[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF MOUNT HOLYOKE COLLEGE]

THE CONDENSATION OF 4,6-DICHLOROQUINAZOLINE WITH ETHYLAMINOETHANOL AND WITH 2-CHLOROETHYLETHYLAMINE. THE FORMATION OF A TRICYCLIC FUSED RING COMPOUND[1]

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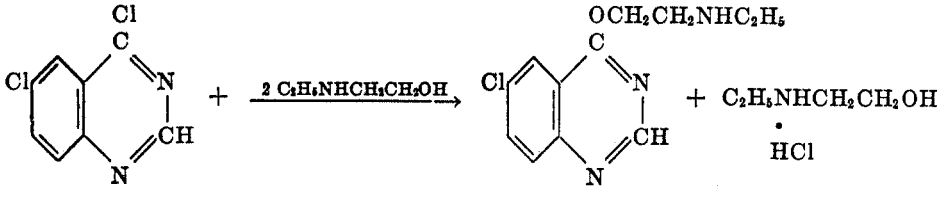
Previous investigations have demonstrated the condensation of 4-chloroquinazolines with primary alcohols (1–4), with the hydroxyl group of dialkylaminoalcohols (4), with primary amines and the amino group of primary aminoalcohols (5), and with the amino group of dialkylaminoalkyl amines (6–9). Two cases of cyclic secondary amines, piperidine and morpholine, condensing with 4-chloroquinazoline have been reported (5). In cases where diamines of the type $H_2NCH_2CH_2CH_2NHR'$ (10, 11) were used the condensation was at the primary amine and not the secondary amino group.

The present study was undertaken to see whether the condensation of 4-chloroquinazolines with a secondary alkylaminoalkanol occurred preferentially with the amino group or with the hydroxyl group. In case of the latter, then to see if, by using the secondary alkylaminoalkyl chloride, condensation with the secondary amine could be accomplished.

4,6-Dichloroquinazoline (I) (4), which hydrolyzes less readily than 4-chloroquinazoline, was condensed with ethylaminoethanol (II). A benzene solution of I with two equivalents of II gave 6-chloro-4-(2′-ethylaminoethoxy)quinazoline (IV) and the hydrochloride of ethylaminoethanol indicating a preferential condensation through the hydroxyl group. There was no evidence of a condensation through the secondary amine to form 4′-(6′-chloroquinazolyl)-2-hydroxy-



I II IV

ethylethyl amine (VI). The only products isolated were IV, the hydrochloride of II, and some unreacted I.

A confirmation of this structure was obtained by treating 6-chloro-4-ethoxyquinazoline (III) (4) with an equivalent amount of sodium ethylaminoethoxide. The product was identical with IV obtained in the preceding reaction.

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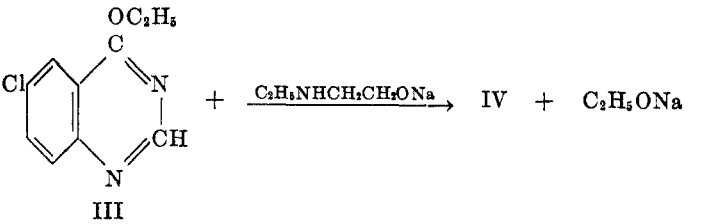
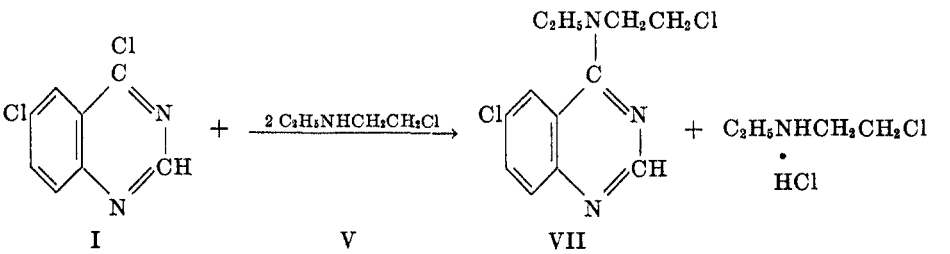
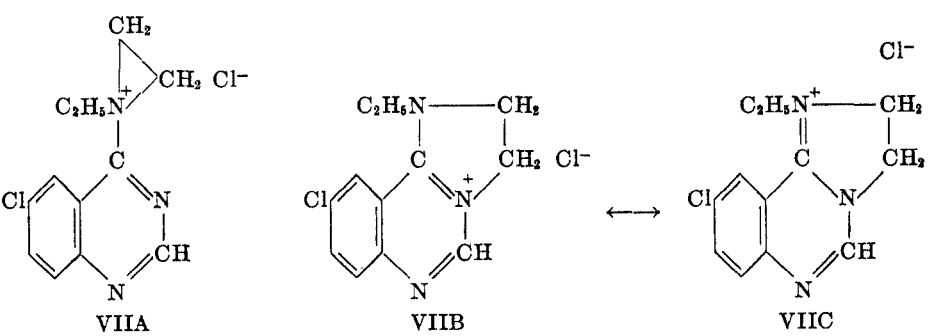


The condensation of 4,6-dichloroquinazoline (I) with 2-chloroethylethylamine (V) in benzene solution gave a compound corresponding in molecular weight and analysis ($C_{12}H_{13}Cl_2N_3$) to the tertiary amine 4′-(6′-chloroquinazolyl)-2-



chloroethylethyl amine (VII). However, the properties of the condensation product did not correspond to those expected from an amine of structure VII.

The preparation of a number of derivatives of this condensation product gave cumulative evidence that the condensate was a cyclic quaternary salt. Two cyclic structures seemed possible, one that the 2-chloroethylethylamino side chain had cyclized to form 4-(6-chloroquinazolyl)ethylethylenimonium chloride (VIIA); the other that the side chain had cyclized with the pyrimidine ring of the quinazoline nucleus to form a dihydroimidazo-quinazolinium salt. The investigation of the hydrolysis product of the condensate confirmed the latter cyclization. The condensation product in benzene solution is therefore formu-



lated as 9-chloro-1-ethyl-2,3-dihydro-1*H*-imidazo[1,2-*c*]quinazolin-4-ium chloride (VIIB),[2] or 9-chloro-1-ethyl-2,3-dihydro-1*H*-imidazo[1,2-*c*]quinazolin-1-ium chloride (VIIC).[2] The structures VIIB and VIIC represent two of the possible

[2] Acknowledgement is made to Dr. A. M. Patterson and Dr. L. T. Cappell for the names VIIB and VIIC.

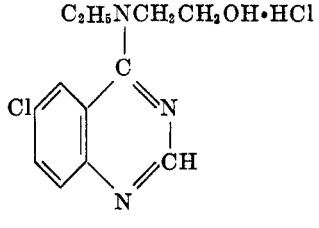
resonance structures and it does not seem possible to differentiate between them. Evidence follows in support of the conclusion that the condensate is a quaternary salt and that it is of the tricyclic fused quinazolinium rather than the ethylenimonium type. In the discussion the condensate refers to VIIB-C.

This condensate is insoluble in acetone, ether and benzene, moderately soluble in chloroform, and very soluble in ethanol and water. A water solution of the condensate gave a halide test and titration experiments showed 0.98 mole of chloride ion present for each mole of the compound which is equivalent to 13.00 per cent of ionic chloride or nearly one-half of the total chlorine content.

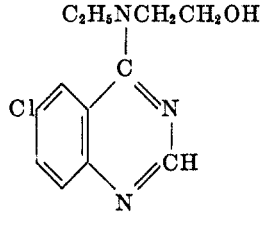
Several derivatives of the condensation product have been prepared that also indicated the presence of the chloride ion. After long refluxing of a chloroform solution of the condensate with methyl iodide a pale green crystalline precipitate separated. The product proved to be an iodide ($C_{12}H_{13}ClIN_3$) formed by replacement of the chloride ion. An identical product was obtained when a chloroform solution was treated with sodium iodide in acetone solution. The iodide was soluble in water and on titration gave an iodide concentration equivalent to the replacement of the chloride ion.

The condensation product with picric acid formed a picrate which by analysis ($C_{18}H_{15}ClN_6O_7$) showed the picrate ion had replaced the chloride ion. With chloroplatinic acid a double salt was formed. Efforts to form a nitroso derivative of the condensate were unsuccessful, indicating that a secondary amino group was not present. These derivatives indicated that the condensate was a cyclic quaternary salt.

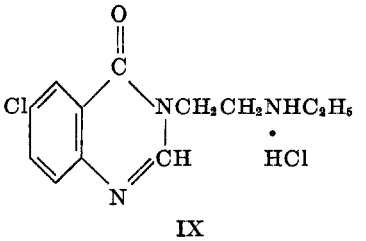
The condensation product hydrolyzed, after several days, in water at room temperature. On removal of the water at diminished pressure, a white crystalline solid was isolated. Analysis ($C_{12}H_{15}Cl_2N_3O$) of the compound and the chloride value obtained on titration corresponded to a hydrochloride. It could be interpreted as having the structure of VIII, the hydrolysis product of VII or VIIA or of IX, the product of hydrolytic cleavage of VIIB-C, since these two hydro-



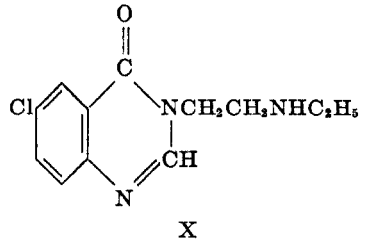
VIII



VI



IX



X

chlorides have the same formula weight. The solution of this hydrochloride treated with ammonia did not give the free amine but on addition of a solution of potassium carbonate a white crystalline precipitate formed which was soluble in acetone, alcohol, and chloroform. This compound by analysis ($C_{12}H_{14}ClN_3O$) corresponded to 4′-(6′-chloroquinazolyl)-2-hydroxyethylethyl amine (VI) or to 6-chloro-3-ethylaminoethyl-4-quinazolone (X). From a solution of this amine in hydrochloric acid a hydrochloride identical with the hydrolysis product was isolated.

The work of various investigators of alkyl-bis-2-chloroalkylamines (12–14) and of tertiary-2-chloroethylamines of the type $RR'NCH_2CH_2Cl$ (15–19) shows the ease of formation of a cyclic ethylenimonium chloride. The application of this cyclization to the condensation product from I and V implies that as originally formed in a nonpolar solvent it may be 4′-(6′-chloroquinazolyl(-2-chloroethylethylamine (VII). However, due to its insolubility in nonpolar solvents it seems that it could be the ethylenimonium salt (VIIA) which on hydrolysis in water would form the hydrochloride (VIII) of 4′-(6′-quinazolyl(-2-hydroxyethylethylamine and with base the corresponding amine (VI). However, one of the most characteristic properties of the ethylenimonium ion is the reaction with a solution of sodium thiosulfate to form a "Bunte salt" (12) and the progress of this reaction can be determined by iodine titration. The quaternary salt failed to give this reaction and the only product isolated, after treatment with sodium thiosulfate, was identical with the hydrochloride VIII or IX. This seemed to eliminate VIIA as representing the structure of the quaternary condensation product.

The free amine formed from hydrolysis of the condensate gave an addition product with picric acid, a quaternary salt with methyl iodide, and a nitroso derivative in accord with structure VI or X. All attempts to esterify the amine with acetyl chloride or with 3,5-dinitrobenzoyl chloride were negative, showing the absence of an alcohol group. This indicated that the suggested structure VI did not represent the hydrolysis product of the quaternary salt and therefore eliminated the ethylenimonium structure VIIA for the condensation product as well as the suggested structures VIII and VI for the hydrolysis products.

Consideration was then given to the cyclization of the side chain with the pyrimidine ring of the quinazoline nucleus to form a quaternary imidazoquinazolinium salt VIIB-C. Although the formation of imidazopyrimidinium or imidazoquinazolinium salts by side chain cyclization has not been found in the literature, the closely related imidazopyrimidine cyclization has been indicated. Majima (20) and Diels (21) reported the formation of these bicyclic fused rings by the cyclization of 2-haloalkyl-substituted pyrimidines. These two cases are not identical with the proposed cyclization VIIB-C but there is a similarity in that the 2-halosubstituted side chain has condensed with an imino-nitrogen in the pyrimidine ring. Several investigators (22–25) have shown that 3-alkyl-substitution in 4-quinazolones takes place with different methods of alkylation, which gives some support to the formation of VIIB-C.

Cyclic ethylenimonium ions have been used as alkylating agents for nitrogen

in ammonia (26), primary and secondary amines (27, 28), nitriles (29), and amino acids (12d). Recently Elderfield (30) indicated that alkylation of aminoquinolines took place through a trialkylazetidinium ion intermediate. Alkylation of potassium phthalimide and succinimide has been accomplished by means of a trialkylpyrrolidinium bromide (31). By analogy to these alkylations the imidazopyrimidine cyclization in VIIB-C could be postulated in three ways. If alkylation were through an ethylenimonium ion the steps should be: the initial formation of VII, the cyclization of the side chain to the quaternary structure VIIA, followed by the alkylation of the 3-nitrogen of the pyrimidine ring. A second path would imply the original condensation VII and rapid cyclization to form the imidazoquinazolinium salt VIIB-C. The third path would be simultaneous reaction of 2-chloroethylethylamine (V) with the 4-carbon and the 3-nitrogen of the quinazoline nucleus of I. No evidence of intermediate products has been obtained nor is there evidence to support any of the suggested paths. Additional experimental evidence in support of the proposed structure VIIB-C follows.

Since the quinazoline ring is resistant to mild hydrolysis, the hydrolytic products of VIIB-C should be due to the cleavage of the imidazoline ring. Urech and coworkers (32) have shown that the hydrochlorides of imidazolines are stable in neutral or dilute acid (2 *N*) solutions. Concentrated hydrochloric acid, however, splits the ring; for example, 2-benzylimidazoline hydrochloride gives phenylacetic acid and ethylenediamine dihydrochloride. In the case of the imidazoline free base, cleavage easily occurs by heating in water to give the 2-aminoacylamide. The product of hydrolytic cleavage of the imidazoline ring of VIIB-C would be the hydrochloride (IX) of the free base 6-chloro-3-ethylaminoethyl-4-quinazolone (X). The molecular formulas and reactions given for the hydrolysis products VIII and VI are equally applicable to IX and X. The difference lies in the presence of a carbonyl group and a secondary amine in IX and X instead of the alcohol and tertiary amine of VIII and VI. The presence of the secondary amine in the free base has been shown by the formation of a nitroso compound. The carbonyl group is not an aldehyde nor a ketone but part of an acid amide. The free base failed to react with 2,4-dinitrophenylhydrazine which is also true of 4-quinazolone compounds. Further proof of the presence of the secondary amine in X was the reaction with potassium cyanate which gave very readily a compound corresponding by analysis ($C_{13}H_{15}ClN_4O_2$) to a disubstituted urea. When the original condensation product was treated similarly no reaction occurred until after 12 hours. The product isolated was identical with that obtained from X. The slowness of this reaction indicated that the disubstituted urea formed only after hydrolysis of VIIB-C had occurred. The potassium cyanate had increased the speed of this hydrolysis just as the sodium thiosulfate had. The cumulative chemical evidence supports the suggested structures VIIB-C, IX, and X for the respective compounds.

Ultraviolet absorption spectra measurements[3] have given further evidence in support of the proposed structures. Figure 1 gives the absorption curves for

[3] The ultraviolet absorption spectra were obtained on a Beckman Model DU spectrophotometer.

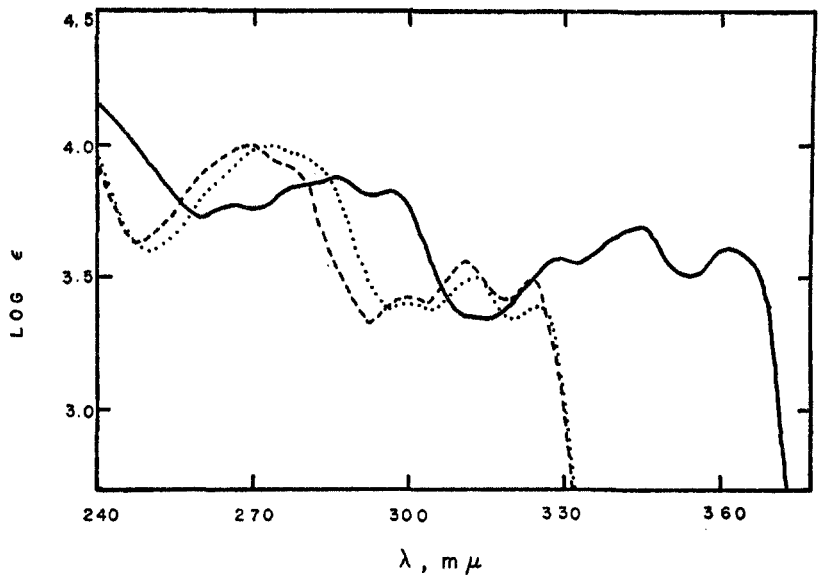


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA: 9-Chloro-1-ethyl-2,3-dihydro-1*H*-imidazo-[1,2 *c*]quinazolin-4-ium chloride (VII B-C)————; 6-Chloro-3-ethylaminoethyl-4-quinazolone (X) – – – –; 6-Chloro-4-quinazoline ••••

ethanol solutions of compounds VIIB-C, X, and 6-chloro-4-quinazolone. There is a close similarity in the curves of X and the quinazolone, whereas that of the quaternary salt VIIB-C is very different. The absorption spectrum of the hydrochloride IX was measured and is almost identical with that of the free base X. The hydrolysis of VIIB-C in an ethanol solution was followed spectrometrically. After five days there was evidence of change into IX and after 30 days the hydrolysis was complete.

At this point in the work a series of papers appeared from the Lederle Laboratories (33) in which it was shown that 3-alkyl-4-quinazolones had a characteristic ultraviolet absorption spectrum and that variation of the 3-substituent, unless it contained an absorbing group, produced practically no change. Fortunately it was possible to compare the spectra of similarly substituted compounds, 3-ethylaminoethyl-4-quinazolone[4] and 6-chloro-3-(propylaminocyclohexyl)-4-quinazolone hydrochloride[4] with those of X and IX. The similarity was most satisfactory, giving further support in confirmation of the 3-substituted-4-quinazolone structures suggested for IX and X.

Infrared absorption spectra measurements[5] of 6-chloro-4-quinazolone, of compounds IV, VIIB-C, IX, X, and of 6-chloro-3-propylaminocyclohexyl-4-quinazolone hydrochloride[4] have been made. The spectra seem to correspond

[4] Acknowledgement is made to Dr. B. R. Baker, Lederle Laboratories, for making available the ultraviolet spectra measurements of 3-alkylamino-substituted-4-quinazolones.

[5] Acknowledgement is made to Dr. Barbara K. Campbell for the infrared absorption spectra measurements made in the organic laboratory of Notre Dame University and for the interpretation of these spectra.

with the structures as given. The presence of the carbonyl group in the 6-chloro-4-quinazolone and in compounds IX and X was well defined. There was no evidence of the carbonyl group in compounds IV and VIIB-C.

EXPERIMENTAL[6]

4,6-Dichloroquinazoline (I). m.p. 155–156° (4).

6-Chloro-4-ethoxyquinazoline (III). m.p. 104.5–105° (4).

Ethylaminoethanol[7] (II). The ethylaminoethanol distilled at 65–66° (1 mm.); b.p. 167.7°/760 mm.; n_D^{20} 1.4400 and electrometric titrations indicated at least 90% purity.

2-Chloroethylethylamine hydrochloride. The compound was prepared from the ethylaminoethanol by two methods (36–38). The recrystallized salt melted at 226–227° and a sample neutralized with sodium bicarbonate showed, at the end of half an hour, 1.005 moles of chloride ion present per mole of salt. At the end of two and 23 hours respectively the chloride ion was 1.24 and 1.60 moles per mole of salt, showing the gradual hydrolysis of 2-chloroethylethylamine.

2-Chloroethylethylamine (V). The 2-chloroethylethylamine hydrochloride (4.8 g., 0.033 mole) was dissolved in 50 ml. of cold water and a cold saturated solution of potassium hydroxide was added. The free base V separated as an oil and an ether extract (total volume 100 ml.) of this was dried over solid potassium hydroxide. The ether was then removed at diminished pressure and the residue distilled. Two grams (55% yield) of a colorless oil, distilling at 40° (27 mm.), was obtained. This began to solidify within 15 minutes and was completely solid at the end of an hour. The white solid, the dimer or polymer, insoluble in ether, after recrystallization from acetone, melted at 208–214°. It was soluble in water and gave a positive halide test with silver nitrate. This rapid polymerization necessitated using solutions of the amine for most of the condensations with I. For these the hydrochloride (9 g., 0.085 mole) was neutralized with potassium carbonate solution, the amine was extracted with 100 ml. of benzene, dried several times, and used as soon as possible for the condensation.

6-Chloro-(2'-ethylaminoethoxy)quinazoline (IV). (*A*). To a benzene solution of 4,6-dichloroquinazoline (I) (6.3 g., 0.032 mole in 150 ml.), in a three-necked flask equipped with stirrer, reflux condenser, and drying tube, 5.6 g. (0.063 mole) of ethylaminoethanol (II) was added in small portions. The solution gradually became cloudy and fluorescent and after two hours a flaky crystalline solid began to precipitate. After three days at room temperature the mixture was refluxed for several hours; the solid dissolved but reprecipitated, on cooling, as a hard cake, the hydrochloride of II. The benzene solution was filtered, the benzene removed at diminished pressure, and the solid residue extracted three times with 150-ml. portions of boiling ligroin (90–120°). From the cooled solution white crystals separated, 4 g., 50% yield, m.p. 111–114°. After recrystallization from ligroin the white rosette crystals melted at 116–117°.

Anal. Calc'd for $C_{12}H_{14}ClN_3O$: C, 57.25; H, 5.60; N, 16.70.

Found:[8] C, 57.32; H, 5.40; N, 16.90.

(*B*). Sodium (0.24 g., 0.01 mole) was added in thin pieces to ethylaminoethanol (II) (3.6 g., 0.04 mole), in a three-necked flask equipped with a stirrer, reflux condenser, and drying tube. When the reaction was complete 6-chloro-4-ethoxyquinazoline (III) was slowly added. After the heat of reaction diminished the mixture was heated for half an hour at 70°. The mixture was stirred into 100 ml. of cold water and after three hours a fine yellowish

[6] Melting points are corrected. For those below 200° an oil-bath was used, for those higher than 200° a metal block was used.

[7] Acknowledgement is made to Dr. George Rieveschl, Parke, Davis & Co., for some of this compound used in the early work. The commercial product was also obtained from the Carbide and Carbon Chemical Corp.

[8] Analysis by Oakwold Laboratories, Alexandria, Virginia.

precipitate separated from the emulsion. The crude product obtained after filtration and washing melted at 114–115.5°. Recrystallized from ligroin it formed white rosettes, m.p. 116–117°. The yield was 53%. This product was identical with that from (*A*), and a mixture melting point showed no depression.

Condensation product VIIB-C. *9-Chloro-1-ethyl-2,3-dihydro-1-H-imidazo[1,2-c] quinazolin-1-ium chloride.* (*A*). In one instance, 2-chloroethylethylamine (V) (1.8 g., 0.017 mole) was distilled as rapidly as possible and dissolved in 50 ml. of benzene. This was added slowly, with stirring, to a solution of 4,6-dichloroquinazoline (I) (3.0 g., 0.015 mole) in 125 ml. of benzene. No immediate reaction occurred but after the mixture was refluxed a fine creamy solid separated. After 30 hours of refluxing no more solid separated.

The benzene solution was filtered, the benzene was removed by distillation at diminished pressure, and the solid residue was recrystallized from ligroin (90–120°) to give 1 g. of unreacted 4,6-dichloroquinazoline, m.p. 155–156°. A mixture melting point with I showed no depression.

The creamy crystalline solid, which separated in the reaction flask, was dissolved in chloroform and on addition of acetone a white fine crystalline precipitate formed (m.p. 260–263°). By redissolving in chloroform and reprecipitating with ligroin several times a substance of constant melting point, 273–274° (uncorr.) was obtained. The 2-chloroethylethylamine hydrochloride, although fairly soluble in acetone, was difficult to separate. The yield of purified product was 1.0 g. (36% yield based on the 2 g. of 4,6-dichloroquinazoline which reacted).

(*B*). To avoid the polymerization loss, which occurred in the distillation of 2-chloroethylethylamine, the remaining condensations were carried out as follows. The freshly prepared 2-chloroethylethylamine from 9.0 g. of the hydrochloride (*B*) in 100 ml. of benzene was placed in a pressure bottle with 4,6-dichloroquinazoline (5 g., 0.025 mole) dissolved in 100 ml. of benzene. The bottle was closed and placed in a water-bath which was heated while the white crystalline material slowly formed. The best yield, (19.2%) was obtained by heating the mixture for 32 hours at 60–65°. After cooling the precipitate was filtered and dissolved in 25 ml. of chloroform, then the product VIIB-C was precipitated with 75 ml. of acetone; this process was repeated if necessary. Variations in length of heating, 14–188 hrs., and the addition of the amine at intervals did not change the yields markedly. The product obtained after heating more than 48 hrs. required more purification. The yields were from 14–19.2%, but this did not take into account the loss of amine in the preparation nor the unreacted 4,6-dichloroquinazoline. The purified compound crystallized in white rosettes, m.p. 281–282°.

Anal. Calc'd for $C_{12}H_{13}Cl_2N_3$: C, 53.34; H, 4.85; N, 15.55; Cl, 26.25.
Found:[8] C, 53.05; H, 4.85; Cl, 26.00.
Found:[9] C, 53.44; H, 4.82; N, 15.29.

Molecular weight. Calc'd: 270.1. Found:[10] 270.6, 251.8, 241.9, Avg. 254.8.

Titration of VIIB-C by Fajan's method (39) with silver nitrate, using diiodofluorescein as indicator, gave a value of 0.98 mole of chloride ion per mole of VIIB-C which corresponds to 13.00 per cent of chloride ion.

Preparation of an iodide. (*A*). VIIB-C (0.2 g.) was dissolved in chloroform and excess methyl iodide was added. There was no reaction after 12 hours. The solution was then refluxed for 30 hours; after 3–4 hours a crystalline precipitate gradually formed, increasing as the heating continued (m.p. 256–257°). On recrystallization from absolute alcohol 0.125 g. of pale green-yellow rosette needles (m.p. 260–261°) were obtained. Analysis showed this compound was not the quaternary salt expected by the addition of methyl iodide to VII ($C_{13}H_{16}Cl_2IN_3$) but an iodide ion ($C_{12}H_{13}ClIN_3$) replacement of a chloride ion.

(*B*). A solution of condensation product VIIB-C in chloroform was refluxed for several hours with an excess of sodium iodide in acetone. An excess of chloroform was added and

[8] Analysis by Clark Microanalytical Laboratories, Urbana, Ill.
[10] Ebulliscopic method in absolute ethanol.

the inorganic salts were removed by filtration. After the excess of solvent was removed at diminished pressure, a pale green solid separated (m.p. 255.5–256°). When recrystallized from absolute ethanol, yellow-green crystals (m.p. 261.6–262.2°) were obtained. A mixture melting point with the product obtained in (*A*) showed no depression, confirming the identity of the two compounds.

These compounds were soluble in water, formed a yellow precipitate with silver nitrate, and on addition of a drop or two of bromine water and carbon tetrachloride, the characteristic purple color of iodine appeared.

Anal. Calc'd for $C_{13}H_{16}Cl_2IN_3$: C, 37.88; H, 3.92; N, 10.20.
Calc'd for $C_{12}H_{13}ClIN_3$: C, 39.85; H, 3.62; N, 11.63.
Found:[8] C, 39.69; H, 3.54; N, 11.46.
C, 39.85; H, 3.52; N, 11.84.

Titration of the iodide by Fajan's Method (39) gave a value for iodine equivalent to 1.002 mole of iodide ion per mole of the compound ($C_{12}H_{13}ClIN_3$).

Preparation of a picrate. The condensation product (0.2 g.) dissolved in 1–2 ml. of absolute ethanol was treated with an alcoholic solution of picric acid. There was an immediate precipitation of a yellow picrate. The crude product (0.3 g., m.p. 152–153°) recrystallized from hot absolute ethanol formed fine yellow needles, m.p. 154.2–154.7°. Analysis of this product proved that it was not an addition product of picric acid to VIIB-C but a compound in which the chloride ion of VIIB-C had been replaced by a picrate ion.

Anal. Calc'd for $C_{18}H_{16}Cl_2N_6O_7$: C, 43.30; H, 3.23; N, 16.83.
Calc'd for $C_{18}H_{15}ClN_6O_7$: C, 46.73; H, 3.27; N, 18.17.
Found:[8] C, 46.91; H, 2.91; N, 18.10.
C, 46.85; H, 3.21; N, 18.10.
Found:[9] C, 47.16; H, 3.30; N, 17.65.
C, 46.95; H, 3.25; N, 17.68.

Preparation of a chloroplatinate. A sample of VIIB-C (0.044g., 0.0016 mole) dissolved in water was treated with approximately 0.0008 mole of 10% platinic chloride. A curdy orange precipitate was formed. An attempt was made to recrystallize the product in hot ethanol. The melting point of the compound could not be determined as decomposition occurred. A sample of the compound (0.0193 g.) gave 0.0040 g. of platinum residue.

Molecular weight. Calc'd for $(C_{12}H_{13}Cl_2N_3)_2H_2PtCl_6$: 950. Found: 941.

Reaction with sodium thiosulfate (12a, c). A solution of VIIB-C was treated with standard sodium thiosulfate solution and the mixture was titrated at intervals over 24 hours with standard iodine solution. The concentration of thiosulfate remained constant in both buffered and unbuffered solutions. The slightly yellow solid residue from these solutions, after removal of the water at reduced pressure, was extracted with absolute ethanol. On evaporation of the solution a solid (m.p. 198–200°) was obtained which on recrystallization gave a white crystalline compound (m.p. 223°) which proved to be the hydrochloride IX of 6-chloro-3-ethylaminoethyl-4-quinazolone. A mixture melting point showed no depression. Only hydrolysis of VIIB-C had occurred. The possibility of an ethylenimonium ion structure for the condensation product was thus eliminated.

Reaction with potassium cyanate. The condensation product VIIB-C (0.1 g. in 5 ml. of water) was added to a solution of potassium cyanate (0.032 g. in 3 ml.). The solution was swirled occasionally but at the end of nine hours there was no evidence of any precipitate. After remaining overnight (total time 24 hours) a crystal nucleus had appeared. Twenty minutes after swirling the solution a crystalline precipitate formed throughout. This product (m.p. 177–178°) on recrystallization from absolute ethanol melted at 187–188° and was identical (mixture m.p.) with the disubstituted urea from compound X, a hydrolysis product of VIIB-C.

Attempted preparation of a nitroso derivative. Compound VIIB-C, in acid solution, failed to react with sodium nitrite.

6-Chloro-3-(2'-ethylaminoethyl)-4-quinazolone hydrochloride (IX). Throughout the entire investigation of compound VIIB-C the only purified organic compound isolated from water

solutions had been the hydrochloride IX. Also there was evidence that the presence of weak bases, ammonia, sodium thiosulfate, and potassium cyanate, hastened the hydrolysis. For comparison a solution of compound VIIB-C (2 g. in 100 ml. of water) was divided into two equal portions. (*A*). To one portion, 1 ml. of dilute ammonia was added and the solution was refluxed for 4½ hours. After the solvent was removed at reduced pressure, the residue (1 g.), dried in a vacuum desiccator, had m.p. 217–218°. On recrystallization from absolute ethanol by addition of acetone, white rosette crystals (m.p. 225.3–225.8°) were obtained. (*B*). From the water solution treated in the same manner the residue (1 g. approx.) melted at 255–260°. After two recrystallizations the product was identical with that obtained in (*A*). The presence of the ammonia had facilitated hydrolysis but did not give the free base X.

Anal. Calc'd for $C_{12}H_{15}Cl_2N_3O$: C, 50.00; H, 5.25; N, 14.58.

Found:[8] C, 50.05; H, 5.36; N, 15.24.[11]

Chloride titration of IX with silver nitrate (39), under the same conditions used for VIIB-C, gave 0.99 mole of ionic chloride for one mole of IX.

Preparation of 6-chloro-3-(2'-ethylaminoethyl)-4-quinazolone (X). To a solution of the condensation product VIIB-C (2 g. in 25 ml.) a concentrated solution of potassium carbonate was added until precipitation was complete. The filtered solid was dissolved in chloroform, and the solution was dried over Drierite and the chloroform was removed at diminished pressure. The residue was dissolved in acetone and ligroin was added to incipient precipitation. Crystal needles formed slowly. The product (1 g.) melted at 103.5–104°. On recrystallization from acetone and ligroin glistening asbestos-like crystals (m.p. 107.2–107.9°) were obtained. Further recrystallization did not change the melting point. It was found that ammonia, even a gaseous stream, did not hydrolize VIIB-C to the free amine X but only to the hydrochloride IX.

Anal. Calc'd for $C_{12}H_{14}ClN_3O$: C, 57.26; H, 5.60; N, 16.69; Cl, 14.09.

Found:[8] C, 57.56; H, 5.51; N, 16.22.

C, 57.30; H, 5.84; N, 15.95.

Found:[9] C, 57.09; H, 5.71.

Found: [12] C, 56.92; H, 5.65; N, 16.79; Cl, 14.44.

Preparation of IX *from* X. A sample of X was dissolved in an equivalent of hydrochloric acid. The melting point (222–223°) of the residue after evaporation of the solvent was in agreement with that of IX and a mixture melting point showed no depression. On similar treatment of X with a considerable excess of hydrochloric acid the same product was obtained.

Reaction with methyl iodide. When a sample of X in chloroform was refluxed with excess methyl iodide, no precipitate formed in 1½ hours.

After standing overnight the solution was cloudy. It was refluxed then for eight hours. The fine white precipitate was filtered and dried (m.p. 218–219°). It gave a qualitative iodide test but analysis indicated that the product was not pure.

Anal. Calc'd for $C_{14}H_{19}ClIN_3O$: C, 42.26; H, 4.82; N, 10.57.

Calc'd for $C_{13}H_{17}ClIN_3O$: C, 39.65; H, 4.35; N, 10.67.

Found:[8] C, 39.82; H, 4.75; N, 9.16.[13]

C, 39.54; H, 4.66; N, 9.11.

Preparation of a picrate. A sample of compound X was transformed into a picrate. The product, recrystallized from alcohol-acetone, melted at 247.2–248.2°. The melting point did not change on further recrystallization. The picrate was an addition product of picric acid to X.

Anal. Calc'd for $C_{18}H_{17}ClN_6O_8$: C, 44.96; H, 3.56; N, 17.48.

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[11] Miniature sample.

[12] Analysis by the Microanalytical Laboratory, Massachusetts Institute of Technology, Cambridge, Mass.

[13] Values unsatisfactory, the nitrogen content of a number of compounds investigated was lower than theoretical.

Found:[9] C, 45.14; H, 3.72; N, 17.35.

Reaction with potassium cyanate. Formation of a disubstituted urea. A sample of Compound X was treated with a solution of potassium cyanate as in the case of VIIB-C. In less than four hours a considerable precipitate had formed and a few hours later precipitation seemed complete. The large mass of crystals was filtered, washed with ice-water, and dried (m.p. 183–184°). On recrystallization from hot ethanol the product formed fluffy white rosettes (m.p. 187.9–188.1°). This was identical with the product obtained by prolonged action of potassium cyanate on VIIB-C.

Anal. Calc'd for $C_{13}H_{15}ClN_4O_2$: C, 52.97; H, 5.13; N, 19.01.

Found:[12] C, 52.70; H, 5.19; N, 18.92.

Preparation of a nitroso compound. Compound X (0.15 g.) in 8 ml. of water was treated with several drops of concentrated hydrochloric acid until it dissolved. The solution was cooled in an ice-bath and four drops of sulfuric acid (2 *N*) were added and then solid sodium nitrite, in slight excess, was added. After a few minutes the solution became cloudy and in two hours a white gummy substance had separated. This was extracted with ether. On evaporation of the ether solution a yellowish, oily, semicrystalline substance remained. Extraction with ethyl acetate, followed by addition of ether did not give crystalline material. The residue, after the removal of the solvents, was dissolved in warm ethanol and the solution was filtered. After most of the alcohol had evaporated, at room temperature, slightly yellow rectangular crystals (m.p. 158.6–158.8°) were obtained.

Anal. Calc'd for $C_{12}H_{13}ClN_4O_2$: N, 19.95. Found:[12] N, 19.89.

Compound X failed to react with either acetyl chloride or 3,5-dinitrobenzoyl chloride, indicating the absence of an alcohol group. It also failed to react with 2,4-dinitrophenylhydrazine, indicating the absence of an aldehyde or ketone group.

The *absorption spectra* measurements of certain of the above compounds have been measured in the ultraviolet[3] and infrared[5] regions. Discussion of the results are given in the dicussion part of the paper.

SUMMARY

Two methods of synthesis of 6-chloro-4-(2′-ethylaminoethoxy)quinazoline have been given.

An investigation of the product of the condensation of 2-chloroethylethylamine with 4,6-dichloroquinazoline has been made. Several possible structures of the compound have been considered. The reactions of the compound have been studied and derivatives have been made. Evidence has been obtained that it is a quaternary chloride of a tricyclic fused ring system. The structural formula which is proposed corresponds to the compound 9-chloro-1-ethyl-2,3-dihydro-1-*H*-imidazo[1,2-*c*]quinazolin-1-ium chloride.

The hydrolysis products of the condensation product have been identified as the hydrochloride of 6-chloro-3-ethylaminoethyl-4-quinazolone and the corresponding free base. Derivatives of this compound have been made.

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