

II. When amine hydrochlorides were used, the reaction was carried out in the presence of 40% sodium hydroxide. The mycological findings will be described elsewhere.

### Summary

Twenty-four  $\alpha,\alpha$ -dichloroacetamides have been

prepared preliminary to their evaluation as fungicidal agents. Twenty-one of these are new compounds.

WASHINGTON, D. C.

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[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, SCHOOL OF SCIENCE, OREGON STATE COLLEGE]

## Quinazolines. VII. The Synthesis of Methyl 2,4-Dimethyl-8-quinazolyl Ketone<sup>1</sup>

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The problem of synthesizing amino alcohols from quinazoline compounds is best approached through the preparation of the acetyl or carboxy intermediate which by means of the Mannich or diazomethane reaction can usually be converted to the amino ketone and finally to the alcohol.

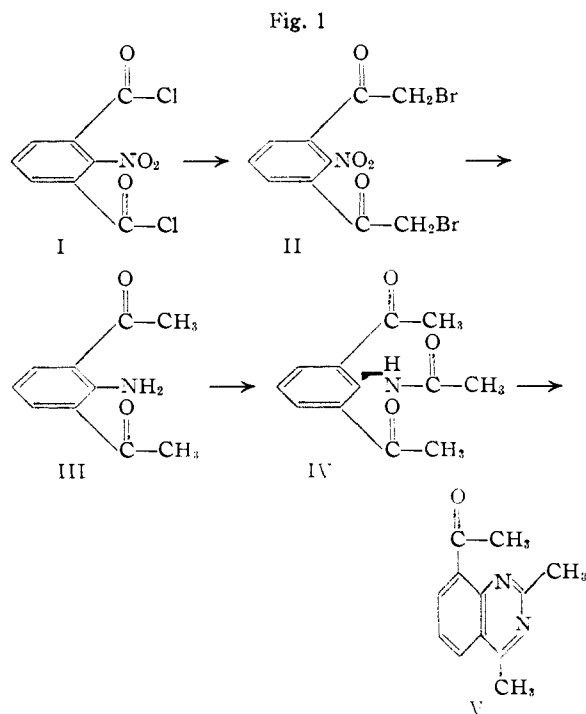
For example, in a recent study, *p*-toluic acid was used to synthesize acetamino-1,4-diacetylbenzene which on cyclization gave the 7-acetyl-2,4-dimethylquinazoline.<sup>2</sup> In the current work, *m*-toluic acid was nitrated<sup>3</sup> and then oxidized<sup>4</sup> to 2-nitroisophthalic acid which served as the initial intermediate for the continuation of these studies.

Fusion of 2-aminoisophthalic acid according to the directions of Niementowski<sup>5</sup> yielded 4-hydroxy-8-quinazolinecarboxylic acid, which was readily converted to the bromomethyl ketone by the usual procedures. Although there was evidence that the bromomethyl ketone would couple with various secondary amines, it was not possible to isolate any product because of the apparent instability of the amino ketone.

In the earlier work the intermediate 1,4-diacetylbenzene was obtained by the condensation of sodio acetoacetic ester and terephthalyl chloride followed by an acid and a basic hydrolysis, as described by Ruggli and Gassenmeier.<sup>6</sup> This method for the preparation of diacetylbenzene proved however to be a laborious process productive of low yields. For this reason 2-nitroisophthalyl chloride (I) (see Fig. 1) was converted to 1,3-dibromoacetyl-2-nitrobenzene (II), by means of the diazomethane reaction. The product subsequently was reduced with stannous chloride to the 2-amino-1,3-diacetylbenzene (III). This procedure proved to be so superior to the acetoacetic ester condensation that it was later used for the preparation of *p*-diacetylbenzene. The acetylation of the 2-amino-1,3-diacetylbenzene,

as one might predict, proved to be quite difficult, while the acetamino derivative (IV) gave poor yields on cyclization in contrast to other similar reactions.

The methyl 2,4-dimethyl-8-quinazolyl ketone (8-acetyl-2,4-dimethylquinazoline) (V) gave a Mannich product with cold aqueous formaldehyde and dimethylamine hydrochloride. Although the acetyl substituent appears to be the one most likely involved in this reaction the active methyl group in certain cases<sup>7</sup> are also reactive. Considering the fact that these condensations proceed at room temperature<sup>2</sup> together with the activity of certain groups at the 4-position<sup>8</sup> it is possible that the reaction may have involved an active methyl rather than the acetyl substituent.



(1) The work described in this paper was made possible by a grant in aid from the Research Corporation. Published with the approval of the Monograph Publications Committee, Oregon State College, as Research Paper No. 129, School of Science, Department of Chemistry.

(2) Christensen, Graham and Griffith, *THIS JOURNAL*, **67**, 2001 (1945).

(3) Muller, *Ber.*, **42**, 430 (1909).

(4) Vohl, *Ber.*, **43**, 3480 (1910).

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

(6) Ruggli and Gassenmeier, *Helv. Chim. Acta*, **22**, 496 (1939).

(7) Heou-Feo, *Compt. rend.*, **192**, 1242 (1931).

(8) Tomisek and Christensen, *THIS JOURNAL*, **67**, 2112 (1945).

This appears to be quite probable in view of the fact that similar experiments with 2,4-dimethylquinazoline yields a Mannich product; further-

more, the Mannich product from the 7-acetyl-2,4-dimethylquinazoline gave a positive haloform test. Because of the inconclusive evidence it was not possible to assign a definite structure to the condensation product. The reduction of the amino ketone hydrochloride yielded a very hygroscopic amino alcohol which was very similar to the 7 isomer.<sup>2</sup>

### Experimental

**4-Hydroxy-8-quinazolinecarboxylic Acid.**—Eleven grams of 2-aminoisophthalic acid and 20 ml. of formamide were heated at 130° for seven hours. One hundred ml. of water was added to the cooled reaction product which was then removed by filtration. The product was again suspended in 100 ml. of water, filtered, washed and air dried to yield 5.5 g. (47.5%) of a light yellow solid which titration data indicated to be only 95% pure. A small sample of this material was purified for analytical purposes by decolorization using charcoal and recrystallization from water; m. p. of light yellow crystals 310–315° with decomposition.

*Anal.* Calcd. for  $C_9H_6N_2O_3$ : C, 56.9; H, 3.18; N, 14.7; neut. equiv., 190. Found: C, 57.0; H, 3.7; N, 14.5; neut. equiv., 187.

**4-Hydroxy-8-quinazolinecarbonyl Chloride Hydrochloride.**—4-Hydroxy-8-quinazolinecarboxylic acid (4.3 g.) was refluxed for two hours with 45 ml. of thionyl chloride. Although complete solution was not attained the mixture was cooled, filtered, washed with several portions of dry ether and finally dried in vacuum over sodium hydroxide. The yield (4.8 g.) of a light yellow crystalline solid was insoluble in such ordinary inert solvents as benzene, carbon tetrachloride or chloroform, making further purification very difficult.

*Anal.* Calcd. for  $C_9H_6Cl_2N_2O_2$  (crude material): Cl, 29.0; Found: Cl, 27.0.

**8-Bromoacetyl-3-methylquinazol-4-one.**—Four grams (0.016 mole) of 4-hydroxy-8-quinazolinecarbonyl chloride hydrochloride was added in portions with stirring to 180 ml. of a cold benzene solution containing 0.125 mole of diazomethane. The evolution of gas was immediate with the color changing from yellow to orange after two hours of standing. The solution was then filtered to remove a small amount of unknown residue and then treated portionwise with dry hydrogen bromide.

It was necessary to exercise care in this latter operation since discharge of hydrogen bromide under the surface of the solution or the use of an excess of this reagent caused the formation of a hydrobromide which turned to a dark gummy hygroscopic mass immediately on exposure to air. The crude bromomethyl ketone (2.6 g., 57% yield) was removed by filtration; due to its solubility characteristics, it was difficult to purify. A small amount was purified for analytical purposes by dissolving it in acetone, decolorizing with charcoal and then adding heptane which precipitated a flocculent light yellow material, m. p. 165–185° (with decomposition).

*Anal.* Calcd. for  $C_{11}H_9BrN_2O_2$ : Br, 28.5; N, 9.96. Found: Br, 28.5; N, 9.90.

**2-Nitroisophthaloyl Chloride (I).**—One hundred grams of phosphorus pentachloride, 40 ml. of phosphorus oxychloride and 25 g. of 2-nitroisophthalic acid were placed in the above order in a reaction flask equipped with a reflux condenser. The mixture was very carefully heated to bring it to a fluid state after which the mixture was refluxed gently for ten hours. The contents of the flask were then slowly poured with stirring into approximately 900 g. of cracked ice. After the phosphorus pentachloride had been hydrolyzed the light yellow solid was removed by filtration, washed well with water and finally dried in vacuum over sodium hydroxide; the yield was 27 g. (92%) which contained only 93% of the theoretical chloride content.

A sample of the acid chloride recrystallized for analytical purposes from heptane and decolorized with

the aid of charcoal gave a white crystalline solid, m. p. 125–127°.

*Anal.* Calcd. for  $C_8H_5Cl_2NO_4$ : Cl, 28.6. Found: Cl, 28.0.

**1,3-Dibromoacetyl-2-nitrobenzene II.**—The crude, finely powdered 2-nitroisophthaloyl chloride (25 g., 0.1 mole) was added slowly to 900 ml. of a cold stirred solution of benzene containing 0.625 mole of diazomethane. After the acid chloride addition had been completed and gas evolution had subsided, the ice-bath was removed and the stirring continued for at least one hour. The cream-colored diazo ketone was removed by filtration, washed with benzene and immediately suspended in 300 ml. of ether. To the stirred suspension were added in portions 50 ml. of 48% hydrobromic acid which converted the diazo ketone to the bromomethyl ketone. After the evolution of nitrogen had ceased (about one hour) the white fluffy precipitate was removed, washed with water and dried in vacuum; yield 31.3 g. (84%). Recrystallization from either heptane or chloroform gave a white silky solid, m. p. 143°.

*Anal.* Calcd. for  $C_{10}H_7Br_2NO_4$ : Br, 43.8. Found: Br, 44.5.

**2-Amino-1,3-diacetylbenzene III.**—1,3-Dibromoacetyl-2-nitrobenzene (15.0 g.) was gradually added to 200 ml. of a stirred concentrated hydrochloric acid solution containing 75 g. of stannous chloride dihydrate. This mixture was then heated on a water-bath with stirring for two and one-half hours during which time most of the solid dissolved to yield a light red colored solution. The cooled mixture was then filtered and poured with stirring into 1100 ml. of water. The yellow precipitate which immediately formed was removed by filtration, washed with water and air dried; yield was 6.4 g. (88%). A sample decolorized by charcoal prior to recrystallization from water melted at 143–145°.

*Anal.* Calcd. for  $C_{10}H_{11}NO_2$ : C, 67.8; H, 6.26; N, 7.91. Found: C, 67.9; H, 6.50; N, 7.58.

**2-Acetamino-1,3-diacetylbenzene (IV).**—2-Amino-1,3-diacetylbenzene (2 g.) was acylated over a period of ninety minutes with refluxing acetic anhydride. The dark solution was poured into 100 ml. of an ice-water mixture which after one hour was filtered. The filtrate was evaporated to a very dark red viscous mass on a steam-bath. The dry residue was thoroughly extracted with three 40-ml. portions of warm ether, which on evaporation left 1.13 g. of extract. This crude product was dissolved in 60 ml. of hot petroleum ether (b. p. 97–140°) treated with charcoal and filtered. The cooled solution yielded 0.84 g. (34%) of light yellow crystals, m. p. 101–103°.

*Anal.* Calcd. for  $C_{12}H_{13}NO_3$ : C, 65.7; H, 5.98; N, 6.39. Found: C, 65.2; H, 6.27; N, 6.02.

**Methyl 2,4-Dimethyl-8-quinazolyl Ketone (8-Acetyl-2,4-dimethylquinazoline) V.**—A solution of 2-acetamino-1,3-diacetylbenzene was heated for one hour in a bomb at 105°. The alcohol was then removed under reduced pressure and the residue redissolved in 100 ml. water (solution was not always complete), decolorized with charcoal and cooled. A slow crystallization from the aqueous solvent gave 0.25–0.5 g. yield (23–46%) of white fibers, m. p. 97–98°. Usually another small crop of crystals could be obtained by concentrating the mother liquor.

*Anal.* Calcd. for  $C_{12}H_{12}N_2O$ : C, 72.0; H, 6.04; N, 14.0. Found: C, 72.1; H, 6.37; N, 13.8.

**Mannich Product Derived from 8-Acetyl-2,4-dimethylquinazoline.**—A solution of 1 g. of V, 0.43 g. of dimethylamine hydrochloride, 0.37 ml. of 40% aqueous formaldehyde and 25 ml. of absolute ethanol was stirred for four and one-half hours at room temperature; 20 ml. of dry ether was added and the solution was placed in refrigerator overnight. The yield of yellow product was 0.4 g.; further concentration and dilution with ether gave an additional 0.3 g. (total yield 41%). The product recrystallized from a small amount of isopropyl alcohol melted at 131–133°.

*Anal.* Calcd. for  $C_{11}H_{20}ClN_2O$ : Cl, 12.1; N, 14.3; Found: Cl, 12.0; N, 14.4.

**Reduced Mannich Product Derived from V.**—The Mannich product was hydrogenated in the usual manner with palladized charcoal catalyst at two atmospheres for two hours using methanol as a solvent. The product after vacuum drying at  $50^\circ$  was a very hygroscopic yellow plastic solid which gave no definite melting point.

The dipicrate of the amino alcohol was prepared from the ethereal solutions of both the free base and picric acid, m. p.  $92-94^\circ$ .

*Anal.* Calcd. for  $C_{27}H_{27}N_3O_3$ : C, 45.2; H, 3.79; N, 17.6. Found: C, 45.6; H, 3.81; N, 17.3.

### Summary

Directions for the synthesis of methyl 2,4-dimethyl-8-quinazolyl ketone and 4-hydroxy-8-quinazoline carboxylic acid from 2-nitroisophthalic acid are given.

CORVALLIS, OREGON

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

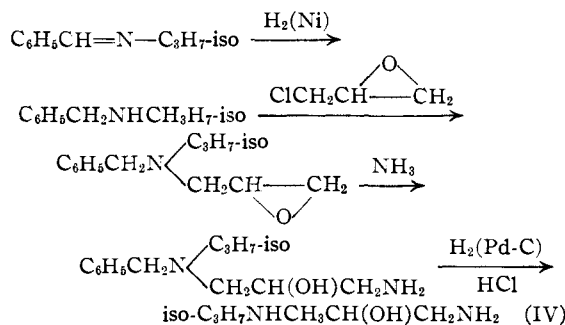
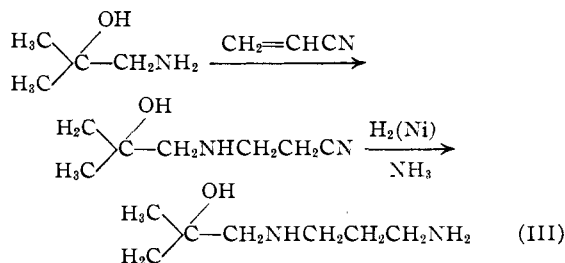
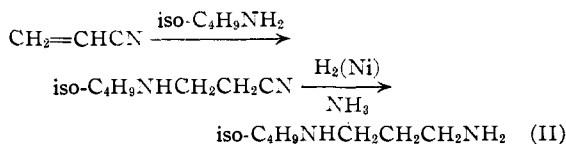
## Quinolines VI. Some 4-Aminoquinoline Derivatives

BY EDGAR A. STECK, LOUIS L. HALLOCK<sup>1</sup> AND C. M. SUTER

As has been well indicated in a monograph on the subject, a considerable portion of recent research on antimalarials has centered about 4-aminoquinoline derivatives,<sup>2</sup> chloroquine<sup>3</sup> (7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline<sup>4-6</sup> being the most important member of the series. The work described here was planned to determine certain aspects of the influence of structure upon activity in new 4-aminoquinoline types. Most of the compounds here reported bear an hydroxyl group in the basic side chain, as indicated in Table I.

The preparation of 4-(4-diethylamino-1-methylbutylamino)-quinoline has been mentioned in the patent literature,<sup>7,8</sup> but was synthesized from 4-chloroquinoline and 4-diethylamino-1-methylbutylamine (I) for purposes of comparison with related types and given the designation SN-6732.<sup>2</sup>

A number of amines were desired for reaction with 4,7-dichloroquinolines<sup>9</sup>; these included 3-isobutylaminopropylamine (II), 3-(2-hydroxy-2-methylpropylamino)-propylamine (III), 2-hydroxy-3-isopropylaminopropylamine (IV) and 2-(2-hydroxyethylamino)-ethylamine (V). Since only the last-mentioned of these was commercially available, the others were synthesized according to the equations.



4,7-Dichloro-3-methylquinoline<sup>9</sup> was readily obtainable, but 4,7-dichloro-6-methylquinoline had to be prepared for reaction with 4-diethylamino-1-methylbutylamine (I). The application of recent modifications<sup>10,11</sup> of the Conrad-Limpach synthesis<sup>12</sup> to 4-amino-2-chlorotoluene gave satisfactory results. The products obtained in the synthesis were apparently free of isomeric compounds which might have been formed during the cyclization. Since this was true, it was assumed that the quinolines produced were all 6,7-disubstituted rather than the alternative 5,6-type. These assumptions are in harmony with earlier work using ethyl ethoxymethylenemalonate in the preparation of related quinoline types.<sup>11,13</sup>

Of all the 4-aminoquinoline derivatives prepared in this investigation, the one having the most prom-

(1) Present address: Commercial Solvents Corp., Terre Haute, Ind.

(2) Wiselogle, editor, "Antimalarial Drugs, 1941-1945," Edwards Bros., Ann Arbor, Mich. All drugs identified by Survey Numbers (SN) in the files of the Antimalarial Survey office have been tabulated, together with antimalarial activities, in this monograph.

(3) Loeb, *et al.*, *J. Am. Med. Assoc.*, **130**, 1069 (1946).

(4) Andersag, Breitner and Jung, U. S. Patent 2,233,970.

(5) Surrey and Hammer, *THIS JOURNAL*, **68**, 113 (1946).

(6) Designated as SN-7618 by the Antimalarial Survey.<sup>2</sup>

(7) Zerweck and Kunze, German Patent 615,184; *Frdl.*, **22**, 485 (1939).

(8) Eli Lilly and Co., Brazilian Patent 35,166; *Diario Oficial (Brasil)* 934 (1945).

(9) Steck, Hallock and Holland, *THIS JOURNAL*, **68**, 380 (1946).

(10) Gould and Jacobs, *ibid.*, **61**, 2890 (1939).

(11) Price and Roberts, *ibid.*, **68**, 1204 (1946).

(12) Conrad and Limpach, *Ber.*, **20**, 944 (1887); Limpach, *ibid.*, **64**, 969 (1931).

(13) Riegel, *et al.*, *THIS JOURNAL*, **68**, 1264 (1946).