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RESEARCHES ON QUINAZOLINES (SEVENTEENTH PAPER). THE SYNTHESIS OF QUINAZOLINECARBOXYLIC ACIDS FROM 4-AMINOISOPHTHALIC ACID AND FROM AMINOTEREPHTHALIC ACID[1]

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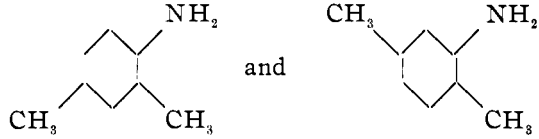
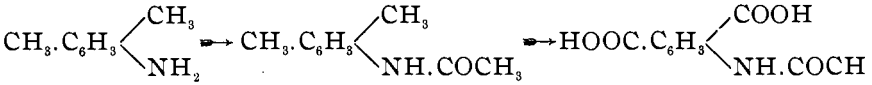
So far as the authors are aware, only one quinazoline carboxylic acid with the carboxyl on the benzene nucleus is described in the literature. It was obtained by Niementowski[2] by oxidizing 7-methylbenzoyleneurea with potassium permanganate in alkaline solution, and he ascribed to it the following formula :— (7)HOOC.C_6H_3<NH — CO / CO — NH>. It decompose at about 405°, is practically insoluble in water and in all indifferent or acid organic solvents, but dissolves in basic solvents. In its purification considerable difficulty was encountered due to its tendency to form gummy colloidal masses.

By methods previously used in this laboratory for the synthesis of other quinazolines, we have succeeded in preparing various alkyl derivatives of the 6- and 7-carboxy-4-ketodihydroquinazolines from 4-aminoisophthalic acid and from aminoterephthalic acid.

The starting points for these syntheses were the two xylidines, 2-amino-1, 5-xylene and 2-amino-1, 4-xylene(*m*-xylidine and *p*-xylidine):—



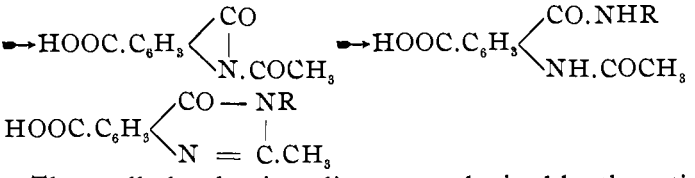
These xylidines were acetylated, the methyl groups oxidized to carboxyls, the resulting acetaminophthalic acids converted into acetanthranilcarboxylic acids by the action of acetic anhydride, and from these anthranils the quinazolines were obtained by the action of the various primary amines.[3] The changes involved in these syntheses may be concisely represented thus :—



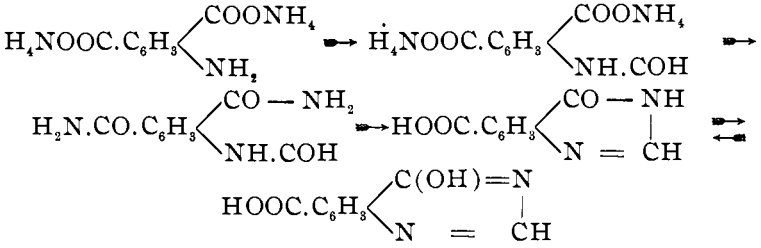
[1] Read before the New York Section of the American Chemical Society June 8, 1906.

[2] Ber. 29, 1357 (1896).

[3] Anschütz, Schmidt and Greiffenberg : Ber. 35, 3480 (1902); Bogert and Chambers : this Journal 27, 649 (1905); Bogert and Seil : Ibid. 27, 1305 ; Bogert and Steiner : Ibid. 27, 1327, etc.



The unalkylated quinazolines were obtained by the action of formamide upon the ammonium salt of the unacetylated aminophthalic acid[1]



Of the various substances prepared, those we believe to be new are as follows :— 2-acetaminoterephthalic acid, acetanthranil-4-carboxylic acid, acetanthranil-5-carboxylic acid, 4-ketodihydroquinazoline 6- and 7-carboxylic acids, the corresponding 2-methyl-, 2, 3-dimethyl- and 2-methyl-3-phenyl carboxylic acids.

Most of these of quinazoline carboxylic acids are colorless crystalline solids, generally melting with decomposition above 300°. They are difficultly soluble in water, insoluble or very difficultly soluble in ether, benzene, chloroform, carbon tetrachloride or acetone, more or less readily soluble in alcohol, insoluble in acids, and soluble in aqueous solutions of the alkalies or of ammonia. From the latter solutions they are precipitated by mineral acids or by carbon dioxide. They form salts with the heavy metals.

EXPERIMENTAL.

Separation of m- and p-Xylidines from Commercial m-Xylidine. While awaiting the arrival of pure xylidines from Germany, we made one or two experiments on the separation of *m*- and *p*-xylidine from the commercial *m*-xylidine. Two methods were tried. (1). That of Limpach[2] which depends upon the fact that the acetate of *m*-xylidine is much more difficultly soluble than that of *p*-xylidine, while the hydrochloride of the latter is less soluble than that of the former. (2). The process patented by Meister, Lucius and Brüning[3] in which a dilute aqueous solution of the hydrochloride of the crude xylidine is treated with formaldehyde, the latter condensing with *p*-xylidine to diamino di-*p*-xylylmethane, but not reacting with the *m*-xylidine. If the solution be then treated with excess of caustic alkali

[1] Niementowski ; J. pr. Chem. [2], 51, 564, (1895).

[2] D.R.P., No. 39947.

[3] D.R.P., No. 87615.

and distilled with steam only *m*-xylidine will pass over. Of these two processes we found the second much the better, and good yields of pure *m*-xylidine were obtained by its means. As the *p*-xylidine was present in but small amount in the original crude material, and its separation is a much more troublesome undertaking, we did not attempt to isolate it. Most of the *m*-xylidine used in the experiments described below, and all of the *p*-xylidine, came from Kahlbaum.

I. EXPERIMENTS WITH METAXYLIDINE (2-AMINO-1, 5-XYLENE).

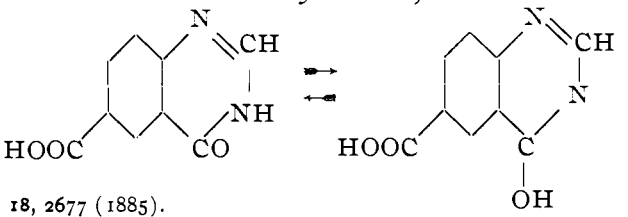
Acet-m-xylidide, (2)$CH_3CONHC_6H_3(CH_3)_2$ (1,5), was prepared by the action of acetic anhydride upon *m*-xylidine, and when re-crystallized from dilute alcohol showed a melting-point of 129-130°. Nölting and Forel[1] gave the melting point as 129°.

Acetaminoisophthalic Acid, (2)$CH_3CONHC_6H_3(COOH)_2$ (1,5). The acetxylidide was oxidized with potassium permanganate in presence of magnesium sulphate.[2] The acetaminoisophthalic acid obtained agreed in all its properties with the acid described by Loewenherz[3] and by Ullman and Uzbachian.[4] The yield was nearly quantitative.

Aminoisophthalic Acid, (2)$H_2NC_6H_3(COOH)_2$ (1,5). The free amino acid was prepared from the acetyl derivative by hydrolysis with sulphuric acid.[5] It melted above 300°. Ullman and Uzbachian[6] give its melting point as 328-329°.

Acetanthranil 5-Carboxylic Acid, (5) $HOOCC_6H_3\langle^{NCOCH_3\,(2)}_{CO\,(1)}\rangle$ The acetaminoisophthalic acid was gently boiled with excess of acetic anhydride, and on cooling the acetanthranilcarboxylic acid crystallized out in pale yellow crystals. It was recrystallized twice from acetic anhydride, the anhydride being finally washed out with carbon tetrachloride in which the anthranil is practically insoluble. It forms minute colorless crystals, which melt at 264° and are not easily hydrolyzed by moisture. The yield of pure anthranil was about 75 per cent of the theoretical. Nitrogen found, 6.64. Calculated for $C_{10}H_7O_4N$: N. 6. 82.

4-*Ketodihydroquinazoline-6-carboxylic Acid* (*4-hydroxyquinazoline-6-carboxylic Acid.*)

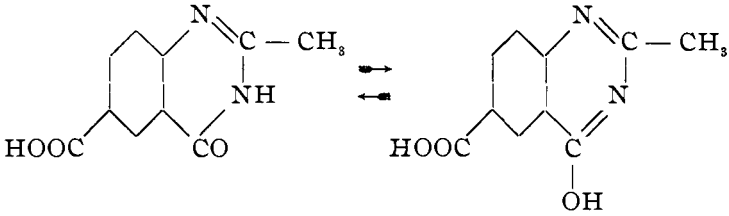


[1] Ber., 18, 2677 (1885).
[2] D.R.P., No. 94629.
[3] Ber., 25, 2795 (1892).
[4] Ber., 36, 1803 (1903).
[5] Loewenherz; Loc. cit.
[6] Loc. cit.

The ammonium salt of the aminoisophthalic acid was heated with an excess of formamide at 150°.[1] When cold the mixture was acidified with hydrochloric acid and the quinazoline thereby precipitated. The precipitate was recrystallized from water and then appeared in small crystals colored slightly yellow. It melts with decomposition above 300°. It is difficultly soluble in boiling water, insoluble in acids or in indifferent organic solvents, but dissolves freely in alkalies.

Nitrogen found, 14.86. Calculated for $C_9H_6O_3N_2$: N, 14.74.

2-Methyl-4-ketodihydroquinazoline-6-carboxylic Acid (*2-Methyl-4-hydroxyquinazoline-6-carboxylic Acid.*)



This was prepared by the following two methods:—

(1). Acetanthranil-5-carboxylic acid was heated for ten minutes with a slight excess of ammonia and the solution then allowed to cool. On adding hydrochloric acid, the quinazoline was precipitated. It was filtered out, washed thoroughly, and recrystallized from boiling water, in which it is only slightly soluble. It forms minute colorless needles, which darken at about 310° and decompose in the neighborhood of 340°. The yield was nearly theoretical.

(2). The ammonium salt of acetaminoisophthalic acid was heated for six hours at 220° in an oil bath. The product was warmed with dilute alkali, and the alkaline extract then acidified with hydrochloric acid. The same substance was obtained as by the first method, but the yield and quality of the product were poor.

Found: C, 58.60 and 58.90; H, 4.09 and 4.14; N, 13.26. Calculated for $C_{10}H_8O_3N_2$: C, 58.82; H, 3.92; N, 13.26.

2, *3-Dimethyl-4-ketodihydroquinazoline-6-carboxylic Acid* was prepared from acetanthranil-5-carboxylic acid in much the same manner as the monomethylquinazoline described above. It was purified by recrystallization from boiling water, and then formed a colorless microcrystalline powder, melting with decomposition above 300°. It is only slightly soluble in hot water or in alcohol, insoluble in acids, but easily soluble in alkalies.

Found: C, 60.14; H, 4.43; N, 12.74. Calculated for $C_{11}H_{10}O_3N_2$: C, 60.55; H, 4.58; N, 12.78.

[1] Niementowski: Loc. cit.

[2] Bishler and Burkart: Ber. **26**, 1350 (1893).

2-Methyl-3-phenyl-4-ketodihydroquinazoline-6-carboxylic Acid, prepared in similar fashion from acetanthranil-5-carboxylic acid and aniline, was purified by washing with dilute hydrochloric acid to remove excess of aniline, and was then crystallized from dilute alcohol, from which it separated in minute colorless needles.

Found: N, 10.15. Calculated for $C_{16}H_{12}O_3N_2$: N, 10.0.

Our attempts to prepare quinazolines by fusion of the aminoisophthalic acid with urea and with thiourea[1] resulted only in decomposition, and no quinazoline was isolated from the products.

EXPERIMENTS WITH PARAXYLIDINE (2-AMINO-1,4-XYLENE).

The derivatives of *p*-xylidine described in the following, unless stated otherwise, were prepared by the same methods as have been already outlined for the preparation of the corresponding meta isomers.

Acet-p-xylidide, (2)$CH_3CONHC_6H_3(CH_3)_2$(1,4), forms colorless crystals, m.p. 138–139°, as found by Schaumann.[2]

Acetaminoterephthalic Acid, (2)$CH_3CONHC_6H_3(COOH)_2$ (1, 4), was obtained in nearly theoretical yield by the oxidation of the acetxylidide. It is soluble in boiling water, and separates on cooling in colorless feathery crystals, which darken at about 256° and decompose above 300° without melting.

Nitrogen found, 6.45. Calculated for $C_{10}H_9O_5N$: N, 6.28.

Aminoterephthalic Acid; (2)$H_2NC_6H_3(COOH)_2$(1,4). The acetamino acid was dissolved in dilute alcohol and hydrolyzed with sulphuric acid. The resulting aminoterephthalic acid exhibited the properties described by Burkhardt,[3] and by de la Rue and Müller,[4] as characteristic of this substance.

At the same time there was formed another *substance* which was much less soluble in water, and which crystallized from the latter solvent in colorless, pearly scales, melting at 59°. On the assumption that it was probably an ester of the acetamino- or aminoterephthalic acid, it was treated with acetic anhydride and then with ammonia, to convert it into a quinazoline. There resulted from this treatment a small amount of a *compound*, which crystallized in colorless, silky needles, m.p. 92°. The yield of both these substances was small, and they have not been further investigated.

Acetanthranil-4-carboxylic Acid, (4) $HOOCC_6H_3\langle^{NCOCH_3(2)}_{CO(1)}$ In the formation of this anthranil from the acetaminoterephthalic acid, a larger amount of acetic anhydride is necessary than in the case of acetanthranil-

[1] Griess ; Ber. 2, 416 (1869); Pawlewski ; Ibid. 38, 130 (1905).

[2] Ber. 11, 1538 (1878).

[3] Ber. 10, 145 (1877).

[4] Ann. 121, 91.

5-carboxylic acid, as it is much less soluble. The yield of pure substance was about 75 per cent. of the theory. The pure anthranil forms minute colorless crystals, insoluble in carbon tetrachloride, which darken at 250–260° and melt with decomposition above 300°.

Nitrogen found, 6.81. Calculated for $C_{10}H_7O_4N$: N, 6.82.

4-Ketodihydroquinazoline-7-carboxylic Acid (*4-Hydroxyquinazoline-7-carboxylic Acid*). By the action of formamide upon the aminoterephthalic acid a yellow, gelatinous mass was obtained, from which the quinazoline was separated and purified by recrystallization from water. It forms a colorless, microcrystalline powder, which melts with decomposition above 300°.

Nitrogen found, 14.48. Calculated for $C_9H_6O_3N_2$: N, 14.74.

Attempts to prepare a diketotetrahydroquinazoline by fusion of the amino acid with urea failed, as they had with the meta isomer. Apparently the high melting-points of these acids and their insolubility in molten urea, make it exceedingly difficult to get any condensation below the decomposing point of the urea.

2-Methyl-4-ketodihydroquinazoline-7-carboxylic-Acid (*2-Methyl-4-hydroxyquinazoline-7-carboxylic Acid.*) Acetanthranil-4-carboxylic acid was boiled with excess of ammonia, a small amount of dilute potassium hydroxide solution was added, and the boiling continued for a short time longer. The quinazoline was precipitated on acidifying the solution with hydrochloric acid, and was purified by crystallization from water. In appearance and solubilities it resembles the isomeric 6-carboxylic acid, and melts with decomposition above 300°.

Nitrogen found, 13.41. Calculated for $C_{10}H_8O_3N_2$: N, 13.23.

2,3-Dimethyl-4-ketodihydroquinazoline-7-carboxylic Acid, from acetanthranil-4-carboxylic acid and methylamine, is soluble in alcohol or boiling water. From the latter it crystallizes in small, colorless prisms, which melt with decomposition at 298°.

Found : C, 60.50 and 60.70 ; H, 4.80 and 4.86 ; N, 12.94. Calculated for $C_{11}H_{10}O_3N_2$: C, 60.55 ; H, 4.58 ; N, 12.84.

2-Methyl-3-phenyl-4-ketodihydroquinazoline-7-carboxylic Acid, prepared in a similar manner, using aniline instead of methylamine, is soluble in alcohol, but only very slightly so in water. Crystallized from dilute alcohol, it appears in small, colorless crystals, which decompose above 300° without melting.

Nitrogen found, 10.15. Calculated for $C_{16}H_{12}O_3N_2$: N, 10.0.

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