[CONTRIBUTION OF THE CHEMISTRY DEPARTMENT, OREGON STATE COLLEGE]

Quinazolines. V. The Synthesis of 2-(and 3)-*o*-Aminobenzyl-4-quinazolones[1]

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During an investigation of the acid hydrolysis of 3-(4′-quinazolyl)-4-quinazolone it became necessary to synthesize both the 2- and 3-*o*-aminobenzylquinazolones.

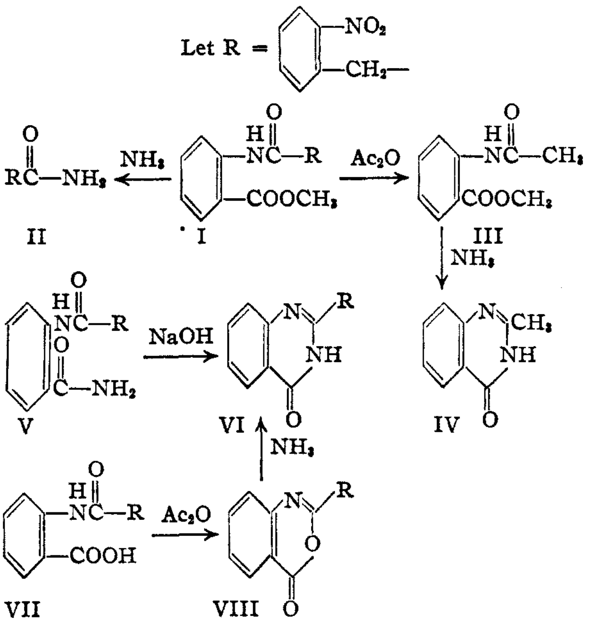
Methyl N-(*o*-nitrophenylacetyl)-anthranilate (I) was prepared as a possible intermediate for the synthesis of the 2-(*o*-aminobenzyl)-4-quinazolone. Weddige,[2] Zacharias,[3] and Thieme[4] had successfully cyclized similar compounds (I) (R = methyl) using ammonia. However, Thieme[4] had reported amide ammonolysis as a side reaction. In this instance (R = nitrobenzyl) (I) the ammonolysis product (*o*-nitrophenylacetamide) (II) was obtained in good yield with no trace of the quinazolone.

Methyl N-(*o*-nitrophenylacetyl)-anthranilate (I) was then refluxed with acetic anhydride in an attempt to prepare the anthranil. The un-isolated product of this reaction was in turn converted to the quinazolone by the use of concentrated ammonia. However, 2-methyl-4-quinazolone (IV) was obtained instead of the desired product, which indicated that transacylation to the methyl acetylanthranilate (III) had preceded the cyclization. Since both mono and diacetyl methyl anthranilate instead of acetanthranil are obtained by the action of acetic anhydride on methyl anthranilate,[5] the course of the above reaction was probably *via* methyl acetylanthranilate (III) and acetylanthranilamide.

The synthesis of the 2-(*o*-nitrobenzyl)-4-quinazolone (VI) was finally accomplished by two methods. N-(*o*-Nitrophenylacetyl)-anthranilamide (V) was prepared by the condensation of anthranilamide with *o*-nitrophenylacetyl chloride and then converted to 2-(*o*-nitrobenzyl)-4-quinazolone (VI) by aqueous base.

N-(*o*-Nitrophenylacetyl)-anthranilic acid (VII) was readily dehydrated to 2-(*o*-nitrobenzyl)-4-keto-3,1,4-benzoxazine (VIII), which in turn was also converted to the desired quinazolone in good yield. This last reaction probably proceeds *via* the anthranilamide (V) since this intermediate has been isolated in certain analogous cases.[6]

The synthesis of 3-(*o*-nitrobenzyl)-4-quinazolone was based upon the work of Bogert and Geiger,[7] in which it was shown that the N-alkylation of sodium 4-quinazolonate could be carried out with benzyl chloride. The extent of O-alkylation involved in the benzylation has been determined, but the precaution was taken to destroy by acid hydrolysis any O-ether which may have formed.



Experimental[8]

Methyl N-(*o*-Nitrophenylacetyl)-anthranilate (I).—A benzene solution of O-nitrophenylacetyl chloride, prepared with thionyl chloride from 5 g. of the acid,[9] was added to a dry benzene solution containing 4 ml. of methyl anthranilate. To this mixture was added gradually with stirring 40 ml. of 25% potassium hydroxide.

After washing the *warm* benzene solution with acid and then removing the solvent, the residue was dissolved in hot acetone, decolorized with charcoal, cooled and crystallized. The yield was 6.0 g. (69%), m. p. 131–133°. Recrystallization from alcohol or acetone gave white crystals, m. p. 133.5–134°.

Anal. Calcd. for $C_{16}H_{14}N_2O_5$: C, 61.1; H, 4.49; N, 8.92. Found: C, 61.3; H, 4.64; N, 8.92.

Methyl N-(*o*-nitrophenylacetyl)-anthranilate (I) was heated in a bomb with absolute alcoholic ammonia for eight hours at 180°. A good yield of *o*-nitrophenylacetamide (II) was obtained in place of a cyclized product.

One gram of methyl N-(*o*-nitrophenylacetyl)-anthranilate (I) was refluxed for fifteen hours in 4 ml. of acetic anhydride. The reaction mixture was added cautiously to an excess of hot 14% ammonia, containing a few drops of 10% potassium hydroxide. The mixture was heated on the steam-bath for one hour, and then refluxed with an excess of potassium hydroxide to destroy the acetamide. The cooled, filtered solution was brought to neutrality with hydrochloric acid. After standing two days, 0.14 g. of crude 2-methyl-4-quinazolone (IV) crystallized. This material was recrystallized from alcohol and identified by a mixed melting point test.

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[1] Published with the approval of the Monographs Publication Committee, Oregon State College, as Research Paper No. 120, School of Science.

[2] Weddige, *J. prakt. Chem.*, [2] **36**, 145 (1887).

[3] Zacharias, *ibid.*, [2] **43**, 441 (1891).

[4] Thieme, *ibid.*, [2] **43**, 473 (1891).

[5] Private communication.

[6] Bogert, Amend and Chambers, THIS JOURNAL, **32**, 1297 (1910).

[7] Bogert and Geiger, *ibid.*, **34**, 527 (1912).

[8] All melting points are corrected.

[9] Mayer and Balle, *Ann.*, **403**, 188 (1914).

N-(*o*-Nitrophenylacetyl)-anthranilamide (V).—A dioxane solution of *o*-nitrophenylacetyl chloride prepared from 5 g. of the acid was added to 50 ml. of a dioxane solution, containing 7.6 g. of anthranilamide.[10]

After several hours the precipitate was removed, triturated with water, refiltered and thoroughly dried. Additional product was obtained by concentrating the dioxane solution. The combined fractions were decolorized and recrystallized from hot pyridine–benzene solution, yield, 6.06 g. (73%), m. p. 167–170°. Recrystallization from pyridine–benzene and pyridine–water gave product with m. p. 172–173°.

Anal. Calcd. for $C_{15}H_{13}N_3O_4$: C, 60.2; H, 4.38; N, 14.04. Found: C, 59.9; H, 4.64; N, 14.24.

2-(*o*-Nitrobenzyl-4-quinazolone (VI) from Nitrophenylacetylanthranilamide.—A mixture consisting of 3.46 g. of N-(*o*-nitrophenylacetyl)-anthranilamide (V), 12 ml. of pyridine, 12 ml. of water and 1 ml. of 10% sodium hydroxide after standing for one day at room temperature was made more basic by the addition of 75 ml. of 10% sodium hydroxide. The solution was then filtered and the crude product isolated by neutralizing the filtrate. The precipitate was extracted with boiling glacial acetic acid from which it crystallized on cooling; yield 2.85 g. (88%) of 2-(*o*-nitrobenzyl)-4-quinazolone, (VI). The product recrystallized from glacial acetic acid and pyridine–water for analytical purposes was white granular crystals, m. p. (dec.) 254.5°.

Anal. Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 64.15; H, 3.73; N, 14.76.

N-(*o*-Nitrophenylacetyl)-anthranilic Acid (VII).—A dioxane solution of *o*-nitrophenylacetyl chloride prepared from 5 g. of the acid was mixed with 50 ml. of dioxane solution containing 20 g. of anthranilic acid. After several hours the crude N-(*o*-nitrophenylacetyl)-anthranilic acid (VII) was removed by filtration, triturated with water and then recrystallized from glacial acetic acid. A second fraction was obtained by dissolving the residue left after evaporation of the mother liquor in dilute sodium hydroxide and then reprecipitating the product with hydrochloric acid, recrystallizing it from glacial acetic acid and dioxane–water. The yield was 82% (4.9 and 1.9 g.). This combined yield, recrystallized again, melted with slow evolution of gas, m. p. 224–225°.

Anal. Calcd. for $C_{15}H_{12}N_2O_5$: C, 60.0; H, 4.03; N, 9.33. Found: C, 60.1; H, 4.02; N, 9.03.

2-(*o*-Nitrobenzyl-4-keto-3,1,4-benzoxazine (VIII).—Five grams of N-(*o*-nitrophenylacetyl)-anthranilic acid (VII) was refluxed for thirty minutes in 20 ml. of pure acetic anhydride. Four and four-tenths grams of 2-(*o*-nitrobenzyl)-4-keto-3,1,4-benzoxazine (VIII) crystallized from the cooled and seeded solution, m. p. 162–164°. This product when recrystallized from pyridine–water, alcohol, then pyridine–alcohol gave white plates, m. p. 165–166°.

Anal. Calcd. for $C_{15}H_{10}N_2O_4$: C, 63.8; H, 3.57; N, 9.92. Found: C, 63.6; H, 3.85; N, 10.10.

2-(*o*-Nitrobenzyl-4-quinazolone (VI) from Nitrobenzylbenzoxazone.—A suspension of 5 g. of 2-(*o*-nitrobenzyl)-4-keto-3,1,4-benzoxazine (VIII) in 25 ml. of 50% pyridine was saturated with ammonia and allowed to stand with occasional stirring for six hours. One milliliter of 10% sodium hydroxide was then added and the mixture was set aside for an additional twenty-four hours. Isolation procedure was the same as for the synthesis from the anthranilamide; yield 3.6 g. (72%).

2-(*o*-Aminobenzyl)-4-quinazolone.—To a suspension of 5 g. of 2-(*o*-nitrobenzyl)-4-quinazolone in 300 ml. of dilute sodium hydroxide was added a solution containing 33 g. (10% excess) of hydrated ferrous sulfate in 100 ml. of water. The reaction mixture was maintained at 80° for seven hours. The ferrous–ferric hydroxides were separated by centrifuging and washed repeatedly with dilute sodium hydroxide until the wash liquors gave no further precipitate upon neutralization. Combined precipitates obtained by the neutralization of the washings and the mother liquor were decolorized with charcoal and recrystallized from pyridine–water. The yield of 2-(*o*-aminobenzyl)-4-quinazolone was 3.68 g. (80%). It was recrystallized for analysis from dioxane and dioxane–water; the white, voluminous powder melted (decomposition) over a wide range, starting at about 250°.

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.7; H, 5.21; N, 16.72. Found: C, 71.4; H, 5.32; N, 16.58.

2-(*o*-Acetaminobenzyl)-4-quinazolone.—The corresponding amino compound (1.0 g.) was acylated in the usual manner. The product was recrystallized from pyridine–water, and acetic acid–water, to yield white needles of m. p. 258°.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: N, 14.33; Found: N, 14.52.

3-(*o*-Nitrobenzyl)-4-quinazolone.—To an aqueous solution containing ten grams of *o*-nitrobenzyl chloride, prepared according to the directions of Haeussermann and Beck[11] was added 13 g. of 4-hydroxyquinazolone and 5.9 g. of 85% potassium hydroxide pellets and 200 ml. of alcohol.

After refluxing for six hours the alcoholic solvent was removed and replaced with a mixture of dilute hydrochloric acid and benzene. This mixture was refluxed for fifteen minutes to hydrolyze any benzyl quinazolyl ether. The benzene layer was then separated and thoroughly extracted with 3 *N* hydrochloric acid. The combined fractions were treated with an excess of sodium hydroxide and the crude product (3 g.) separated by filtration. After decolorizing with charcoal the product was recrystallized from benzene, pyridine–water and acetic acid–water to yield a pure white product m. p. 169–170°.

Anal. Calcd. for $C_{15}H_{11}N_3O_3$: C, 64.1; H, 3.94; N, 14.94. Found: C, 64.3; H, 4.12; N, 14.96.

3-(*o*-Aminobenzyl)-4-quinazolone.—A uniform suspension of 2.83 g. of 3-(*o*-nitrobenzyl)-4-quinazolone and 7.27 g. of stannous chloride dihydrate in 30 ml. of glacial acetic acid was prepared. The mixture was saturated with dry hydrogen chloride and allowed to stand for ten hours. The gummy precipitate which formed was dispersed by two or three minutes of gentle heating and the mixture was then poured into water. The aqueous suspension was made strongly basic with sodium hydroxide and filtered. The precipitate was extracted with boiling pyridine, and water was added to complete a crystallization from pyridine–water. The 1.62 g. (64%) of crude, white plates were decolorized with charcoal and recrystallized from alcohol, dioxane–water and pyridine, m. p. 178°.

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.7; H, 5.21; N, 16.72. Found: C, 71.5; H, 5.39; N, 16.69.

Summary

2-(*o*-Nitrobenzyl)-4-quinazolone was prepared by (1) the cyclization of N-(*o*-nitrophenylacetyl)-anthranilamide and (2) by ammonolysis of 2-(*o*-nitrobenzyl-4-keto-3,1,4-benzoxazine.

3-(*o*-Nitrobenzyl)-4-quinazolone was prepared by the reaction of *o*-nitrobenzyl chloride and sodium 4-quinazolonate.

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[10] Kolbe, *J. prakt. Chem.*, [2] **30**, 475 (1884); Erdmann, *Ber.*, **32**, 2164 (1899).

[11] Haeussermann and Beck, *Ber.*, **25**, 2445 (1892).