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RESEARCHES ON QUINAZOLINES. XXXIV. THE SYNTHESIS OF CERTAIN NITRO AND AMINO BENZOYLENE UREAS AND SOME COMPOUNDS RELATED THERETO.

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Introductory.

In 1916, the authors published a paper[2] on dinitro-benzoylene urea, calling attention to the fact that its monosodium salt was a very sensitive indicator for hydrogen ion concentrations between the limits of 6 and 8 on the Sörensen scale.

The experimental work set forth in the present paper supplements that given in the article just mentioned, describes the various steps leading up to the synthesis of the dinitro-benzoylene urea, and records the preparation and study of some related compounds.

Briefly, the work followed these main lines:

1. Anthranilic acid was converted into *o*-uramino benzoic acid by the action of potassium isocyanate in acid solution, the uramino acid changed to benzoylene urea by treatment with conc. sodium hydroxide solution, and the benzoylene urea then nitrated and the nitro derivative reduced.

By direct methylation of benzoylene urea with methyl iodide and alkali, 3-monomethyl and 1,3-dimethyl-benzoylene urea were prepared.

2. *o*-Uramino benzoic acid was nitrated to the dinitro derivative and the latter converted into its methyl ester. By heating the latter with ammonia under pressure, 6-nitro-benzoylene urea was obtained.

3. 5-Nitro-2-acetamino toluene was oxidized to 5-nitro-acetanthranilic acid, the product de-acetylated and fused with formamide, yielding thus the 6-nitro-4-quinazolone.

By direct nitration of benzoylene urea, both mono- and dinitro derivatives were obtained. The second nitro group enters the molecule much more readily than the first. In fact, even with calculated (one mole) quantities of nitric acid, it was found difficult to get the mononitro derivative without simultaneous formation of some dinitro.

The structure of the dinitro benzoylene urea is a problem of unusual interest because of the use of its monosodium salt for the purpose mentioned above. The location of one nitro group is quite certainly at position 6, in view of the synthesis of the dinitro derivative from 6-nitro

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[1] This paper is based upon experimental work carried out by Mr. Scatchard as part of the requirements for the degree of Doctor of Philosophy under the Faculty of Pure Science, Columbia University. Its publication has been delayed by the war service of both authors. M. T. BOGERT.

[2] THIS JOURNAL, 38, 1606 (1916).

benzoylene urea. It seems most likely that the other nitro group is in position 8, as this would be the natural place for a second one to enter, *meta* to the first nitro group and to the carbonyl group, and *ortho* to the amine group. The ease with which it enters argues against any other location in the benzene side of the nucleus. Attachment to the nitrogens of the miazine half is improbable, because of the formation of the dinitro compound in acid solution (conditions which generally hydrolyze the $-N.NO_2$ grouping) and of the fact that no nitrogen could be split off from it by boiling with water or with acetic acid. Synthetic proof of this conclusion is still lacking. Since 5-nitro-anthranilic acid refused to react with urea or potassium isocyanate, it seemed useless to attempt the condensation with 3,5-dinitro-anthranilic acid.

Certain of the properties of benzoylene urea merit mention. Like its 7-methyl derivative[1] it forms a dinitro derivative with the greatest ease. This is probably due, in part at least, to its diphenolic character (in the enol form). While benzoylene urea itself readily yields 1- and 3-monomethyl and 1,3-dimethyl derivatives when treated with methyl iodide and a base, dinitro benzoylene urea cannot be methylated at all in the same manner. Connected with this is the fact that neither 3-methyl- nor 1,3-dimethyl-benzoylene urea can be nitrated by long boiling with conc. sulfuric and fuming nitric acids, according to our experiments.

The work of Griess[2] on *o*-uraminobenzoic acid and on its dinitro derivative was repeated and the methyl esters also of these two acids were prepared and studied. The dinitro acid probably has the following constitution: $(2)O_2N.NH.CO.NH.C_6H_3(NO_2)(5)COOH(1)$, since when boiled with water it breaks down into 5-nitro-anthranilic acid, nitrous oxide and carbon dioxide. The formation of nitrous oxide indicates that the second nitro group is on the terminal nitrogen of the urea residue, inasmuch as the two nitrogens are found united in the decomposition product. The reaction may be assumed to be a preliminary hydrolysis to nitro-isatoic acid and nitramide, both of which undergo further hydrolysis in the hot aqueous solution, the former into 5-nitro-anthranilic acid and carbon dioxide, the latter into nitrous oxide and water.

$$O_2N.NH.CO.NH.C_6H_3(NO_2)COOH + H_2O \longrightarrow$$
$$HOOC.NH.C_6H_3(NO_2)COOH + O_2N.NH \longrightarrow$$
$$H_2N.C_6H_3(NO_2)COOH + CO_2 + N_2O + H_2O.$$

The methyl ester of the dinitro acid decomposes similarly, giving methyl-nitro-anthranilate.

If the action of ammonia followed the same course as with the *meta* acid,[3] breaking out only the nitro group from the side chain and forming

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[1] Niementowski, *J. prakt. Chem.*, [2] **51**, 564 (1895).

[2] *J. prakt. Chem.*, [2] **5**, 369 (1872).

[3] Griess, *Ibid.*, [2] **5**, 227 (1872).

5-nitro-2-uramino-benzoic acid, the latter should condense in the alkaline solution to 6-nitro-benzoylene urea. This reaction could not be realized with the free dinitro acid, for the apparent reason that its instability and velocity of decomposition were too great. The condensation was accomplished, however, with the methyl ester of this acid.

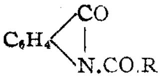
This is in line with the behavior of *o*-uramino-benzoic acid itself, which decomposes when boiled with water, whereas its methyl ester under similar conditions condenses smoothly to benzoylene urea.

The literature of 5-nitro-anthranilic acid was found to be rather badly confused and we hope that we have cleared it up somewhat.

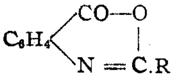
Apparently the nitro group in 5-nitro-anthranilic acid exerts a decided steric hindrance to the replacement of the amino hydrogens by other groups or residues, for it was found impossible to obtain any condensation with urea, or with potassium isocyanate in acid solution, although the attempts were made under various conditions, including the method of Bailey and Read.[1] The method of Sonn[2] for the preparation of substituted ureas was not tried, since Sonn found that the amino groups of anthranilic acid and of *o*-nitraniline were too weakly basic to give the condensation.

Johnson and Scott[3] noted that anthranilic acid refused to condense to a thioquinazolone when treated with ammonium thiocyanate and acetic anhydride. We can corroborate this, and can report that the 5-nitro-anthranilic acid behaves similarly.

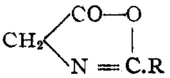
If Johnson's theory[4] of the mechanism of this reaction is correct, the above facts are most simply explained on the assumption of a lactame structure for the intermediate acetanthranil, as the latter is the first product of the action of acetic anhydride upon anthranilic acid. If the anthranil[5] possessed the metoxazone structure, it would resemble the lactone anhydrides of the α-amino acids, which are the intermediate products in the formation of thiohydantoins, and should react, therefore, analogously to form a thiobenzoylene urea.



$C_6H_4\left\langle\begin{matrix}CO\\ |\\ N.CO.R\end{matrix}\right.$



$C_6H_4\left\langle\begin{matrix}CO\text{—}O\\ \quad\ |\\ N=C.R\end{matrix}\right.$



$CH_2\left\langle\begin{matrix}CO\text{—}O\\ \quad\ |\\ N=C.R\end{matrix}\right.$

Acylanthranil

(Lactame.) (Metoxazone.)

Lactone anhydride of α-amino acid.

By fusion of the 5-nitro-anthranilic acid with formamide, 6-nitro-4-quinazolone was obtained and shown to be identical with the compound prepared by Bogert and Geiger[6] by direct nitration of 4-quinazolone. At

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[1] This Journal, 37, 1884 (1915).

[2] *Ber.*, 47, 2437 (1914).

[3] This Journal, 35, 1130 (1913).

[4] *Ibid.*, 35, 1136 (1913).

[5] For a discussion of the structure of acylanthranils, see Heller, *Ber.*, 48, 1183 (1915).

[6] This Journal, 34, 524 (1912).

the time, Bogert and Geiger expressed the opinion that the nitro group would be found to be in position 6, and this synthesis proves the correctness of the deduction.

Experimental.

o-Uramino-benzoic Acid (**o-Ureido-benzoic Acid**), $H_2N.CO.NH.C_6H_4.COOH$, was prepared first by Griess[1] by the interaction of anthranilic acid and potassium isocyanate in presence of hydrochloric acid, but he gave no details of his process or description of his product, other than to note that it crystallized in small, white needles. Gabriel and Colman[2] later prepared it in much the same way and obtained a fine, crystalline powder.

Twenty-seven g. of anthranilic acid was treated with 20 cc. (calculated, 16 cc.) of conc. hydrochloric acid, the mixture dissolved in a liter of hot water, filtered and the filtrate cooled. A solution of 20 g. (calculated, 16 g.) of potassium isocyanate in 50 cc. water was added slowly with mechanical stirring. When about half of the cyanate solution had been run in, the mixture suddenly set to a pasty mass of crystals. After all the cyanate had been added, the mixture was left overnight, the precipitate filtered out, washed with water and dried on a porous tile. Microscopic, colorless needles, decomposing at 162–4° (corr.), were thus obtained. Yield, 27.3 g. or 72.7% of the theoretical amount. The compound was purified by dissolving it in absolute methyl or ethyl alcohol at room temperature, stirring with animal charcoal, filtering, and concentrating the filtrate *in vacuo* at 10–20°. The purified acid separated in tufts of fine, colorless, silky needles, decomposing at 171–2° (corr.) with formation of benzoylene urea. It is so rapidly changed into benzoylene urea by the action of heat, of alkali or of mineral acid, that it cannot be purified satisfactorily either by crystallization from hot solvents or by solution in alkali and reprecipitation by mineral acid.

Subs., 0.1609, 0.2571:21.69 cc. N at 21° and 763.7 mm.; 33.85 cc. N at 18° and 766.7 mm.

Calc. for $C_8H_8O_3N_2$: N, 15.52. Found: 15.34, 15.27.

It is practically insoluble in ligroin; very slightly soluble in water, carbon tetrachloride, carbon disulfide or cold toluene; somewhat more soluble in chloroform, benzene or hot toluene; moderately soluble in ether; and dissolves readily in methyl or ethyl alcohols, acetone or ethyl acetate. Hot water decomposes it.

It is very easily condensed to benzoylene urea by a variety of reagents. Heated in an oil bath to 190–200°, it yields 30% of the theoretical amount, while conc. aqueous sodium hydroxide gives nearly a quantitative yield.

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[1] *J. prakt. Chem.*, [2] **5**, 371 (1872).

[2] *Ber.*, **38**, 3561 (1905).

Gabriel and Colman[1] have shown that heating with 20% aqueous hydrochloric acid also causes this condensation.

Methyl Ester.—The condensation of methyl anthranilate with potassium isocyanate could not be carried out in hydrochloric acid solution, for the reason that the concentration of acid necessary to get the anthranilate into solution decomposed the cyanate; and, as the acid concentration diminished, the unchanged methyl anthranilate separated as an oil. Acetic acid, therefore, was substituted for hydrochloric acid, and the reaction then ensued smoothly and without difficulty. From 20 g. of methyl anthranilate, 600 cc. of 50% acetic acid and 12 g. (calc., 10.9 g.) of potassium isocyanate, 26 g. of methyl uramino benzoate was obtained, which is the theoretical yield. Purified by crystallization from methyl alcohol, it formed glistening, white needles, melting with decomposition at 177–7.5° (corr.).

Subs., 0.1816: 23.00 cc. N at 20° and 761.2 mm.

Calc. for $C_9H_{10}O_3N_2$: N, 14.42. Found: 14.44.

Its solubilities are much the same as those of the free acid. When heated above its melting point, or boiled with water, it gives off odors resembling those of methyl anthranilate and methyl salicylate, but the chief product is always benzoylene urea. The latter is also formed when the ester is dissolved in 30% aqueous sodium hydroxide solution or in conc. sulfuric acid, or when it is treated for a few hours with a saturated solution of ammonia in water, methyl or ethyl alcohol, ether or benzene. In no case was there any evidence of amide formation, as the result of the action of ammonia upon the ester.

Benzoylene Urea (2,4-**Diketo-tetrahydro-quinazoline**), $\overline{NHCONHC_6H_4CO}$.—Of the various methods which have been used for the preparation of benzoylene urea, the most promising seemed to be the fusion of anthranilic acid with urea[2] and the condensation of *o*-uraminobenzoic acid.

The first experiments, therefore, were concerned with the urea method. It is believed that the benzoylene urea formed in this process owes its origin to the following changes:

$$H_2NC_6H_4COOH + H_2NCONH_2 \longrightarrow H_2NCONHC_6H_4COONH_4 \longrightarrow$$

$$\overline{HNCONHC_6H_4CO} + H_2O + NH_3,$$

inasmuch as the *meta-* and *para-*aminobenzoic acids give the corresponding uramino-benzoic acids when fused with urea,[3] ammonia is evolved during the fusion quite freely, and we have shown that both uramino-benzoic acid

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[1] *Loc. cit.*

[2] Griess, *Ber.*, 2, 416 (1869); *J. prakt. Chem.*, [2] 5, 371 (1872). See also Abt., *J. prakt. Chem.*, [2] 39, 143 (1889) and Pawleski, *Ber.*, 38, 130 (1905).

[3] Griess, *J. prakt. Chem.*, [2] 5, 369 (1872).

and its ammonium salt yield benzoylene urea when heated. Further, Paal[1] has proven that *o*-phenyluramino-benzoic acid gives 3-phenylbenzoylene urea, and Pawleski[2] has produced the same substance by fusing anthranilic acid with monophenyl urea. In fact, Weiland[3] states that uramino acids are formed by heating together amino acids and urea, in neutral aqueous solution, even at 42–5°.

In testing the stability of anthranilic acid to heat, it was ascertained that it begins to sublime and to give off carbon dioxide at its melting point (145°), the evolution of gas being quite rapid at 160–5°.

If the temperature is carried too high during the fusion of anthranilic acid and urea, some of the benzoylene urea already formed is decomposed into anthranilic nitrile and carbon dioxide.[4]

In spite of numerous trials and a careful study of the various factors involved, the yields could not be raised above 46% of the theoretical amount. Further, with increasingly large amounts the yields grew steadily poorer, presumably because of the difficulty in heating the larger melts uniformly. As products of the reaction, in addition to benzoylene urea, there were identified, water, ammonia, carbon dioxide and ammonium carbamate, and evidence was obtained also of the presence of anthranilic nitrile and of biuret. As Werner[5] has shown, when urea is heated it suffers decomposition into ammonia and isocyanic acid, at temperatures just above its melting point (132°), some of the latter then polymerizing to cyanuric acid and some combining with unchanged urea to form biuret. At higher temperatures (190–200°), some ammelide is produced, but we did not discover any of this compound in our melts.

By the action of strong aqueous sodium hydroxide upon *o*-uraminobenzoic acid, benzoylene urea can be prepared rapidly and in any desired amount, as already described in our previous article.

From water or dil. acetic acid, it separates in colorless needles, and from glacial acetic in small plates. By careful and repeated crystallization, a melting point of 353–4° (corr.) was obtained, and this could not be raised by further crystallization. It sublimes unchanged at high temperature. Its solubility at 23° is 0.000741 mole (0.129 g.) per liter of water. It is difficultly soluble in ethyl alcohol, and but slightly soluble in amyl alcohol or in carbon tetrachloride. By direct nitration, it gives 6-nitro- and 6,8-dinitro-benzoylene urea. Fused with oxalic acid, it gives no carbazole blue reaction.

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[1] *Ber.*, **27**, 978 (1894).

[2] *Ibid.*, **38**, 130 (1905). See also Kunckell, *Ibid.*, **38**, 1213 (1905) and **43**, 1237 (1910).

[3] *Chem. Zentr.*, **1912**, I, 1230.

[4] Compare Abt, *J. prakt. Chem.*, [2] **39**, 143 (1889) and Haslinger, *Ber.*, **41**, 1451 (1908).

[5] *J. Chem. Soc.*, **103**, 1010, 2275 (1913).

Sodium Salt.—Purified by repeated crystallization from dil. aqueous sodium hydroxide, this salt was obtained in long, white needles, containing water of crystallization which was lost at room temperature *in vacuo* over sulfuric acid.

Subs., 1.0032; Na_2SO_4, 0.3824.
Calc. for $C_8H_5O_2N_2Na$: Na, 12.50. Found: 12.34.

The solubility of this salt at 23° was determined by taking a measured volume saturated at that temperature, heating to boiling, acidifying with hydrochloric acid, cooling, filtering out the precipitated benzoylene urea, and drying it to constant weight in a Gooch crucible at 120°. This gives the difference in solubility between the benzoylene urea itself and its sodium salt.

100 cc. of solution saturated at 23° gave 0.7024 g. benzoylene urea, indicating a solubility of 0.0433 mole per liter, or 0.7967 g. $C_8H_5O_2N_2Na$ per 100 cc., assuming the solubility of the free benzoylene urea to be practically zero.

6-Nitro-benzoylene Urea, $\overline{\mathrm{NHCOC_6H_3(NO_2)NHCO}}$, was prepared by the direct nitration of benzoylene urea, and also by the action of aqueous ammonia upon methyl-dinitro-uramino-benzoate. It could not be obtained by the fusion of 5-nitro-anthranilic acid with urea, nor by the action of ammonia upon the free dinitro-uramino-benzoic acid. This is in harmony with the experience of Lederer[1] who heated an intimate mixture of urea and 5-nitro-2-anilino-benzoic acid at 205°, without accomplishing any quinazoline condensation, the nitro-phenylanthranilic acid being recovered unchanged.

Twenty g. of benzoylene urea was dissolved in 200 cc. of conc. sulfuric acid, and the calculated amount (5.4 cc.) of fuming nitric acid (sp. gr. 1.5) was added slowly. The temperature rose to about 50°. The mixture was then heated for an hour on the water bath, cooled, poured upon ice, the precipitate filtered out, washed, and crystallized from 50% acetic acid (1 liter), in presence of animal charcoal. It formed brownish yellow prisms, decomposing at 326–30° (corr.). Yield 14.5 g., or 56.5% of the theoretical amount. Much was left in the mother liquor.

The crude material was purified by dissolving it in excess of hot dilute aqueous sodium hydroxide, crystallizing the sodium salt thrice from water, reconverting it to the free nitro compound by acidifying the hot solution with acetic acid, and recrystallizing from 50% acetic acid to constant decomposition point. There resulted pale, greenish yellow prisms, decomposing at 330–1° (corr.); moderately soluble in hot methyl alcohol or in boiling glacial acetic acid; slightly soluble in hot water, ethyl alcohol, ethyl acetate, acetone, ether or toluene; and practically insoluble in chloroform, carbon tetrachloride, carbon disulfide, ligroin or benzene.

[1] Rostock, *Inaug. Diss.*, 1906, p. 60.

The same compound was obtained by the following process: One g. of methyl-dinitro-uramino-benzoate was suspended in 20 cc. of water in a pressure bottle and the liquid saturated with ammonia at 0°. It was then heated at 100° for 4 hours, cooled in a freezing mixture, the bottle opened, excess of ammonia driven out by heating on the steam bath, 60 cc. of water added, the solution acidified hot with acetic acid, and allowed to cool. The bright yellow prisms which separated were filtered out, washed with water, and dried at 120°. Yield, 0.75 g., or 100% of the theoretical amount. These crystals were powdered, extracted thrice with boiling alcohol, and recrystallized from glacial acetic acid. The product was identical with the 6-nitro-benzoylene urea obtained by direct nitration as described above.

Subs., 0.1884: 34.62 cc. N at 21.3° and 751.2 mm.
Calc. for $C_8H_5O_4N_3$: N, 20.29. Found: 20.54.

Fifty years ago, Griess[1] reported that when benzoylene urea was treated with nitric acid he obtained a mononitro derivative crystallizing in honey-yellow prisms. He gave no further description of his process or product, but there can be little doubt that it was the 6-nitro derivative.[2]

Sodium Salt.—Long, light greenish yellow needles, containing no water of crystallization. Its aqueous solutions are yellow and it is reprecipitated from such solution by carbon dioxide. Heated dry, it chars without explosion.

0.240 g. of the salt was dissolved in 100 cc. of boiling water. On cooling, a small amount precipitated, leaving a saturated solution of strength slightly less than 0.01 molar. Five drops of this solution were added to 10 cc. of phosphate and borate solutions (Sörensen standard). The solution with index 7 (Sörensen scale) was colorless, and a greenish yellow color developed very slowly from 7.5 until index 11 was reached, and then rapidly up to that with index 13. The development of color was too slow for this salt to be of any use as an indicator.

6,8-Dinitro-benzoylene-urea, $\overline{\text{NHCOC}_6\text{H}_2(\text{NO}_2)_2\text{NHCO}}$, was ob-

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[1] *Ber.*, **2**, 416 (1869).

[2] Griess did state that reduction of this nitro derivative by ammonium sulfide, or by tin and hydrochloric acid, yielded an amino derivative crystallizing in pale yellow needles, difficultly soluble in all neutral solvents, and which combined with acids to give salts which in most cases crystallized well and were very difficultly soluble.

In 1905, Kunckell (*Ber.*, **38**, 1213 (1905)) announced that he had nitrated benzoylene urea, reduced the nitro to the amino derivative, and prepared various compounds from the latter, on all of which he expected to report later, since Mr. Lederer, one of his Ph.D. candidates, was engaged upon this investigation. No subsequent publication on this research by Kunckell has been located, and the dissertation of Karl Lederer, *Ueber einige Derivate des Ketotetrahydrochinazolins*, Rostock, **1906**, fails to record any work upon the nitration of benzoylene urea or the reduction of any nitro derivatives thereof.

tained by the direct nitration of benzoylene urea and of its 6-nitro derivative. Its production from benzoylene urea itself is set forth in our earlier paper.

The preparation from the mononitro derivative was carried out as follows: One g. of 6-nitro-benzoylene urea was dissolved in 10 cc. of conc. sulfuric acid, and 6 cc. (calc., 4 cc.) of conc. nitric acid added. The yellow solution turned red upon the addition of the nitric acid, but soon changed to yellow again. After an hour's heating on the steam bath, it was cooled, poured into 100 cc. of cold water, and the precipitated dinitro derivative purified in the manner described in our other paper. The following additional observations were made on this compound:

Mixed with soda lime, it gives a brick-red color which changes to orange on exposure to the moisture of the atmosphere. This mixture explodes when heated, with evolution of ammonia, and the residue chars. When 2 g. of the compound was dissolved in a solution of 10 g. sodium hydroxide in 30 cc. of water, there resulted a bright red solution and an orange precipitate. On short boiling of this mixture, both solution and precipitate turned black and considerable ammonia was given off. After 12 hours' boiling, the mixture was acidified with hydrochloric acid, but only a slimy, black precipitate was obtained, from which no pure compounds could be recovered.

The anhydrous monosodium salt is orange, and when heated turns red and finally explodes. Its other properties are given in our former paper.

The potassium and ammonium salts, prepared in similar manner, resemble the sodium salt in appearance and general behavior, except that the ammonium salt decomposes without explosion. The solubilities of these salts were determined at 20° by the method used for the sodium salt.

(1) 50 cc. solution of the potassium salt saturated at 20° gave 0.1791 g. of dinitro-benzoylene urea, indicating a solubility of 0.0142 mole per liter.

(2) 50 cc. solution of the ammonium salt saturated at 20° gave 0.2656 g. of dinitro-benzoylene urea, indicating a solubility of 0.0211 mole per liter.

6,8-Diamino-benzoylene Urea.—80 g. (calc. 45 g.) of stannous chloride was dissolved in 300 cc. of conc. hydrochloric acid, the solution heated to boiling, 10 g. of dinitro benzoylene urea added slowly, and the solution boiled for 4 hours. On cooling, the hydrochloride of the diamine separated in bunches of pink prisms, which were filtered out, washed with water, dried at 120°, boiled 15 minutes with 50 cc. of conc. hydrochloric acid, the solution diluted with an equal volume of water, boiled a few minutes longer, cooled, the precipitate filtered out, heated with 300 cc. of freshly boiled water and made alkaline with ammonia. The result was a yellow precipitate and a yellow solution with greenish fluorescence. Yield of diamine, 6 g., or 78.9% of the theoretical amount.

Crystallized from freshly boiled water containing some ammonia, it separates in long, dull, yellow needles, which darken at about 200° and decompose at 335° (corr.). Treatment with freshly boiled water made slightly acid with acetic acid did not alter the appearance or the decomposition point.

Subs., 0.1292: 34.38 cc. N at 24.5° and 747.2 mm.
Calc. for $C_8H_8O_2N_4$: 29.15. Found: 29.11.

The compound is slightly soluble in boiling water, but practically insoluble in cold water or in the other ordinary solvents. It gives a very difficultly soluble hydrochloride. In hot dil. sodium or ammonium hydroxide solutions it dissolves somewhat, apparently with the formation of easily hydrolyzable salts. Its alkaline solution soon turns red, due to oxidation, and a flocculent violet precipitate separates, which turns black when dried and is insoluble in all common solvents. This oxidation ensues still more rapidly in neutral or faintly acid solutions. In dil. acids, it gives a purple solution in which the purple precipitate forms more slowly. Distillation with soda lime completely breaks down the compound.

2,4-Dichloro-quinazoline, $\overline{\mathrm{N:CCl.C_6H_4.N:C}}\mathrm{Cl}$, was prepared from benzoylene urea, phosphorus oxy- and pentachlorides, by the method of Gabriel and Colman[1] and was purified by distilling off the phosphorus halides under diminished pressure, as recommended by Abt.[2] Yield of crude product, 82% of the theoretical amount. This was fully pure enough for most purposes and was used in subsequent syntheses.

A sample very carefully purified by recrystallization from benzene and distillation under reduced pressure, formed white, lustrous blades, melting point 119.5° (corr.). Abt gives the melting point as 115°. Crystallization from benzene alone is not very satisfactory, on account of the small temperature coefficient of solubility.

2,4-Dimethoxy-quinazoline was obtained from the dichloro derivative by following the directions of Bogert and May.[3] Yield, 26.5% of the theoretical amount. By very careful purification, involving distillation with steam and recrystallization, long, white, silky needles were secured, m. p. 74°, which melting point could not be raised by further crystallization from dil. alcohol. Abt[4] gives the melting point as 66°; Bogert and May, as 67°. It was further proven that this high melting point was not due to any admixture of 1,3-dimethyl-benzoylene urea, as the latter is not volatile with steam, and the addition of some of it to the dimethoxy derivative lowered the melting point to 69.5–71.5°.

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[1] *Ber.*, **38**, 3559 (1905).

[2] *J. prakt. Chem.*, [2] **39**, 140 (1889).

[3] THIS JOURNAL, **31**, 512 (1909).

[4] *Loc. cit.*

1,3-Dimethyl-benzoylene urea, $CH_3\overline{NCOC_6H_4N(CH_3)C}O$, was prepared first by Abt[1] by the direct methylation of benzoylene urea, or of its 1- or 3-monomethyl derivative, with methyl iodide. Later, it was produced in much the same way by Bogert and May.[1]

On repeating the process, the crude product was crystallized from 50% alcohol, giving slender, white needles, melting point 153–6° (corr.). These crystals were boiled for 15 minutes with 60 cc. of conc. hydrochloric acid, to hydrolyze any methoxy derivatives, the solution made slightly alkaline with sodium hydroxide, diluted with water, the crystals filtered out, washed and dried. Slender, white needles resulted, m. p. 167–8° (corr.). Abt gives the melting point of this compound as 151°, Bogert and May, as 163–5°. The melting point of our product could not be raised further by recrystallization, nor by a second treatment with hydrochloric acid followed by recrystallization. Yield of crude product, 94% of the theoretical amount.

The alkaline filtrate from the first hydrochloric acid treatment was acidified with the same acid, the precipitate filtered out, washed, dried and crystallized from dil. alcohol. Fine, white needles, m. p. 237–8° (corr.), were thus obtained, which contained no halogen. Abt gives the melting point of 3-methyl-benzoylene urea as 234°, as does also Söderbaum.[2] The second treatment of dimethyl-benzoylene urea with hydrochloric acid yielded no monomethyl derivative. The amount of monomethyl recovered from the crude dimethyl derivative was always considerable. Its origin is evidently to be ascribed to the incomplete methylation of the benzoylene urea, inasmuch as pure 1,3-dimethyl-benzoylene urea is unchanged by boiling hydrochloric acid, and because we obtained the same compound from benzoylene urea and one mole of methyl iodide.

1,3-Dimethyl-benzoylene urea is not appreciably volatile with steam nor is it changed by 4 hours' boiling with fuming nitric acid and conc. sulfuric acid.

3-Methyl-benzoylene Urea.—Abt reported that with one mole of alcoholic sodium hydroxide, he obtained a monosodium salt, carrying alcohol of crystallization, which yielded 1-methyl-benzoylene urea (melting point 147–8°) on treatment with methyl iodide. Our results do not tally with this, for we found that limited methylation of benzoylene urea gave the 3-methyl and not the 1-methyl derivative.

Eight g. of benzoylene urea and the calculated amount (2 g.) of sodium hydroxide were dissolved in 250 cc. of 50% methyl alcohol by warming. The solution was cooled to room temperature, causing the monosodium salt of benzoylene urea to separate; 8 g. (calc. 7 g.) of methyl iodide was

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[1] *Loc. cit.*

[2] *Ber.*, 23, 2183 (1890).

added, the solution boiled under a reflux condenser until all the methyl iodide had disappeared (3 hours), filtered hot, and the filtrate cooled. The crystals which separated were filtered out, washed, dissolved in 150 cc. of 0.7 molar sodium hydroxide solution, the solution filtered, the filtrate acidified with hydrochloric acid, the precipitated crystals removed, washed, and dried at 110°. Yield, 7.5 g., or 80% of the theoretical amount. This crude product was recrystallized from alcohol, giving slender, white needles, melting point, 230–3° (corr.). Mixed with 3-methyl-benzoylene urea from the preparation of the 1,3-dimethyl derivative, a melting point of 230–6° (corr.) was obtained.

Since the purpose of this synthesis was to identify the monomethyl derivative formed in the preparation of the dimethyl, it was not further purified. In the synthesis it is advisable to use some excess of methyl iodide, since it is much easier to free the 3-methyl derivative from dimethyl than from benzoylene urea itself.

From the first filtrate, acidified with hydrochloric acid, a small amount (0.4 g.) of 1,3-dimethyl-benzoylene urea was recovered.

3-Methyl-benzoylene urea was unchanged by 4 hours' boiling with fuming nitric and conc. sulfuric acids.

5-Nitro-2-nitrouramino-benzoic Acid (Dinitro *o*-Uramino-benzoic Acid), $(2)O_2NNHCONHC_6H_3(NO_2)(5)COOH(1)$.—In 1878, Griess[1] reported that the action of nitric acid upon *o*-uramino-benzoic acid yielded but one dinitro derivative, and that this product resembled in its general behavior the isomeric dinitro derivatives of the *meta* and *para* series. He gave no analytical figures or further characterization of the new dinitro acid, except the statement that when boiled with water it yielded 5-nitro-anthranilic acid, nitrous oxide and carbon dioxide. This work we have repeated and confirmed.

Sixty cc. of fuming nitric acid (sp. gr. 1.5), free from lower oxides of nitrogen was cooled to —5° to —10° and 7.5 g. of *o*-uramino-benzoic acid added slowly. At the end of an hour, the mixture had changed to a pasty mass, which was allowed to stand for 3 hours at a temperature below 0°, then poured upon 500 g. of ice and filtered immediately. A yellowish solid resulted, which softened at 170° and largely distilled to a bright, yellow liquid, the residue decomposing at about 230°. Yield, 8 g., or 76.3% of the theoretical amount.

Considerable difficulty was experienced in endeavoring to free the product from the nitro-anthranilic acid into which water slowly decomposes it. After digestion with boneblack in anhydrous acetone solution and repeated crystallization from the same solvent, pale greenish yellow plates were obtained, decomposing at 256–8° (corr.). One fraction charred without melting at 286–95° (corr.), the others gave a constant decomposition point

[1] *Ber.*, 11, 1730 (1878).

after several recrystallizations, and a mixture of the two decomposed partially at 256–8° (corr.), the remainder charring at 286–95° (corr.). Both forms gave 5-nitro-anthranilic acid when boiled with water.

Analytical figures were not obtained, for the reason that the small amount of purified material available was lost through repeated explosions in the combustion tubes.

The substance is more or less readily soluble in methyl or ethyl alcohol, acetone, ethyl acetate or glacial acetic acid; but is practically insoluble in ether, benzene, toluene, ligroin, chloroform, carbon tetrachloride or carbon disulfide. It crystallizes from glacial acetic acid in flat prisms, decomposing at 255–60° (corr.). In boiling water, it dissolves, but yellow needles of 5-nitro-anthranilic acid soon separate; cold water acts similarly but more slowly. The action of saturated aqueous ammonia at 100° gave a mixture of products which were not separated or identified further than to prove that no nitro- or dinitro-benzoylene urea was present.

Methyl Ester.—Eighty cc. of fuming nitric acid (sp. gr. 1.5), free from lower oxides, was cooled to —5° to —10°, and 10 g. of methyl-*o*-uramino-benzoate added slowly. The mixture was allowed to stand for 4 hours, then poured upon 400 g. of ice and filtered immediately. The precipitate when spread on a porous plate appeared as a pasty, salmon-colored mass, turning to buff when fully dried. Crystallized from alcohol, in presence of animal charcoal, pale greenish yellow rhombic plates were obtained, decomposing at 184–5° (corr.) to yellow crystals which melted at 217–33° (corr.), neither of which points was changed by recrystallization of the ester from absolute or diluted alcohol. Yield, 7.5 g., or 52% of the theoretical amount.

Subs., 0.1631: 28.10 cc. N at 18.5° and 757.2 mm.
Calc. for $C_9H_8O_7N_4$: N, 19.72. Found: 19.68.

The compound is practically insoluble in chloroform, carbon tetrachloride, carbon disulfide, acetone or cold water. It is slightly soluble in ligroin or benzene; and more or less easily soluble in methyl or ethyl alcohol, glacial acetic acid, ethyl acetate or toluene. Boiled with water, it gives methyl-5-nitro-anthranilate.

The dry substance when heated puffed suddenly at about 180–5° (corr.) with formation of yellow vapors. The residue gave 36% of the theoretical yield of methyl-5-nitro-anthranilate, together with small amounts of other products which were not identified. No attempt was made to identify the impure crystalline yellow product (m. p. 217–33°) resulting from the action of heat upon the ester, other than to establish the fact that it was not a nitro-benzoylene urea. Treatment of the ester with conc. aqueous sodium hydroxide or sulfuric acid also gave mixtures of various undetermined products, but among which there was no nitro-or dinitro-benzoylene urea. By the action of conc. aqueous ammonia upon the ester, however, 6-nitro-benzoylene urea was obtained.

5-Nitro-2-acetamino-benzoic Acid (5-Nitro-acetanthranilic Acid), $(2)CH_3CONHC_6H_3(NO_2)(5)COOH(1)$.—5-Nitro-2-acetamino toluene (5-nitro-2-acetotoluide) was prepared from C. P. 5-nitro-2-toluidine (m. p. 129.5–32°, corr.) by direct acetylation with acetic anhydride in glacial acetic solution. Yield, practically the theoretical amount. Pale yellowish, silky needles (from alcohol), melting point 197.5–8° (uncorr.), or 204.–4.5° (corr.), as reported by Bogert and Cook.[1]

From this acetamino derivative, 5-nitro-2-acetanthranilic acid was obtained by oxidation with potassium permanganate, following the process of Bogert and Cook, in light yellow prisms (from water), melting point 218° (corr.). Yield, 65.5% of the theoretical amount. Some nitro-anthranilic acid was recovered from the filtrate.

Barium Salt.—Bright yellow tufts of fine hairs, or flat prisms; slightly soluble in cold water, easily in hot.

Calcium Salt.—Similar to the barium salt, except that it crystallizes in needles.

Ferric Salt.—Dull, chocolate, gelatinous precipitate, only slightly soluble in hot water, from which it separates in amorphous condition.

Cupric Salt.—Light green, gelatinous precipitate, crystallizing from water in fine, green hairs. Soluble in ammonium hydroxide solutions.

Lead Salt.—Bright yellow precipitate, crystallizing from water in balls of hair-like needles.

Silver Salt.—Curdy, light yellow precipitate, resembling silver iodide, and crystallizing from water in sheafs of hair-like needles.

Many of the statements in the literature concerning this acid are, to say the least, confusing.

Rupe[2] by direct nitration of acetanthranilic acid with mixed acids at about 40°, claimed to have obtained the 5-nitro derivative, and gave a melting point of 152° for his acid. We have repeated Rupe's process, and by frequent crystallization of the product from water have obtained a substance melting at 174–7° (corr.), which was evidently still impure, its impurities being probably nitro-anthranilic acid formed by de-acetylation[3] and *p*-nitraniline formed by loss of carbon dioxide from the latter.

Ullmann and Uzbachian[4] make the astonishing announcement that they prepared 5-nitro-acetanthranilic acid by oxidation of 4-nitro-acetotoluide of melting point 151°. This may have been due to an error in copying, with the melting point filled in from Beilstein and not from the laboratory note book, as the acid obtained was evidently the 5-nitro derivative.

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[1] THIS JOURNAL, **28**, 1451 (1906).

[2] *Ber.*, **30**, 1097 (1897).

[3] Compare Seidel and Bittner, *Monatsh.*, **23**, 435 (1902).

[4] *Ber.*, **36**, 1797 (1903).

Baly, Tuck and Marsden[1] prepared the acid both by oxidation of the nitro-acetotoluide with potassium permanganate and by direct nitration of acetanthranilic acid, claiming a yield by the latter method of 85%. They failed to record the melting point of their products, however. Numerous repetitions of this direct nitration method, have failed to yield us pure products, the results being much the same as from the Rupe method. By nitrating at lower temperatures, however, a fairly good product was secured.

Ten g. of acetanthranilic acid was added slowly to 20 cc. of fuming nitric acid (sp. gr., 1.5), keeping the temperature below 5°. The mixture was maintained at that temperature for 4 hours, then for 2 hours at laboratory temperature, when a red color developed. It was poured upon ice and the light yellow precipitate recrystallized from alcohol in presence of animal charcoal. Yield, 5 g., or 39% of the theoretical amount; melting point, 206–10° (corr.). Further recrystallization from alcohol raised the melting point to 214–5° (corr.). This product was hydrolyzed to nitro-anthranilic acid without further purification.

5-Nitro-2-amino-benzoic acid (5-nitro-anthranilic acid), was prepared according to the process of Rupe[2] by boiling the foregoing acetyl derivative with conc. hydrochloric acid and recrystallizing the product from the dil. acid. Long, bright yellow needles were thus secured, which blackened at 240–50° (corr.), and melted with decomposition at 275–6° (corr.). Yield, 98% of the theoretical amount.

The pure acid separates from 95% alcohol in pale yellow, satiny blades; from water, or dilute alcohol, in fine, golden yellow needles. Recrystallized to constant decomposition point, it decomposes at 278° (corr.), with blackening and some sublimation above 240°. As the decomposition point varies considerably depending upon the rapidity of the heating, it is not surprizing that the melting point (really decomposition point) recorded in the literature shows a confusing range, being variously stated from 261° to 280°.

The solubilities of the acid were determined roughly at laboratory temperature (about 18°) by taking a known volume of saturated solution, evaporating to dryness and weighing the residue. The results expressed in g. per liter were as follows: water, 1.0; glacial acetic acid, 3.0; mixture of glacial acetic acid and ethyl acetate (50:50), 4.0; ether, 7.0; ethyl acetate, 7.5; alcohol, 14.0; boiling glacial acetic acid, 15.0–20.0.

Salts.—The sodium, potassium and ammonium salts are moderately soluble in cold water, easily soluble in hot. All form fine, brownish orange needles, those of the sodium salt being rather darker than the other two.

Methyl Ester.—This was formed by esterification of the acid with

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[1] *J. Chem. Soc.*, 97, 1502 (1910).

[2] *Loc. cit.*

either methyl alcohol and hydrochloric acid, or with methyl sulfate. Yield by the former method, 61% of the theoretical amount; by the latter, 46.5%.

Recrystallized from slightly diluted alcohol until the melting point remained constant, it formed pale yellow needles of greenish tinge, melting point 168° (corr.), difficultly soluble in cold water, more or less readily soluble in the other ordinary solvents. It is slowly volatile with steam with partial decomposition, and can be sublimed unchanged.

Subs., 0.1457: 18.32 cc. N at 19.5° and 765.0 mm.

Calc. for $C_8H_8O_4N_2$: N, 14.29. Found: 14.43.

All efforts to convert this ester into the amide by the action of ammonia proved fruitless, the ammonium salt of the acid being the only product. This coincides with the experience of Thieme[1] in the case of the ethyl ester.

6-Nitro-4-quinazolone, $\overline{NHCOC_6H_3(NO_2)N{:}CH}$.—A mixture of 10 g. of 5-nitro-anthranilic acid and 10 g. of formamide (calc. 2 g.) was fused at 150–70° for 6 hours, the melt cooled, extracted with 40 cc. of cold water, and the residue crystallized from 50% acetic acid. Light brown prisms resulted, melting point 283–5° (corr.). Yield, 3.5 g., or 33.4% of the theoretical amount. Dissolved in alkali and reprecipitated with acetic acid, pale brownish crystals were obtained, m. p. 286–7° (corr.).

Bogert and Geiger[2] nitrated 4-quinazolone and obtained a nitro derivative, m. p. 286.5–7.5° (corr.), which they believed to be the 6-nitro-4-quinazolone. The compound prepared from 5-nitro-anthranilic acid, as described above, proved to be identical in all respects with the product of Bogert and Geiger, and the melting point of a mixture of the two was 285.5–6.5° (corr.). This supplies the synthetic proof that the product of direct nitration of 4-quinazolone is really the 6-nitro derivative.

Experiments on the availability of this compound as an indicator showed that its range of color change was from index 7 to 9.3, and the change from colorless to greenish yellow. To get a satisfactory color, it was found necessary to use 10 drops of a 0.05 molar solution. This is too concentrated for good results, and the free nitro-quinazolone was precipitated in acid solutions.

6-Nitro-2-methyl-4-quinazolone was also tested for use as an indicator. Its range of color change proved to be from index 7.2 to 9.5. Otherwise, it behaved exactly like the 6-nitro-4-quinazolone.

Summary.

1. A further study has been made of the preparation and properties of benzoylene urea, and of the following derivatives: 6-nitro, 6,8-dinitro, 6,8-diamino, 3-monomethyl and 1,3-dimethyl.

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[1] *J. prakt. Chem.*, [2] **43**, 470 (1891).

[2] THIS JOURNAL, **34**, 524 (1912).

2. In the methylation of benzoylene urea, results have been obtained differing from those of Abt.

3. Dichloro- and dimethoxy-quinazoline have been prepared in purer form than hitherto.

4. Our knowledge of *o*-uramino benzoic acid and of its dinitro derivative has been extended.

5. 5-Nitro-anthranilic acid and its acetyl derivative have been studied and some of the existing confusion in the literature cleared up.

6. The structure of 6-nitro-4-quinazolone has been proven by its synthesis from 5-nitro-anthranilic acid.

7. The serviceability of certain quinazolines as indicators has been tested.

8. The following new compounds have been prepared: methyl-*o*-uramino benzoate, the sodium salt of 6-nitro-benzoylene urea, the potassium and ammonium salts of 6,8-dinitro-benzoylene urea, methyl-dinitro-*o*-uramino benzoate, various salts of 5-nitro-acetanthranilic acid and of 5-nitro-anthranilic acid, and the methyl ester of the latter.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA.]

MOLECULAR REARRANGEMENT IN THE ACYLATION OF CERTAIN AMINOPHENOLS.

BY L. CHAS. RAIFORD.

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During the course of a research now in progress in this laboratory, the purpose of which is the study of the steric relations involved in the acylation of aminophenols, it became necessary in the identification of one of the products isolated to prepare a diacylated derivative of an *o*-aminophenol in which the acyl radicals bound to oxygen and to nitrogen, respectively, were different. In the case under consideration the two radicals were acetyl and benzoyl. It may be stated at the outset that further examination of the product showed that the heavier of these radicals, benzoyl in this case, was always found attached to nitrogen, regardless of the order in which they were introduced, which indicates that a rearrangement must have occurred in one case.

As will appear below, the rearrangement in this case involved the migration of acetyl from nitrogen to oxygen, and possibly the shift of benzoyl in the opposite direction, though the mechanism of the reaction has not yet been satisfactorily determined. The migration of acyl from oxygen to nitrogen has previously been observed in several different cases, following the work of Böttcher[1] on 2-benzoyl-aminophenol.[2] The replacement of

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[1] *Ber.*, 16, 629 (1883).

[2] For a bibliography of the subject see Weyl, "Die Methoden der Organischen Chemie," II, p. 1281; Leipzig, 1911 (Thieme).