soluble in cold water, chloroform, acetone, ethyl acetate, or oil of turpentine, moderately soluble in the same solvents at the boiling-point; difficultly soluble in cold methyl, ethyl or isoamyl alcohols, glycerol, or nitrobenzene, easily soluble in the same on boiling. An alcoholic solution of the base, treated with concentrated hydrochloric acid, gives an immediate crystalline precipitate of the chloride. The latter sublimes unchanged, without melting, and is less soluble in dilute hydrochloric acid than in water. The crystals of the free base and also of the chloride frequently show a faint yellowish green cast.

Tube 2.—2.5 grams of the nitrile and 3 cc. of the anhydride were heated for ten hours at 274° - 282° , the crude product dissolved in hot alcohol, the solution bone-blackened, filtered hot, and the filtrate concentrated. On cooling, crystals of the quinazoline compound separated, melting at 237.5° to 238.5° . Some of the purified crystals (m. p. 239°) were dried to constant weight at 135° and analyzed:

I. 0.1814 gram substance gave 29.1 cc. nitrogen at 23° and 748 mm. = 17.78 per cent. nitrogen.

II. 0.2000 gram substance gave 0.4960 gram carbon dioxide and 0.0900 gram water = 67.63 per cent. carbon and 5 per cent. hydrogen.

	Calculated for $C_6H_8ON_2$.	Found.	
		I.	II.
Nitrogen	17.50	17.78
Carbon	67.50	67.63
Hydrogen	5.00	5.00

The *picrate*, recrystallized from water, forms yellow prisms (m. p. 207.5° - 208.5°).

(3) *Anthranilic Nitrile and Propionic Anhydride*. Tube 1.—2.5 grams of the nitrile and 3 cc. of the anhydride were heated for five hours at 250° , and then for three hours at 275° - 280° . On opening the tube no pressure was evident, and the contents were dissolved in boiling alcohol, the solution bone-blackened, filtered hot, and the filtrate concentrated. On cooling, crystals separated melting at 220° - 231° , brownish in color and evidently a mixture. Washed with boiling water and recrystallized from dilute alcohol, brownish crystals were obtained melting at 220° - 232° . As the amount of these crystals was small, further purification was deemed useless, the reaction being evidently incomplete.

Tube 2.—This tube contained the same charge as Tube 1, but was heated for six and a half hours at 270° - 280° , then two hours at 230° , and finally for six hours longer at 274° - 285° . There was no pressure in the tube when cold, and the contents were repeatedly crystallized from carbon tetrachloride, yielding crystals which were easily soluble in boiling carbon tetrachloride but difficultly soluble in it cold, and which melted at 232.5° - 233.5° , softening somewhat at 231° . These crystals are identical in all their properties with the 2-ethyl-4-ketodihydroquinazoline prepared from anthranilic acid, the melting-point of which is 234° .

The *picrate* melted at 193°-194°, while that obtained from anthranilic acid melted a trifle lower (191°-192°).

(4) *Anthranilic Nitrile and Normal Butyric Anhydride*. Tube 1.—The nitrile and anhydride were heated together for three hours at 160°-198°, and then for five hours at 192°-220°. The contents of the tube appeared gray and crystalline, and by extracting with boiling water, crystals were obtained melting at 198°, which, when recrystallized from water, formed fine colorless needles, identical in all their properties with the 2-*n*-propyl-4-ketodihydroquinazoline prepared from anthranilic acid.

Tube 2 contained 2.5 grams of the nitrile and 3 cc. of *n*-butyric anhydride, and was heated four hours at 130°-211°, then for seven hours at 210°-212°, and finally for three hours longer at 215°-255°. The product was dissolved in boiling alcohol, the solution bone-blackened, filtered hot, and the filtrate concentrated; on cooling, small crystals of the quinazoline separated, which, when recrystallized from dilute alcohol, melted sharply at 200°-200.8°.

The *picrate*, after repeated crystallization, showed a melting-point of 184.5°-185°. Gotthelf¹ gives the melting-point as 183°-184°.

(5) *Anthranilic Nitrile and Isobutyric Anhydride*.—2.5 grams of the nitrile and 3 cc. of the anhydride were heated for six hours at 224°-229° and then for six and a half hours at 275°. On cooling, no pressure was evident in the tube. The crude product was worked up in exactly the same manner as described for Tube 2 above, the crystals which separated from the alcoholic solution being recrystallized from dilute alcohol. Colorless needles were thus obtained, melting at 231.5°-232°, agreeing in all their properties with the 2-isopropyl-4-ketodihydroquinazoline obtained from anthranilic acid.

The *picrate* melts at 208.5°-209.5°. The melting-point of 213°-214° recorded for this *picrate* by Gotthelf² is evidently a mistake, as we have tested his own product and found its melting-point to be 208°-208.5°.

(6) *Anthranilic Nitrile and Isovaleric Anhydride*.—2.5 grams of the nitrile and 3 cc. of the anhydride were heated for six hours

¹ This Journal, 23, 611.

² *Loc. cit.*

at 224°-229° and then for six and a half hours at 275°, there being no pressure in the tube when cold. The crude product was treated in the manner just described, the first crystals obtained being recrystallized from dilute alcohol, when they showed a melting-point of 194°-195°, and proved to be identical with 2-isobutyl-4-ketodihydroquinazoline prepared from anthranilic acid.

The *picrate* melted at 188.5°-189.5°. The melting-point recorded by Gotthelf¹ for the same substance is 192. It is not easy to determine the melting-points of these picrates accurately, as they generally darken and soften several degrees below the actual melting-point.

The Preparation of Acyl Derivatives of Anthranilic Nitrile.

(1) *The Action of Glacial Formic Acid upon Anthranilic Nitrile.*—Five cc. of absolute formic acid were poured over five grams of the nitrile, causing the latter to dissolve with absorption of considerable heat. The solution was gently boiled on the sand-bath for two hours and then allowed to cool. The product was a yellow crystalline cake, a portion of which when heated to 200° appeared to suffer decomposition with evolution of gas. The cake itself is composed of a mixture of various substances and we have separated from it white, warty masses easily soluble in boiling water; also long yellow needles, apparently insoluble in boiling water and difficultly soluble in boiling alcohol, together with a flocculent yellow substance soluble in 95 per cent. alcohol. None of these products could be secured in sufficient amount or purity to render an analysis of any value. The white, warty masses are evidently the formyl derivative of the nitrile, since a quinazoline can be obtained from them on treatment with warm, alkaline hydrogen dioxide solution.

(2) *The Action of Acetic Anhydride upon Anthranilic Nitrile.*—Anthranilic nitrile dissolves quite rapidly in acetic anhydride with the absorption of considerable heat; this heat is soon given off again and the solution gradually warms up to the boiling-point of the anhydride; on cooling down again a solid crystalline cake is formed. This cake is melted and gently boiled for a few hours

¹ *Loc. cit.*

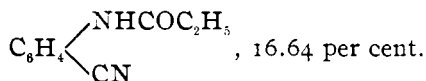
on the sand-bath, the hot liquid is poured into boiling water, the mixture boiled for a few minutes and the solution filtered hot. From the filtrate, on cooling, the acetyl derivative crystallizes in long, white, silky needles (m. p. 132.5), as given by Pinnow and Saemann.¹ By heating for some time above its melting-point, no rearrangement of the compound to the isomeric quinazoline was noted. The crystals are very easily soluble in chloroform, methyl alcohol, ethyl alcohol, isoamyl alcohol, ethyl nitrate, ether, acetone, ethyl acetate, glacial acetic acid, acetic anhydride, or nitrobenzene; easily in carbon bisulphide, benzene, or oil of turpentine; moderately in carbon tetrachloride or in cold water, easily soluble in the latter at the boiling-point; insoluble in cold petroleum ether or benzine, difficultly soluble in the same at the boiling-point. Long boiling of the aqueous solution tends to prevent the crystallization of the substance, giving a milky solution which slowly deposits a fine floury sediment. It is not readily extracted from its aqueous solution by ether. From petroleum solvents, it crystallizes in pulpy masses of minute needles difficult to filter and which pack down upon the filter-paper into a sort of skin. Good crystals may be obtained from water, and also from mixtures of naphtha and chloroform, naphtha and ether, or chloroform and carbon tetrachloride. It can be slowly sublimed at 100° in colorless transparent needles, and is volatile with steam. Warmed with alkaline hydrogen dioxide solution, or heated in a sealed tube with glacial acetic acid or acetic anhydride, 2-methyl-4-ketodihydroquinazoline is produced. 2.5 grams of the acetyl derivative and 3 cc. of toluene were heated for ten hours at 274°-282° without any rearrangement of the acetyl derivative occurring. Toluene was selected as the solvent on account of its inertness and because its boiling-point is near that of acetic anhydride and acetic acid, and also because the quinazolines are difficultly soluble in it.

Once or twice, in the preparation of this acetylanthranilic nitrile, on recrystallizing the crude product from water, there was obtained a small amount of a substance crystallizing in perfect little cubes, of faint yellowish cast, which melted sharply at 91°, but the amount obtained was insufficient for further investigation.

(3) *The Action of Propionic Anhydride upon Anthranilic Nitrile.*—Five grams of the nitrile were mixed with 7 cc. of the

¹ *Loc. cit.*

anhydride. The nitrile dissolved slowly in the anhydride with absorption of considerable heat; the solution then gradually warmed up and on cooling down again solidified in a white crystalline cake. This mass was boiled gently for several hours and the product crystallized from dilute alcohol after bone-blackening. Beautiful, colorless, glassy prisms were thus obtained, melting at 119° . If heated quickly, these crystals melt much lower than this. They liquefy in boiling water. At 100° , they slowly sublime in long colorless needles. They are difficultly soluble in boiling water, nearly insoluble in cold; readily soluble in alcohol. They dissolve in cold 5 per cent. aqueous potassium hydroxide solution, and do not reprecipitate when this solution is made acid with hydrochloric acid; if an excess of strong ammonia water be then added, colorless needles of the original substance are obtained. The compound is volatile with steam. A portion was dried to constant weight *in vacuo* over concentrated sulphuric acid. This gave 16.89 and 16.44 per cent. nitrogen. Calculated for



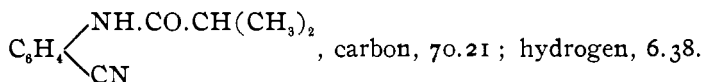
Heated in a sealed tube with propionic anhydride, or warmed with alkaline hydrogen dioxide solution, 2-ethyl-4-ketodihydroquinazoline is produced.

(4) *The Action of n-Butyric Anhydride upon Anthranilic Nitrile.*—This reaction was carried out in a similar manner to the last, using 5 grams of the nitrile and 8 cc. of the anhydride. The nitrile dissolves slowly with absorption of heat, but does not warm up or appear to change on standing. The solution is boiled for an hour, the crude product crystallized from dilute alcohol and bone-blackened, giving colorless glassy needles or long flattened prisms. By repeated crystallization, a sharp melting-point of 89° - 89.5° was recorded. These crystals are difficultly soluble in water, but easily soluble in alcohol, and volatilize with steam. With 5 per cent. aqueous potassium hydroxide solution, followed by hydrochloric acid and ammonia, this compound behaves like the propionyl derivative.

ted in a sealed tube with *n*-butyric anhydride, or warmed alkaline hydrogen dioxide solution, 2-*n*-propyl-4-ketodihy-

droquinazoline results. The substance is therefore the *n*-butyryl anthranilic nitrile. Long boiling in aqueous or alcoholic solution tends to change this butyryl derivative to the quinazoline.

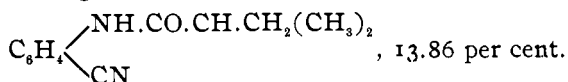
(5) *The Action of Isobutyric Anhydride upon Anthranilic Nitrile*.—This reaction was carried out in a manner entirely similar to the last, the crude product being recrystallized from dilute alcohol till the melting-point remained constant at 111°-111.5°. The compound forms long, white, silky needles, which are slowly soluble in cold carbon tetrachloride or benzene, but easily soluble in the same on boiling; difficultly soluble in carbon bisulphide, petroleum ether, or gasoline; easily soluble in cold ether or alcohol. At 100° it slowly sublimes in colorless glistening scales. It is volatile with steam. A sample, dried to constant weight, gave the following results upon analysis: Carbon, 70.21, 70.22; hydrogen, 5.84, 5.83. Calculated for



Heated in a sealed tube with isobutyric anhydride, or warmed with alkaline hydrogen dioxide solution, the product is 2-isopropyl-4-ketodihydroquinazoline.

(6) *The Action of Isovaleric Anhydride upon Anthranilic Nitrile*.—The reaction proceeds in the same manner as noted for the foregoing, but much greater difficulty was experienced in the purification of the crude product, repeated crystallization from dilute alcohol failing to give any substance with constant sharp melting-point. By recrystallizing from carbon tetrachloride, however, beautiful fine needles were produced, melting quite sharply at 105.5°-106.5°, and which are evidently the isovaleryl anthranilic nitrile. They are difficultly soluble in water, readily so in alcohol. In boiling water, they liquefy, and are volatile with steam. Heated in a sealed tube with *i*-valeric anhydride, or warmed with alkaline hydrogen dioxide solution, 2-isobutyl-4-ketodihydroquinazoline is the product.

A portion of the substance, dried to constant weight, gave 14.01 per cent. nitrogen. Calculated for



The Preparation of 2-Alkyl-4-Ketodihydroquinazolines by the Action of Warm Alkaline Hydrogen Dioxide Solution upon Acylantranilic Nitriles.

The compounds obtained in this manner were, in every case, identical with the corresponding substances prepared from either anthranilic acid, its nitrile, or their acyl derivatives, in sealed tubes, as already described.

(1) *4-Ketodihydroquinazoline*.—Some of the crude formyl-anthranilic nitrile already mentioned was dissolved in 10 per cent. potassium hydroxide solution, some hydrogen dioxide solution (3 per cent.) added, and the mixture warmed at 40°-50° for an hour and a half. The solution was then filtered from a small amount of insoluble matter, the filtrate neutralized with hydrochloric acid, excess of strong ammonia water added, the solution evaporated to dryness, the residue dissolved in 99 per cent. alcohol and the solution concentrated. On cooling, crystals separated, which were filtered out, washed, dried and sublimed, giving beautiful white crystals (m. p. 215.5°-216.5°). Knapé¹ gives the melting-point of 4-ketodihydroquinazoline as 211°-212°. Not sufficient of the substance was available for an analysis.

The *picrate* forms long yellow needles or plates, melting at 203.5°-204.5°, softening somewhat at 202°.

(2) *2-Methyl-4-Ketodihydroquinazoline*.—5.6 grams acetyl-anthranilic nitrile were mixed with 75 cc. hydrogen dioxide solution and 20 cc. of a 10 per cent. potassium hydroxide solution, and the mixture warmed at 30°-45°. In about fifteen minutes complete solution resulted, and fine white needles then began to separate, the separation being apparently complete after warming about fifteen minutes longer, since further addition of hydrogen dioxide or of potassium hydroxide caused no increase in the precipitate. These needles dissolve instantly upon the addition of a small amount of strong potassium hydroxide solution, and may be reprecipitated by carefully neutralizing with hydrochloric acid, but any excess of acid redissolves the precipitate again. From this acid solution it may be completely thrown down by adding an excess of strong ammonia water. The voluminous white pre-

¹ *J. prakt. Chem.*, (2) **43**, 209 (1891).

precipitate thus obtained is crystallized from boiling water and bone-blackened, yielding beautiful glassy prisms of the 2-methyl-4-ketodihydroquinazoline (m. p. 239°). From 5.6 grams of the acetylanthranilic nitrile there was obtained 3.47 grams of the pure quinazoline compound. Some of the substance was dried to constant weight at 100°-140° and analyzed, with the following results: Carbon, 67.36, 67.32; hydrogen, 5.08, 5.02; nitrogen, 17.28, 17.47. Calculated: Carbon, 67.50; hydrogen, 5.00; nitrogen, 17.50.

When the acetylanthranilic nitrile is heated with hydrogen dioxide alone, or with alkali alone, the yield of quinazoline is not nearly so good.

The *picrate* from the above crystals separated in clusters of reddish prisms (m. p. 206°).

(3) *2-Ethyl-4-Ketodihydroquinazoline*.—1.1 grams propionylantranilic nitrile were warmed with alkaline hydrogen dioxide solution as just indicated, the temperature being kept at 30°-65°. A clear solution was not obtained, but the propionyl derivative gradually changed to a bulky white mass of pearly scales instantly soluble in a little strong caustic alkali. The alkaline solution was treated with an excess of hydrochloric acid, then with an excess of concentrated ammonia water. The precipitate thus produced was recrystallized from water, giving fine white hairy needles of the 2-ethyl-4-ketodihydroquinazoline. The melting-point of these needles was rather low, probably because the propionylantranilic nitrile used in the reaction was itself not perfectly pure (second-crop crystals). Recrystallization failed to raise the melting-point above 232°, while the same compound prepared from anthranilic acid melted at 234°. The yield of first-crop crystals was 0.836 gram.

The *picrate* crystallized in yellow scales (m. p. 191°-192°).

(4) *2-n-Propyl-4-Ketodihydroquinazoline*.—It was prepared from *n*-butyrylantranilic nitrile and alkaline hydrogen dioxide solution at 30°-80°, in a similar manner to the last. The crude product was recrystallized from dilute alcohol, giving a woolly mass of fine colorless needles (m. p. 201°-202°), of 2-*n*-propyl-4-ketodihydroquinazoline.

The *picrate* crystallized in bunches of long yellow needles

(m. p. 184° - 184.5°); difficultly soluble in cold water, moderately in boiling; quite soluble in cold alcohol, easily in boiling.

(5) *2-Isopropyl-4-Ketodihydroquinazoline*.—About 2 grams of the isobutyrylanthranilic nitrile, 25 cc. hydrogen dioxide solution, and 25 cc. 10 per cent. potassium hydroxide solution, were warmed together at 50° , all gradually dissolving. The solution was precipitated by hydrochloric acid, the precipitate not readily dissolving in an excess of the precipitant, and excess of strong ammonia water was then added. The bulky white precipitate which was thrown down, when recrystallized from dilute alcohol, appeared as long, colorless, silky hairs (m. p. 233°), readily identified as the 2-isopropyl-4-ketodihydroquinazoline.

The *picrate* crystallized from alcohol in yellow prisms (m. p. 208° - 208.5°), at which point they turned brown and appeared to decompose. They began to darken at 205° .

(6) *2-Isobutyl-4-Ketodihydroquinazoline*.—This substance was prepared from the isovalerylanthranilic nitrile in the manner just outlined. The bulky white precipitate thrown down by ammonia water was recrystallized from dilute alcohol, giving crystals of the quinazoline, melting at 194.5° - 195.5° .

The melting-point of the *picrate* was found to be 188° - 189° .

In general, the yield of quinazoline obtained by the use of warm, alkaline hydrogen dioxide solution was much better than that resulting from heating the acylanthranilic nitriles in sealed tubes with anhydrides.

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COLUMBIA UNIVERSITY, JUNE, 1902.

THE ACTION OF ISO-VALERIC ALDEHYDE UPON ANTI-PYRINE.¹

BY DAVID C. ECCLES.

Received July 14, 1902.

THE investigations of Knorr² and Schuftan³ show that anti-pyrine is capable of forming condensation products with both aliphatic and aromatic aldehydes. Knorr, by treating a slightly

¹ The work here reported was done in Havemeyer Hall, Columbia University, under the direction of Prof. M. T. Bogert.

² *Ann. Chem.* (Liebig), **238**, 214.

³ *Ber. d. chem. Ges.*, **1**, 1181, 1189 (1895).