[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Quinazolines. I. Synthesis of an Amino Alcohol Derived from Quinazoline[1]

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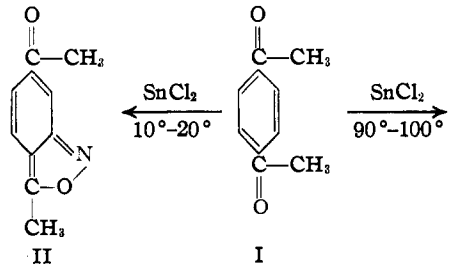
The synthesis of a gamma amino alcohol derived from quinazoline was undertaken as a continuation of a previous problem pertaining to similar compounds derived from pyrimidines.[2] The most obvious synthesis of such a compound entails the use of a Mannich reaction on an acetylquinazoline, followed by reduction. However, no acetylquinazoline had been previously reported in the literature.

Attempts to prepare acetylquinazolines by application of the Friedel-Crafts reaction to 2-methylquinazoline and to 2,4-dimethylquinazoline failed. Preliminary attempts to produce acetylquinazolines from quinazolinecarboxylic acid chlorides by the Blaise method did not seem promising. For these reasons a synthesis was devised in which the acetyl group was attached to the benzene nucleus which was later to become part of the quinazoline nucleus.

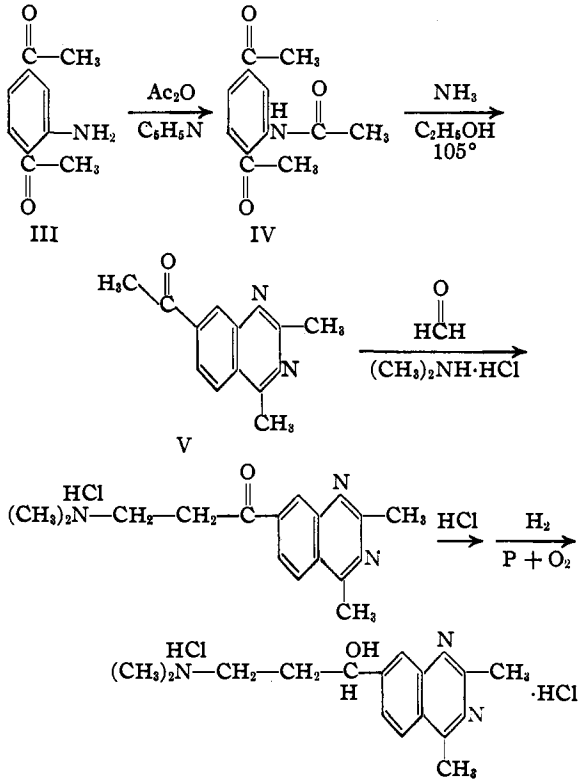
Bischler and Burkart[3] prepared 2,4-dimethylquinazoline by treating 2-acetylaminoacetophenone with alcoholic ammonia in a bomb at 130° for seven hours. A similar cyclization of 2-acetylamino-1,4-diacetylbenzene (IV) produced the desired 7-acetyl-2,4-dimethylquinazoline (V). The intermediate compound, 2-amino-1,4-diacetylbenzene (III), was synthesized in this laboratory by stannous chloride reduction of 1,4-diacetyl-2-nitrobenzene (I). The reduction produced 6-acetyl-3-methylanthranil (II) when the reaction temperature was kept at 10–20°. It was necessary to carry out the reaction at 90–100° to obtain (III).

The complete synthesis of the amino alcohol may be represented as shown.

The acetylquinazoline (V) produced a more satisfactory Mannich product with aqueous formaldehyde at room temperature than with paraformaldehyde at reflux temperatures.



II I



The amino ketone dihydrochloride was reduced readily with a platinum black catalyst at room temperature and two atmospheres of hydrogen.

Experimental

1,4-Diacetyl-2-nitrobenzene.—The synthesis used was essentially that of Ruggli and Gassenmeier, *i. e.*, the nitration of 1,4-diacetylbenzene with fuming nitric acid and acetic anhydride. However, it was found in this Laboratory that nitric acid of specific gravity 1.60 gave better results than the acid with a specific gravity of 1.52 recommended by the literature.[4] The compound we prepared melted at 63°. Ruggli and Gassenmeier reported a melting point of 46°. *Anal.* Calcd. for $C_{10}H_9NO_4$: N, 6.76. Found: N, 6.93.

6-Acetyl-3-methylanthranil.—1,4-Diacetyl-2-nitrobenzene (2 g.) was added to a solution of 8.2 g. of stannous chloride dihydrate in 21 ml. of concentrated hydrochloric acid. The reaction was maintained at 15–25° by a cold water-bath. A few seconds after the addition of the nitro compound, a white solid precipitated. This failed to dissolve even though the mixture was stirred for three hours. The mixture was diluted with 100 ml. of water and then extracted with ether. The ether extract was washed with dilute sodium carbonate solution and with water, before being dried over anhydrous calcium chloride; the ether extract yielded 1.5 g. of white solid; m. p., 113–114°. Analysis calculated for $C_{10}H_9NO_2$: C, 68.55; H, 5.18; N, 8.00. Found: C, 68.40; H, 5.52; N, 8.05.

2-Amino-1,4-diacetylbenzene.—1,4-Diacetyl-2-nitrobenzene (117 g.) was added to a solution of 500 g. of stan-

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(2) Christensen, *et al.*, THIS JOURNAL, **67**, 1294 (1945).

(3) A. Bischler and E. Burkart, *Ber.*, **26**, 1350 (1893).

(4) P. Ruggli and E. Gassenmeier, *Helv. Chim. Acta.*, **22**, 507 (1939).

nous chloride dihydrate in 1270 ml. of concentrated hydrochloric acid. The flask was warmed to 90° on a water-bath and maintained at this temperature for two and one-half hours with good stirring. During the reaction the solution became orange-colored; cooling failed to produce any precipitation. The solution was then neutralized with solid sodium carbonate. The resulting yellow precipitate was collected and the filtrate extracted with four liters of ether in one-liter portions. The ether extract was washed with sodium carbonate solution, and with water. After being dried with sodium sulfate, the ether was removed by distillation. The residue from the ether extraction and the precipitate collected by filtration were combined and crystallized from water. Seventy-five grams (76%) of yellow crystals was obtained; m. p. 125°. Further recrystallization from water did not change the melting point of the aminodiacetylbenzene. *Anal.* Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.45; H, 6.18; N, 7.69.

2-Acetylamino-1,4-diacetylbenzene.—Fifty grams of 2-amino-1,4-diacetylbenzene was treated with 150 ml. of acetic anhydride and 120 ml. of pyridine and the solution allowed to stand for sixty hours at 25°. The solution was poured into 600 ml. of water, cooled and filtered. The precipitate was crystallized from 2500 ml. of water. A gummy, brown impurity failed to dissolve in the boiling water and was removed by decantation. The cooled solution yielded 48 g. (78%) of long, white fibers melting at 103°. *Anal.* Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.85; H, 6.17; N, 6.35.

7-Acetyl-2,4-dimethylquinazoline.—A solution of 2-acetylamino-1,4-diacetylbenzene (12 g.) in 125 ml. of cold, saturated ammoniacal alcohol was heated in a bomb at 105° for one hour. The alcohol was evaporated. The residue was taken up in hot water, treated with charcoal and cooled. Six grams (55%) of white fibers precipitated. The compound, after being dried in an Abderhalden dryer, melted at 100°. *Anal.* Calcd. for $C_{12}H_{12}N_2O$: C, 71.97; H, 6.04; N, 13.99. Found: C, 71.87; H, 6.23; N, 13.93.

7-(3-Dimethylamino-1-oxopropyl)-2,4-dimethylquinazoline.—A solution of 7-acetyl-2,4-dimethylquinazoline (3.00 g., 0.015 mole), dimethylamine hydrochloride (1.22 g., 0.015 mole) and 1.12 ml. of 40% formaldehyde solution (0.015 mole) in 25 ml. of ethanol was shaken for four and one-half hours at room temperature. After cooling overnight in an icebox, the mixture was filtered and triturated with warm ether. Two grams (46%) of white powder resulted. A fraction of this product was recrystallized from ethanol yielding a precipitate that was gelatinous and difficult to filter. However, after being dried the product was a solid melting at 145–147°. The alcohol crystallization was not practical except for characterization purposes. *Anal.* Calcd. for $C_{15}H_{20}ClN_3O$: Cl, 12.07; N, 14.30. Found: Cl, 12.35; N, 14.30.

The mono-picrate of the amino ketone was prepared by dissolving a sample of the mono-hydrochloride in water and adding aqueous sodium picrate. The resulting precipitate, when recrystallized from absolute ethanol, melted at 162°. *Anal.* Calcd. for $C_{21}H_{22}N_6O_8$: C, 51.85; H, 4.56; N, 17.28. Found: C, 51.52; H, 4.38; N, 17.28.

The di-picrate prepared from an ethereal solution of the free base of the amino ketone and ethereal picric acid melted at 98–99°.

The mono-hydrochloride of the amino ketone (17 g.) was converted to the di-hydrochloride by passing dry hydrogen chloride into a methanol (200 ml.) solution of the former. The methanol was removed under a vacuum at 40°. The product was washed with boiling ethanol. The yield of white crystals, melting at 170–173°, was 14.2 g. (74%). *Anal.* Calcd. for $C_{15}H_{21}Cl_2N_3O$: Cl, 21.47; N, 12.72. Found: Cl, 20.65; N, 12.88.

Conversion of the mono-hydrochloride to the di-hydrochloride made possible the separation of impurities without too great a loss of product. The relative insolubility of the di-hydrochloride in ethanol is worthy of note.

7-(3-Dimethylamino-1-hydroxy-*n*-propyl)-2,4-dimethylquinazoline (SN 11,641[5]).—The di-hydrochloride of the amino ketone (14.2 g.) was dissolved in 160 ml. of methanol by warming and shaking. Platinum oxide catalyst (0.5 g.) was added and the compound was reduced at two atmospheres of hydrogen pressure and at room temperature. The theoretical amount of hydrogen had been absorbed at the end of one hour. The solution was filtered to remove the catalyst, and the methanol was evaporated under a vacuum. The resulting product was a very hygroscopic sirup that could not be crystallized with facility from the usual solvents. Drying at 78° in a good vacuum gave a white plastic solid. No satisfactory melting point could be obtained for the compound. *Anal.* Calcd. for $C_{15}H_{23}Cl_2N_3O$: Cl, 21.34; N, 12.65. Found: Cl, 21.0; N, 12.72, 12.73.

The di-picrate of the amino alcohol was prepared from an ethereal solution of the free base and ethereal picric acid. The resulting precipitate after being washed with ether and dried, melted at 78–80°. *Anal.* Calcd. for $C_{27}H_{27}N_9O_{15}$: C, 45.20; H, 3.79; N, 17.57. Found: C, 45.35; H, 3.46; N, 17.75.

Summary

7-Acetyl-2,4-dimethylquinazoline, synthesized by cyclization of 2-acetylamino-1,4-diacetylbenzene with ammoniacal alcohol, was subjected to a Mannich reaction, with subsequent reduction of the product; thus was formed a quinazoline possessing a dialkylaminoalcoholic substituent at its 7-position.

6-Acetyl-3-methylanthranil and 2-amino-1,4-diacetylbenzene were produced by stannous chloride reductions of 1,4-diacetyl-2-nitrobenzene.

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(5) The Survey number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey numbers have been assigned will be tabulated in a forthcoming monograph.