

ether and of piperonal with nitromethane in alcoholic sodium hydroxide solution.

CLEVELAND, OHIO

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, CASE SCHOOL OF APPLIED SCIENCE]

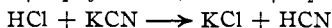
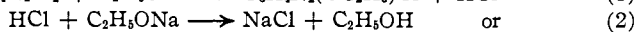
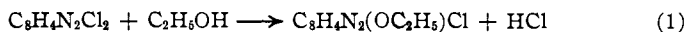
## QUINAZOLINES. II. THE INTERACTION OF 2,4-DICHLOROQUINAZOLINE IN ALCOHOL WITH SALTS AND BASES

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RECEIVED JUNE 26, 1931

PUBLISHED OCTOBER 5, 1931

In a previous communication<sup>1</sup> it was shown that when 2,4-dichloroquinazoline was treated with sodium alcoholates in the presence of phenols only the chlorine atom on position 4 was replaced yielding 2-chloro-4-alkoxyquinazolines, the chlorine atom on position 2 remaining unaffected. In attempting to prepare the nitrile of the as yet unknown quinazoline-2,4-dicarboxylic acid by treatment of dichloroquinazoline with potassium cyanide in alcoholic solution, the same reaction occurred with the formation of 2-chloro-4-ethoxyquinazoline; a similar treatment of dichloroquinazoline in methyl alcoholic solution gave the corresponding 2-chloro-4-methoxyquinazoline. From this it appears that such chloromonoethers are formed by the splitting out of hydrogen chloride as a result of the interaction of the alcohol and the chlorine atom on position 4; the sodium ethylate (or the potassium cyanide) acting as the salt of a weak acid subsequently removes the hydrogen chloride as it is formed and permits the reaction to proceed to completion; thus

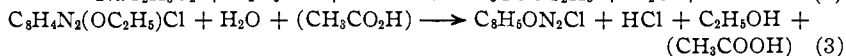
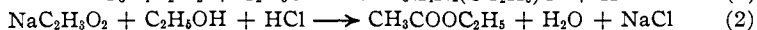


In the work previously reported, it was found more or less empirically that the best yields of the chloro-alkoxy derivatives were obtained by using dichloroquinazoline, sodium and phenol in the molar proportions of 1:2:1 in the presence of a large excess of alcohol; but when the proportion of phenol was increased, chlorophenoxyquinazoline was formed with a corresponding decrease in the yields of the chloroalkoxy compound. The reason for this is that when two molecular proportions of sodium are treated with an excess of alcohol and one molecular proportion of phenol is added, one-half of the sodium ethylate reacts to form sodium phenolate; greater proportions of phenol will reduce the amount of sodium ethylate available as an acid remover resulting in the formation of a correspondingly smaller amount of chloroalkoxyquinazoline; the increasing yields of the chlorophenoxy derivative with increasing amounts of sodium phenolate

<sup>1</sup> Lange, Roush and Asbeck, *THIS JOURNAL*, **52**, 3696 (1930).

indicate that the latter, unlike sodium ethylate, reacts directly with the dichloroquinazoline by splitting out sodium chloride to form chlorophenoxyquinazoline. Similar reactions with the chlorine atom on position 2 are much slower and judging from the reaction with potassium cyanide in alcohol (in which the chlorine atom on position 2 remains intact) are directly with sodium alcoholate and not with alcohol; the remarkably greater stability of this chlorine atom is shown by the fact that even some preparations of diethoxyquinazoline, from dichloroquinazoline and excess sodium ethylate in alcohol, yield appreciable amounts of chloroethoxyquinazoline.

These results led to attempts to replace the sodium ethylate or the potassium cyanide with other substances which might act in a similar manner as acid removers; sodium acetate which has been employed as an acid remover in halogenation reactions,<sup>2</sup> potassium cyanate and sodium carbonate suggested themselves as suitable for this purpose. Potassium cyanate and sodium carbonate were found to act in the same manner, yielding a chloroalkoxyquinazoline; sodium acetate, however, gave a different product. When a mixture of sodium acetate and dichloroquinazoline in alcohol was boiled for a short time, sodium chloride separated, and ethyl acetate, chloroethoxyquinazoline, benzoylene urea and a compound which appears from analysis to be 2-chloro-4-ketodihydroquinazoline are formed. Attempts to establish its constitution with more certainty by reduction to 4-keto-dihydroquinazoline, or by treatment with sodium ethylate to give 2-ethoxy-4-ketodihydroquinazoline, have not as yet succeeded. The mechanism of the formation of such a chloro-ketoquinazoline is probably as follows



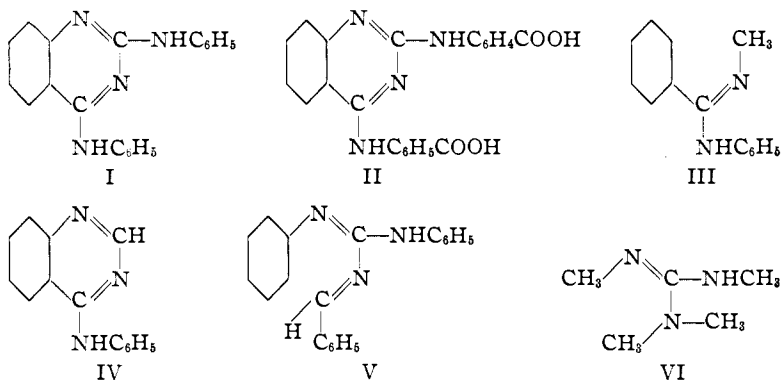
It was thought that aniline through salt formation with the hydrogen chloride might act as an acid remover, but the hydrochloride of a monobasic substituted diamine, 2,4-dianilinoquinazoline (I), was formed instead. The free base of this compound was found to crystallize with solvent of crystallization (alcohol); of the other anilinoquinazolines which are known, McCoy<sup>3</sup> records one containing alcohol of crystallization. Kötzt<sup>4</sup> has mentioned very briefly the interaction of 2,4-dichloroquinazoline with aniline, in a paper which he terms a preliminary report and in which he requests the reservation of this field of investigation to himself. A search of the literature to date does not disclose any further work with this reac-

<sup>2</sup> Raiford and Stoesser, *THIS JOURNAL*, **49**, 1078 (1927).

<sup>3</sup> McCoy, *Am. Chem. J.*, **21**, 166 (1899).

<sup>4</sup> Kötzt, *J. prakt. Chem.*, [2] **47**, 303 (1893).

tion. The aminobenzoic acids then suggested themselves as compounds suitable for this study. All three of these acids readily condense with dichloroquinazoline in alcoholic solution to form compounds which are probably the hydrochlorides of 2,4-dianilinoquinazoline dicarboxylic acids (II). The amphoteric nature and the difficulties encountered in their purification resulted in failure to isolate the free bases. The position of attachment of the hydrogen chloride in the salts of these bases remains



a matter of doubt. The substituted amidine<sup>5</sup> as shown by formula III also forms salts and has a central carbon atom somewhat analogous to the carbon atom in position 4 in formulas I, II and IV. We have prepared 4-anilinoquinazoline (IV) and found that it also forms a hydrochloride. The carbon atom in position 2, on the other hand, is situated as in guanidine. Of the somewhat similar guanidine derivatives the benzylidene-diphenylguanidine (V) seems to be unknown but the tetramethyl-,<sup>6</sup> triphenyl-, tetraphenyl- and pentaphenylguanidines<sup>7</sup> are known to form salts.

The difficulty of purification of the condensation products of dichloroquinazoline and the aminobenzoic acids is partly due to their amphoteric nature and for this reason the ester of one of them was prepared. The compound obtained by the interaction of methyl anthranilate and dichloroquinazoline is the dimethyl ester of 2,4-dianilinoquinazoline-*o,o'*-dicarboxylic acid hydrochloride (II). The values obtained on the analysis of this ester and its hydrolysis to the free dicarboxylic acid give assurance that the products obtained by condensation of the aminobenzoic acids with dichloroquinazoline are as shown by formula II; the discrepancies of the values found on the analyses of the hydrochlorides of the free acids with those calculated for hydrochlorides of formula II are due to similarities

<sup>5</sup> Von Pechmann, *Ber.*, 28, 2371 (1895).

<sup>6</sup> Schenk, *Z. physiol. Chem.*, 77, 328 (1912).

<sup>7</sup> Steindorf, *Ber.*, 37, 964 (1904); Beilstein, "Handbuch der org. Chem.," 4th ed., Vol. 12, p. 452.

in the solubilities of the compounds and their impurities, one of which is probably benzoylene urea.

All melting points recorded in this paper were determined with Anschütz short-scale thermometers, standardized by the U. S. Bureau of Standards, the entire mercury column being immersed in the heating medium.

### Experimental Part

**Preparation of 2-Chloro-4-ethoxyquinazoline,  $\text{N}=\text{COC}_2\text{H}_5\text{C}_6\text{H}_4\text{N}=\text{CCl}$ , with Potassium Cyanide.**—A mixture of 3 g. of 2,4-dichloroquinazoline<sup>8</sup> and 1.97 g. of potassium cyanide was covered with 50 cc. of ethyl alcohol and heated on the steam-bath for fifteen minutes (longer heating than fifteen minutes is unnecessary and only intensifies the color of the product). After cooling to room temperature it was poured into 500 cc. of water and allowed to stand for about fifteen minutes until the coagulation of the precipitate was complete. The yellow precipitate was filtered with suction, washed with water and pressed thoroughly on the filter; it was then dissolved in alcohol, filtered from a small amount of insoluble matter and allowed to crystallize on cooling and standing; after a recrystallization from alcohol, the product was washed with a little cold alcohol and dried at 40°; 1.5 g. of golden-yellow needles melting at 91° was obtained. The melting point was unchanged when mixed with a colorless sample of the same compound prepared by the method using sodium ethylate and sodium phenolate in place of the potassium cyanide. The combined mother liquors gave a precipitate on the addition of water and this precipitate on recrystallization from alcohol gave a further 0.9 g. of the same compound. The yellow color which permeates the crystals is probably due to impurities in the phosphorus pentachloride which was used in the preparation of the dichloroquinazoline. Specimens of the yellow chloro-ethoxyquinazoline on boiling with dilute hydrochloric acid were hydrolyzed to benzoylene urea. Similarly on warming with normal sodium hydroxide solution, hydrolysis occurs with the formation of the soluble sodium salt of benzoylene urea, from which benzoylene urea is precipitated on acidification of the alkaline solution. When the chloro-ethoxyquinazoline was added to an excess of sodium dissolved in ethyl alcohol, the mixture allowed to stand overnight, then poured into water and the precipitate recrystallized from alcohol, short, fine, very light yellow needles of 2,4-diethoxyquinazoline were obtained, m. p. 55°; mixed with a colorless specimen of diethoxyquinazoline, the melting point was unchanged.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_9\text{ON}_2\text{Cl}$ : Cl, 17.0. Found: Cl, 16.8.

**Preparation of 2-Chloro-4-methoxyquinazoline,  $\text{N}=\text{COCH}_3\text{C}_6\text{H}_4\text{N}=\text{CCl}$ , with Potassium Cyanide.**—This compound was prepared in a methyl alcoholic solution in the same manner as the analogous chloro-ethoxyquinazoline described above; 2.7 g. of product was obtained from 3 g. of dichloroquinazoline, 1.97 g. of potassium cyanide and 50 cc. of methyl alcohol. Two recrystallizations and a washing with ethyl alcohol gave 1.7 g. of short, fine, slightly yellow needles, m. p. 96°; a crystallization from acetone raised the melting point to 99°. The melting point was unchanged when mixed with chloro-methoxyquinazoline prepared by the method using sodium ethylate and sodium phenolate in place of potassium cyanide.

*Anal.* Calcd. for  $\text{C}_9\text{H}_7\text{ON}_2\text{Cl}$ : Cl, 18.2. Found: Cl, 17.2, 17.9.

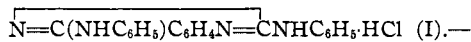
<sup>8</sup> Gabriel and Stelzner, *Ber.*, 29, 1300 (1896); Gabriel and Colman, *ibid.*, 38, 3559 (1905).

**Preparation of 2-Chloro-4-ethoxyquinazoline with Potassium Cyanate and with Sodium Carbonate.**—Twenty cc. of 95% ethyl alcohol, 2 g. of potassium cyanate and 3 g. of dichloroquinazoline were boiled on a steam-bath for seven hours and filtered hot; on cooling 0.7 g. of 2-chloro-4-ethoxyquinazoline separated, which after washing with a little alcohol and drying at 40° was found to melt at 92°; a second crop of crystals, m. p. 90–92°, weighing 0.6 g. was obtained by adding a little water to the filtrate; the mother liquors from these crystallizations contained unchanged dichloroquinazoline. In a similar manner 0.5 g. of the chloroethoxyquinazoline was obtained on boiling a mixture of 3 g. of dichloroquinazoline, 1.7 g. of anhydrous sodium carbonate and 20 cc. of ethyl alcohol; the mother liquors contained unchanged dichloroquinazoline.

**Preparation of (2?)-Chloro-(4?)-ketodihydroquinazoline,  $\text{HN}=\overline{\text{COC}_6\text{H}_4\text{N}}=\text{CCl}$ .**—Forty cc. of 95% ethyl alcohol, 3.6 g. of dichloroquinazoline and 2 g. of fused sodium acetate were boiled on a steam-bath for one hour, then cooled and filtered from 0.9 g. of benzoylene urea which had separated; 0.5 g. of fused sodium acetate was added to the filtrate and the boiling continued for one hour; the mixture was cooled, filtered and the filtrate evaporated to dryness, the residue washed with water, dissolved in cold normal sodium hydroxide solution and filtered from 0.6 g. of insoluble chloroethoxyquinazoline (m. p. 92°). Acetic acid was added to the alkaline filtrate until it was just acid to litmus, causing a precipitate to form; recrystallization of this precipitate from alcohol gave 1.0 g. of colorless needles, m. p. 211°. This compound is soluble in sodium hydroxide and is reprecipitated unchanged on the addition of acid; on warming with dilute hydrochloric acid in an aqueous alcoholic solution it is hydrolyzed to benzoylene urea, m. p. 351°. Attempts to replace the chlorine with hydrogen by reduction in various ways and thus obtain the known 4-ketodihydroquinazoline were not successful; heating the compound for a period of seven days with sodium ethylate in ethyl alcohol at a temperature of 100° in order to obtain the known 2-ethoxy-4-ketodihydroquinazoline also was not successful. Because of the stability of the halogen-carbon bond, the hydrolysis to benzoylene urea and the solubility in aqueous sodium hydroxide, it seems most likely that this compound is 2-chloro-4-ketodihydroquinazoline and that its formation is a result of the loss by hydrolysis of one of the halogen atoms in dichloroquinazoline.

*Anal.* Calcd. for  $\text{C}_8\text{H}_6\text{ON}_2\text{Cl}$ : C, 53.18; H, 2.79; Cl, 19.6. Found: C, 53.78; H, 2.77; Cl, 19.2.

**Preparation of 2,4-Dianilinoquinazoline Hydrochloride,**



A solution of 1 g. of dichloroquinazoline and 0.5 cc. of aniline in 25 cc. of alcohol was heated to boiling on the steam-bath; the solution became pale yellow in color and after a few minutes rosets of fine needles began to separate; after half an hour considerable crystalline material had separated which was removed by filtration, washed with alcohol and dried at 40°; 1.6 g. of microcrystalline needles was obtained which show a slight softening at 300° and melt at 317°. An almost colorless product was obtained by boiling with acetone. Condensation in a similar manner gave 1.3 g. of product when 1 g. of dichloroquinazoline and 1 cc. of aniline were used; 5 g. of dichloroquinazoline and 4.5 cc. of aniline in 125 cc. of alcohol gave 6.9 g. of product. It is slightly soluble in much boiling alcohol, from which it slowly crystallizes as flocculent colorless particles; it is quite soluble in boiling pyridine, from which it slowly separates in minute flakes on cooling; it is insoluble in boiling acetone, chloroform, ether or petroleum ether. The compound is unaffected by boiling with water or hydrochloric acid. When boiled with normal sodium hydroxide solution it slowly dissolved; the solution was filtered from the insoluble material and after standing for several days

the filtrate deposited long, colorless needles which were removed, dissolved in hot water, filtered and the hot filtrate acidified with hydrochloric acid; the fine colorless needles which formed were benzoylene urea, m. p. 352°. The high value obtained for hydrogen on analysis was due to hydrogen chloride which passed through the combustion tube; the water from the combustion which condensed in the entrance tube of the water absorber was acid and was contaminated with hydrogen chloride.

*Anal.* Calcd. for  $C_{20}H_{17}N_4Cl$ : C, 68.84; H, 4.92; Cl, 10.2. Found: C, 68.44; H, 5.45; Cl, 10.5.

#### Preparation of 2,4-Dianilinoquinazoline Alcoholate,



To 0.9 g. of sodium in 150 cc. of alcohol was added 6 g. of 2,4-dianilinoquinazoline hydrochloride and the solution allowed to stand overnight, when a small quantity of sodium chloride was found to have separated; it was then poured into 600 cc. of water, the yellow gummy clots which precipitated were removed by filtration and allowed to air dry. This material was dissolved in warm alcohol, filtered from a small amount of insoluble sediment and the filtrate concentrated on the steam-bath. When the convection currents seen in the oily solution indicated approximately the correct concentration, the solution was cooled, seeded with a small crystal of the alcoholate (from previous preliminary experiments) and set aside for two days to crystallize. The long standing converts almost all of the solution into a mass of needle-like tufts and markedly improves the yields. The crystals were filtered with suction, washed with a little alcohol and air dried; 4.1 g. of lustrous needles with a faint yellow tinge, similar to *m*-dinitrobenzene in appearance, were obtained; the compound melts rather indefinitely around 65°. It is very soluble in acetone or ether; soluble in ethyl alcohol, methyl alcohol, carbon tetrachloride, ethyl acetate, benzene or toluene; it is slightly soluble in petroleum ether. A methyl alcoholic solution cooled with liquid air gave granular, light yellow crystals melting indefinitely at 70–75°. Determination of loss in weight on heating to 94° was made on a sample which had been brought to constant weight by previous drying at 40°; the curve which was obtained by plotting loss in weight against time became linear around 9.2% loss in weight. The residue after loss of 9.2% of the weight of the original product was a hard, brittle, glassy mass which melted indefinitely around 75°.

*Anal.* Calcd. for  $C_{20}H_{16}N_4 \cdot C_2H_5OH$ : C, 73.70; H, 6.19;  $C_2H_5OH$ , 12.85. Calcd. for  $C_{20}H_{16}N_4 \cdot \frac{1}{2} C_2H_5OH$ :  $C_2H_5OH$ , 6.87. Calcd. for  $C_{20}H_{16}N_4 \cdot 9.2\% C_2H_5OH$ : C, 74.60; H, 5.90. Calcd. for  $C_{20}H_{16}N_4$ : C, 76.88; H, 5.17. Found: (1) C, 74.58; H, 6.10; (2) C, 74.07; H, 5.93; (3) C, 74.49; H, 5.58; (4) C, 73.87; H, 5.71; (5) C, 73.90; H, 5.73; (6) C, 77.17; H, 5.03.

Analyses 1 and 2 are on the same sample kept at 40° and analyzed on succeeding days; 3 was on a specimen again recrystallized from alcohol and dried at 40°; 4 and 5 are on a sample that was air dried at room temperature and evidently contains a higher percentage of alcohol; 6 was on the residue after having lost 9.2% of its weight by heating at 94° to constant weight and agrees with the formula for the compound free from solvent of crystallization.

The salts of 2,4-dianilinoquinazoline are readily precipitated from an alcoholic solution of the alcoholate by gradually adding acid either alone or in an alcoholic solution. The following salts were prepared.

**2,4-Dianilinoquinazoline Hydrochloride**,  $C_{20}H_{16}N_4 \cdot HCl$ .—This compound is instantly precipitated on adding a few drops of aqueous hydrochloric acid to an alcoholic solution of the base. Thus obtained it was almost colorless; it softens at about 304° and melts 317°.

**2,4-Dianilinoquinazoline Sulfate**,  $(C_{20}H_{16}N_4)_2 \cdot H_2SO_4$ .—Addition of concentrated sulfuric acid to the alcoholic solution of the base precipitated the sulfate; after filtering with suction, washing with a large amount of water and drying at  $40^\circ$  it had a light yellow color. Thorough washing with water was necessary to remove the last traces of sulfuric acid, the presence of which caused a decided lowering of the melting point. It forms extremely minute crystals which are insoluble in alcohol, ether, acetone, toluene or water; m. p.  $295^\circ$ .

*Anal.* Calcd. for  $C_{40}H_{34}O_4N_8S$ : S, 4.44. Found: S, 4.61.

**2,4-Dianilinoquinazoline Acetate**,  $C_{20}H_{16}N_4 \cdot CH_3COOH \cdot H_2O$ .—This salt separated rather slowly on adding glacial acetic acid to a solution of the base in alcohol. After washing with water and drying at  $40^\circ$  it was a granular crystalline solid consisting of clusters of fine needles, m. p.  $148^\circ$ .

*Anal.* Calcd. for  $C_{20}H_{16}N_4 \cdot C_2H_4O_2 \cdot H_2O$ : C, 67.66; H, 5.68. Found: C, 67.96; H, 5.45.

Other salts similarly obtained but which were not analyzed were the nitrate, m. p.  $223^\circ$ ; the oxalate, m. p.  $253^\circ$ ; the picrate which forms deep yellow, microscopic needles which are very slightly soluble in hot alcohol or hot acetone, insoluble in ether or toluene, softening at about  $250^\circ$  and melting at  $275^\circ$ .

**Preparation of 2,4-Dianilinoquinazoline-*p,p'*-dicarboxylic Acid Hydrochloride,**

$N=C(NHC_6H_4CO_2H)C_6H_4N=C(NHC_6H_4COOH)HCl$  (II).—A hot filtered solution of 1 g. of dichloroquinazoline in 25 cc. of alcohol was added to a solution of 1.5 g. of *p*-aminobenzoic acid in 25 cc. of alcohol; the mixture was heated on the steam-bath for twenty minutes (crystals began to separate after the first few minutes of heating), cooled, filtered with suction, the precipitate washed with alcohol and dried; the 2.1 g. of product thus obtained was washed with hot acetone until nearly colorless; m. p.  $345^\circ$ . In a similar manner 4.8 g. of product was obtained from 3 g. of dichloroquinazoline and 4.2 g. of *p*-aminobenzoic acid. The compound is insoluble in ether, acetone, toluene, petroleum ether or water; it is soluble in aqueous sodium hydroxide or sodium carbonate, from which solutions it is again precipitated on the addition of hydrochloric acid; the product obtained by precipitation with acid from an alkaline solution had a melting point of  $347^\circ$  and was used for analysis. When boiled with water for some hours, filtered and dried, the melting point was lowered, due possibly to partial hydrolysis with loss of hydrogen chloride. It dissolved in warm pyridine; dilution of the solution with water gave no precipitate until most of the pyridine had been removed by evaporation, when semi-crystalline crusts of material with unchanged melting point separated. Treated with a slight excess over three moles of sodium ethylate in alcohol and allowed to stand overnight, it gave a copious yellow precipitate which dissolved on pouring into water. The alcohol was removed by evaporation with heat, a few drops of hydrochloric acid added (to remove any free alkali), the solution filtered and an aqueous solution of copper sulfate added. The apple-green precipitate which separated was filtered with difficulty and washed with water; after drying at  $40^\circ$  it consisted of hard, shiny, dark green particles which decrepitated on heating; on treating with a few drops of nitric acid it began to foam and on warming suddenly exploded. The pulverized copper salt ignited smoothly, giving off vapors with an unpleasant odor. The high result on the copper determination of this compound indicates the presence of cupric hydroxide as an impurity. Suspending the copper salt in water, passing in hydrogen sulfide and extracting the organic matter from the precipitated cupric sulfide with alcohol gave an impure material with a melting point of about  $283^\circ$ . Attempts to crystallize the sodium salt resulting from the treatment with sodium ethylate were not successful. The values obtained on analysis of this compound and its isomers to be described

below would indicate that the substances are certainly isomeric, although the formulas given to them are not confirmed with certainty by the analyses, a result which is most likely caused by impurities which could not be removed.

*Anal.* Calcd. for  $C_{22}H_{14}O_4N_4Cu$ : Cu, 13.77. Found: Cu, 15.77. Calcd. for  $C_{22}H_{17}O_4N_4Cl$ : C, 60.46; H, 3.92; N, 12.8; Cl, 8.12. Found: C, 58.75, 58.46; H, 3.74, 3.79; N, 8.37; Cl, 8.1.

**2,4-Dianilinoquinazoline-*m,m'*-dicarboxylic acid hydrochloride**, prepared like the *p,p'*-isomer from 1 g. of dichloroquinazoline and 1.4 g. of *m*-aminobenzoic acid, gave 2.0 g. of product, m. p. 344°. The solubilities are the same as those of the *p,p'*-isomer; washing with hot water, hot alcohol and finally with hot acetone gave a product melting at 335° and containing only 7.0% chlorine; evidently hydrolysis had occurred.

*Anal.* Calcd. for  $C_{22}H_{17}O_4N_4Cl$ : C, 60.46; H, 3.92; N, 12.8; Cl, 8.12. Found: C, 58.38; H, 3.77; N, 9.03; Cl, 8.2.

**2,4-Dianilinoquinazoline-*o,o'*-dicarboxylic Acid Hydrochloride**.—A yield of 1.7 g. of this compound was obtained by the interaction of 1.4 g. of anthranilic acid and 1 g. of dichloroquinazoline. Washing successively with hot water, hot alcohol and hot acetone gave a product containing only 3.7% chlorine; evidently the hydrolysis had been greater than in the case of the *m,m'*-isomer on similar treatment. This material was suspended in concentrated hydrochloric acid and allowed to stand overnight, filtered, washed with ether, alcohol, ether and dried first *in vacuo* over sulfuric acid and stick sodium hydroxide at room temperature and then in an oven at 40°; the product thus obtained melted at 271° with preliminary softening at 210° and was used for analysis.

*Anal.* Calcd. for  $C_{22}H_{17}O_4N_4Cl$ : C, 60.46; H, 3.92; N, 12.8; Cl, 8.12. Found: C, 57.87; H, 3.98; N, 11.2; Cl, 8.0.

#### Preparation of 2,4-Dianilinoquinazoline-*o,o'*-dicarboxylic Acid Dimethyl Ester

**Hydrochloride**,  $N=C(NHC_6H_4CO_2CH_3)C_6H_4N=C(NHC_6H_4COOCH_3)HCl$ .—To a filtered solution of 1 g. of dichloroquinazoline in 25 cc. of alcohol was added 1.6 g. of methyl anthranilate and the mixture refluxed on the steam-bath for half an hour. The crystals which began to separate within the first few minutes soon dissolved; cooling the solution at the end of the period of heating caused no separation. The solution was poured into 200 cc. of water, the precipitate which formed was filtered with suction, dried at 40° and weighed 1.5 g. On boiling with alcohol to which a few drops of hydrochloric acid were added, the material dissolved and immediately began to separate as fine, colorless prisms; m. p. 261°. A second experiment in which 2.3 g. of methyl anthranilate was added to a filtered solution of 0.95 g. of dichloroquinazoline in 25 cc. of alcohol, the solution concentrated to half of the volume on the steam-bath gave 1 g. of the same material after standing for three days, m. p. 261°. This compound is very slightly soluble in alcohol, aqueous sodium hydroxide or hot concentrated hydrochloric acid. When heated it shrinks at about 160°, undergoes a partial melting with evolution of gas at 181° and finally melts at 261°. Several hours of warming with aqueous, normal sodium hydroxide, filtering and acidifying the filtrate with hydrochloric acid gave a gelatinous precipitate of the free *o,o'*-dicarboxylic acid hydrochloride mentioned above, which is formed by saponification of the two methyl groups, m. p. 278°. This melting point, which is 7° higher than that of the same compound obtained directly from anthranilic acid and dichloroquinazoline, indicates a product of higher purity.

*Anal.* Calcd. for  $C_{24}H_{21}N_4O_4Cl$ : C, 61.98; H, 4.56; Cl, 7.63. Found: C, 61.80; H, 4.62; Cl, 7.23.



## Preparation of 4-Anilinoquinazoline Hydrochloride,

(IV).—A mixture of 2 g. of 4-chloroquinazoline<sup>9</sup> and 1 cc. of aniline was heated to 100°; after the chloroquinazoline had melted, a vigorous reaction occurred and the mixture solidified to a stiff, pasty mass; alcohol was added and the hot solution was filtered; on cooling, rosetts of short yellow needles separated; a second crystallization from alcohol gave 1.5 g. of material of a lighter color, melting at 251°; the compound is soluble in water, ethyl alcohol or methyl alcohol and insoluble in benzene, ether, chloroform or acetone.

*Anal.* Calcd. for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>Cl: Cl, 13.77. Found: Cl, 14.0.

Preparation of 4-Anilinoquinazoline,  $\overline{\text{N}=\text{C}(\text{NHC}_6\text{H}_5)\text{C}_6\text{H}_4\text{N}=\text{CH}}$ , (IV).<sup>10</sup>—An alcoholic solution of sodium ethylate was added, drop by drop, to 1 g. of 4-anilinoquinazoline hydrochloride dissolved in warm alcohol until the solution was alkaline to litmus; after standing for one-half hour it was poured into 200 cc. of water and the aqueous solution heated to coagulate the precipitate, which was then removed by filtering, washed with cold water and air dried at room temperature; recrystallization from alcohol gave 0.75 g. of light yellow crystals which are soluble in ethyl alcohol, methyl alcohol, benzene, ether, acetone or chloroform and insoluble in water, m. p. 221–222°. An alcoholic solution of the compound when treated with concentrated hydrochloric acid regenerated the hydrochloride salt described above; addition of picric acid in alcohol to an alcoholic solution of the free base precipitated the picrate salt, which was recrystallized from alcohol forming long, yellow needles melting at 233°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>: C, 75.98; H, 5.01. Found: C, 76.07; H, 4.59; C, 75.93; H, 4.82.

## Summary

New methods have been found for preparing 2-chloro-4-alkoxyquinazolines from 2,4-dichloroquinazoline and from these an explanation of the mechanism of their formation has been devised. A partial hydrolysis of the dichloroquinazoline wherein one of the halogens is replaced by an hydroxyl group was observed in one case. Primary aromatic amines have been found to react readily with dichloroquinazoline with the elimination of hydrogen chloride and the substitution of two aryl amino groups, forming substituted diamines which are monobasic. The following new compounds have been prepared: 2,4-dianilinoquinazoline, its alcoholate and six of its salts; chloro-ketoquinazoline; 4-anilinoquinazoline and two of its salts; the *o,o'*-, *m,m'*-, and *p,p'*-isomers of 2,4-dianilinoquinazoline dicarboxylic acid hydrochloride; and the dimethyl ester of 2,4-dianilinoquinazoline-*o,o'*-dicarboxylic acid hydrochloride.

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<sup>9</sup> Niementowski, *J. prakt. Chem.*, [2] 51, 566 (1895).

<sup>10</sup> The writers are indebted to Mr. H. A. Robinson for the preparation of this compound and its salts.