than that of the corresponding primary amines despite the greater basicity of the secondary amines. Steric factors would be expected to have a great effect and this is revealed by comparison of the dimethylamine value with that of the other amines of this class. The catalytic effects of diethylamine, di-*n*-propylamine and morpholine are almost the same. Even though morpholine is a weaker base than the other two, it is almost as active because of reduced steric hindrance around its nitrogen atom. Di-*n*-butylamine is the poorest catalyst of the amines studied.

Again the action of ethylene glycol in promoting the catalysis was observed. The molar value, 0.0305, for the rate constant of dimethylamine in ethylene glycol is far greater than the value, 0.00468, obtained by Miller and Kilpatrick[3e] for that amine in pure water at the same temperature, and Akerlof's results[3b] indicate that diethylamine shows practically no molecular catalysis in pure water.

Westheimer and Cohen[3h] were the first to show conclusively that the tertiary amines, trimethyl- and triethylamine, exhibit little or no molecular catalysis in the dealdolization of diacetone alcohol in water solution, although Koelichen[3a] and Akerlof[3b] had previously obtained data which showed the same lack of catalysis by those amines. The steric hindrance caused by the two methyl groups and the methylene group surrounding the hydroxyl group of diacetone alcohol should render most bases ineffective in the process by which hydroxyl ion catalyzes the breakdown.[3h] Nevertheless, there is no reason to suppose that other bases will not catalyze the reaction by the mechanism exhibited by the hydroxyl ion. Search for such catalysis should be made in non-aqueous media to avoid the domination by hydroxyl ion. With this and the promoting effect of ethylene glycol in mind, triethylamine was tried and definite evidence was found for catalysis by this base in anhydrous ethylene glycol. However, the rate of the reaction was too low to measure. This adds to the evidence that the catalysis by the other amines studied in this solvent is safely taken to be of the same type as found for these amines in water solution.

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

Quinazolines. XII. Mannich Reactions of 4-Methyl Substituted Quinazolines[1]

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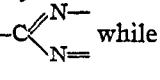
This work was undertaken to determine the structures of the Mannich products prepared from certain acetyl-2,4-dimethylquinazolines. Although this question has still not been settled further information pertaining to the reactivity of methyl substituents in the 2- and 4-positions have been obtained. The methylenic character of the 4-methyl substituent in 4-methyl and 2,4-dimethylquinazoline has been demonstrated by condensation reactions. The 4-methyl substituent acts as a methyl ketone in the presence of alkaline sodium hypobromite; the intermediate product 4-tribromomethylquinazoline has been isolated and identified. A new and improved procedure for the preparation of 4-methylquinazoline is described.

The structures of the amino alcohols prepared from the acetyl derivatives of 2,4-dimethylquinazoline *via* the Mannich reaction[2] have never been assigned due to the uncertainty as to which of the three methyl groups may have been involved in the condensation. This uncertainty stems from the unusually mild conditions necessary to obtain a Mannich product and the fact that Bogert and Nabenhauer had reported certain methyl substituents of methyl substituted quinazolines to be reactive.[3] Although the question of the structure of the Mannich products still has not been settled further information regarding the relative reactivity of methyl substituted quinazolines has been obtained.

The methyl substituents in 2-(and 4)-methylquinazolines are members of entirely different structural units. The 2-methyl substituent is part of an amidine structure  while the 4-methyl substituent is a typical ketimine 

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(2) Isensee and Christensen, THIS JOURNAL, 70, 4061 (1948).

(3) Bogert and Nabenhauer, *ibid.*, 46, 1932 (1924).

which may well impart methylenic character to the 4-methyl substituent. The 4-position in the quinazoline compounds has been found by Tomisek and Christensen[4] to be extremely reactive. Furthermore, similar structural units occurring in α-picoline,[5] 2-methylquinoline[5] and 1-(and 3)-methylisoquinoline[6] have been reported as having methyl substituents sufficiently active to undergo condensation reactions. In view of these considerations the decision was made to investigate the 2- and 4-methyl substituted quinazolines for methylenic activity.

2-Methylquinazoline[3] and 2,4-dimethylquinazoline[7] were prepared for these studies by well known procedures. 4-Methylquinazoline has been prepared by Bogert by the hydrolysis and decarboxylation of 4-methylquinazoline-2-carbonamide.[3] In this Laboratory a new and improved procedure for the preparation of this intermediate was perfected. 4-Methylquinazoline was obtained through the formylation of *o*-aminoacetophenone which in turn was cyclized to 4-methylquinazoline. As had been surmised, the methyl substituent in 2-methylquinazoline was sufficiently unreactive that it did not form condensation products with dimethyl-

(4) Tomisek and Christensen, *ibid.*, 67, 2112 (1945).

(5) Tseou, *Compt. rend.*, 192, 1242 (1931).

(6) Mills and Smith, *J. Chem. Soc.*, 121, 2724 (1922).

(7) Bischler and Burkart, *Ber.*, 46, 1349 (1893).

amine hydrochloride and aqueous formaldehyde; on the other hand, both the 4- and 2,4-dimethylquinazolines yielded the Mannich condensation products. The reactivity under these conditions is somewhat different from those reported by Bogert[3] who found that the methyl group in position 4 condenses less readily with phthalic anhydride than the one in position 2.

In order to confirm the structure assigned to the reaction product of 2,4-dimethylquinazoline, this derivative was subjected to hypobromite oxidation. This yielded a compound which was found to be identical to 2-methyl-4-quinazolone. When 2,4-dimethylquinazoline was subjected to a similar oxidation, it gave a white crystalline compound which was identified as 2-methyl-4-tribromomethylquinazoline; this compound on further treatment in hypobromite solution yielded in turn 2-methyl-4-quinazolone. Attempts to condense 4-methylquinazoline with benzaldehyde in the presence of zinc chloride gave tars from which no pure products could be isolated. This latter reaction at least confirmed the reactive properties of the 4-methyl substituent.

For purposes of documentation the 6-acetyl-2,4-dimethylquinazoline[8] was subjected to a Mannich reaction under conditions described for the 7-(and 8)-acetyl isomers.[2,9] A hypobromite oxidation of 6-acetyl-2,4-dimethylquinazoline yielded 6-carboxy-2-methyl-4-quinazolone.

Experimental

4-Methylquinazoline.—Ten grams (0.061 mole) of *o*-formamidoacetophenone[10] in 250 ml. of absolute alcohol was cooled in an ice-bath, saturated with ammonia, and then placed in a bomb which was maintained at 125–130° for 5 hours, and the alcohol was removed under vacuum. The residue was distilled *in vacuo* at 15 mm. and the fraction b.p. 126–128° was collected; yield 7.4 g. of light yellow oil (83–95%).

2-Methyl-4-(2-dimethylaminomethyl)-quinazoline Hydrochloride.—A mixture containing 2.0 g. (0.013 mole) of 2,4-dimethylquinazoline, 1.04 g. (0.013 mole) of dimethylamine hydrochloride, 0.95 ml. of 37% formaldehyde solution and 21 ml. of absolute alcohol was shaken for 4.5 hours at room temperature. After standing overnight in a refrigerator, the precipitate was filtered and washed with dry ether. The combined filtrates yielded a second crop of crystals. The total yield of colorless crystals, melting at 131.8–141.8°, was 1.28 g. (40.2%). *Anal.* Calcd. for $C_{13}H_{18}ClN_3$: C, 62.0; H, 7.16; Cl, 14.15. Found: C, 62.15; H, 7.24; Cl, 14.0.

4-(2-Dimethylaminoethyl)-quinazoline Hydrochloride.—The procedure was the same as given above. The yield of fine colorless crystals, melting at 133.4–134.4°, was 1.42 g. (40.6%). *Anal.* Calcd. for $C_{12}H_{16}ClN_3$: C, 60.5; H, 7.06; Cl, 14.9. Found: C, 60.4; H, 7.23; Cl, 14.8.

2-Methyl-4-(2-morpholinoethyl)-quinazoline Hydrochloride.—The procedure was the same as given above. The yield of colorless crystals, melting at 151.6–152.6°, was 1.32 g. (35.6%). *Anal.* Calcd. for $C_{15}H_{20}ClN_3O$: C, 61.3; H, 6.82; Cl, 12.1. Found: C, 61.6; H, 6.78; Cl, 12.2.

4-(2-Morpholinoethyl)-quinazoline hydrochloride: The procedure was the same as given above. The yield of colorless crystals, melting at 156.2–158.2°, was 2.19 g. (54.8%). *Anal.* Calcd. for $C_{14}H_{18}ClN_3O$: C, 60.0; H, 6.43; Cl, 12.7. Found: C, 60.0; H, 6.67; Cl, 12.7.

Mannich Reaction with 6-Acetyl-2,4-dimethylquinazoline.—The procedure was the same as given above. The yield of light yellow crystals was 0.85 g. (24.5%), m.p. 149° dec. *Anal.* Calcd. for $C_{15}H_{20}ClN_3O$: C, 61.2; H, 6.8; N, 14.3; Cl, 12.1. Found: C, 60.8; H, 7.0; N, 14.25; Cl, 12.11.

Oxidation of 2-Methyl-4-(2-dimethylaminoethyl)-quinazoline Hydrochloride.—To a solution of 1.38 g. (0.0055 mole) of 2-methyl-4-(2-dimethylaminoethyl)-quinazoline hydrochloride in 2.11 ml. of 10% sodium hydroxide and 13.2 ml. of water was added 25 ml. of sodium hypobromite solution (1.52 ml. of bromine in 25 ml. of 10% sodium hydroxide). The mixture became cloudy; upon warming an oily substance separated. After 15 minutes, an additional 13.2 ml. of sodium hypobromite was added which turned the orange solution to a yellow color. The mixture was diluted to 88 ml., and a saturated solution of sodium bisulfite was added until starch iodide paper no longer gave a positive test. The solution was filtered, acidified with concentrated nitric acid, extracted with two 22-ml. portions of ether, and then placed in a refrigerator. After three days, the solution was filtered, yield 0.19 g. (19–21.6%) of a light yellow crystalline precipitate. A sample recrystallized from water was identified as 2-methyl-4-quinazolone on basis of mixed m.p. and carbon and hydrogen data.

2-Methyl-4-tribromomethylquinazoline.—Twenty-five ml. of water was added to 1.0 g. (0.0063 mole) of 2,4-dimethylquinazoline. The hydrate thus formed was filtered and air-dried. The hydrate was dissolved in 25 ml. of dioxane and added very slowly with shaking to a solution of sodium hypobromite (1.06 ml. bromine in 25 ml. of 10% sodium hydroxide). The solution became warm and cloudy while a white solid separated. After the addition of 50 ml. of water, the solution was filtered and the precipitate air-dried, yield 1.28 g. (48–56%). An analytical sample recrystallized from *n*-heptane melted at 133.4–135.4°. *Anal.* Calcd. for $C_{10}H_7Br_3N_2$: N, 7.09; Br, 6.06. Found: N, 6.95; Br, 6.02.

One gram (0.0025 mole) of 2-methyl-4-tribromomethylquinazoline was dissolved in 10 ml. of dioxane and added in small portions to a solution of sodium hypobromite (0.425 ml. of bromine in 10 ml. of 10% sodium hydroxide). The solution was warmed on a water-bath until the white solid which separated went back into solution. After the addition of the sodium hypobromite, the solution was decanted from the oil which separated, evaporated to a thick paste in front of a fan, and then acidified with dilute sulfuric acid. The resulting precipitate was filtered, washed with a small amount of water, air-dried, yield 0.3 g. (74%) of white crystalline material. A sample was recrystallized from *n*-heptane and identified by a mixed melting point as 2-methyl-4-quinazolone.

6-Carboxy-2-methyl-4-quinazolone.—A solution of 1.0 g. (0.005 mole) of 6-acetyl-2,4-dimethylquinazoline,[2] 10 ml. of water and 8 ml. of dioxane was added slowly to 25 ml. of a sodium hypobromite solution (1.2 ml. of bromine in 25 ml. of 10% sodium hydroxide). Additional hypobromite solution was added to ensure an excess of this reagent. The solution was decanted from an oily material which separated and treated with sodium bisulfite until it no longer gave a test with starch iodide paper. The mixture was then extracted several times with 25-ml. portions of ether and then acidified with concentrated nitric acid and filtered; the yield, light tan colored crystals, 0.41 g. (41.8%). An analytical sample was prepared by dissolving it in dilute sodium hydroxide, treating with charcoal, and reprecipitating with nitric acid. The white powder gradually decomposed above 300°. *Anal.* Calcd. for $C_{10}H_8N_2O_3$: N, 13.71; neut. equiv., 204. Found: N, 13.3; neut. equiv., 203.5.

(8) Siegle and Christensen, THIS JOURNAL, **72**, 4186 (1950).
(9) Graham, *et al.*, *ibid.*, **67**, 2001 (1945).
(10) Camps, *Ber.*, **32**, 3232 (1899); **34**, 2708 (1901).

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