to the combined filtrates. Again the solution was allowed to stand and again the dithiocarbamate was removed and washed with acetone. The filtrate was evaporated to dryness on a steam cone under reduced pressure. The quinazoline remained as a slightly oily, light yellow solid. After being ground once with petroleum ether (b. p. 90–110°) it was collected in a filter. The yield of the crude quinazoline was 23.1 g. (85%) and it melted at 108–111°. It was further purified by recrystallization from 200 cc. of petroleum ether and decolorization with activated charcoal to give 17.7 g. (65%) of white crystals, m. p. 118–119°.

When it was dried at 20° over paraffin, it melted at 120–121°. The analysis indicated that water was present.

*Anal.* Calcd. for $C_{17}H_{25}ClN_4 \cdot 1.77H_2O$: C, 57.87; H, 8.15 Found: C, 57.88; H, 8.11.

A second sample was therefore prepared and analyzed after drying at 70° over phosphorus pentoxide and paraffin under reduced pressure. This sample melted at 115–116°.

*Anal.* Calcd. for $C_{17}H_{25}ClN_4$: C, 63.62; H, 7.85; N, 17.46. Found: C, 63.68; H, 7.56; N, 16.62, 17.66.*

The *dipicrate* was prepared and recrystallized from ethanol. It melted with decomposition at 205–206°.

*Anal.* Calcd. for $C_{17}H_{25}ClN_4 \cdot 2C_6H_3N_3O_7$: C, 44.70; H, 4.01. Found: C, 44.95; H, 4.22.

## Summary

4 - (4′ - Diethylamino - 1′ - methylbutylamino)-7-chloroquinazoline has been prepared readily in good yield from 2,4-dichlorobenzoic acid.

URBANA, ILLINOIS. RECEIVED APRIL 5, 1946

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

# Quinazolines. III. Syntheses of 4-Alkylaminoquinazolines[1]

BY BERT E. CHRISTENSEN, BRUCE GRAHAM AND ARTHUR J. TOMISEK

The introduction of alkylamino side chains to quinolines has resulted in the synthesis of several valuable drugs. A natural extension of this work has been to study the effect of similar substituents on other heterocyclic ring systems.

Because of the similarity of the quinoline to the quinazoline nucleus Magidson and Golovchinskaya[2] synthesized several 4-alkylaminoquinazolines for antimalarial purposes. The possibility of utilizing quinazolines for this purpose was later recognized by Dewar.[3] Although the few quinazoline drugs which have been reported have been found to be relatively inactive as antimalarial agents, the coupling with other effective side chains appears worthy of investigation.

The exceptional reactivity of the 4-chloroquinazoline simplifies the coupling with the amines which proceeds without the catalysts and vigorous conditions sometimes required in related reactions with the 9-chloroacridines. The syntheses were carried out in a benzene solution whenever the solubility of the amines permitted.

Alcohol was chosen as the solvent for the condensations with amino alcohols. The activity of the 4-chloroquinazolines did not appear to cause any complications by reacting with the hydroxyl groups of the amino alcohols or with the solvent, though the reaction probably did proceed in part via the 4-ethoxyquinazoline.[4]

Since the presence of acid[4] is known to activate 4-substituted haloheterocycles, hydrogen chloride was added for purposes of activation as well as isolation of the insoluble hydrochlorides. Condensation of 4-chloroquinazoline with ethanolamine indicated that the presence of acid did increase the reaction rate.

On the other hand, an attempted synthesis of 4-(ω-hydroxyhexylamino)-7-chloroquinazoline under conditions considered suitable resulted in an incomplete reaction. The addition of equimolar amounts of solid sodium hydroxide to the reaction mixture led to satisfactory yields. The function of the base is not known and is being investigated further.

Experiments using additional acid were not attempted with 2-(2′-aminoethoxy)-ethanol and 2-methyl-2-amino-1,3-propanediol since these compounds gave satisfactory yields in the initial trials.

## Experimental[5]

**4,6-Dichloroquinazoline.**—This compound was prepared according to the directions given by Price and Curtin for 4,7-dichloroquinazoline.[6] Sixty-one grams (0.34 mole) of 6-chloro-4-hydroxyquinazoline[2] gave 55 g. (82%) of 4,6-dichloroquinazoline, m. p. 148–153°. The yield by this procedure was much better than reported for the original synthesis[2] of the compound.

**4-(1-Piperidyl)-quinazoline** (SN 12496).—A solution containing 20.75 g. (0.24 mole) of piperidine in 50 cc. of dry benzene was added with stirring to a solution of 20 g. (0.12 mole) of 4-chloroquinazoline in 200 cc. of dry benzene. After the mixture had cooled the piperidine hydrochloride was removed by filtration. The filtrate and washings were concentrated and then distilled *in vacuo*, b. p. 139–140° (5 mm.). The yield was 22 g. (85%) of a colorless sirup. The hydrochloride was obtained by dissolving the sirup in warm absolute alcoholic hydrogen chloride solution, cooling and filtering. A second fraction was obtained by evaporating the filtrate *in vacuo*. Both fractions were analytically pure white crystals, m. p. (dec.) 230° (obtained by dropping on a hot block).

**4-(1-Morpholinyl)-quinazoline.**—Five and four-tenths grams (0.062 mole) of morpholine and 5.08 g. (0.031 mole) of 4-chloroquinazoline in benzene solution were allowed to react according to the above directions. Morpholine

(1) The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Oregon State College. The Survey Number (SN) identifies a drug in the records of the Survey of Antimalarial Drugs. Published with the approval of the Monographs Publication Committee, Oregon State College, as Research Paper No. 101, School of Science.

(2) Magidson and Golovchinskaya, *J. Gen. Chem.* (U. S. S. R.), **8**, 1797 (1938).

(3) Dewar, *J. Chem. Soc.*, 619 (1944).

(4) Tomisek and Christensen, THIS JOURNAL, **67**, 2112 (1945); Banks, *ibid.*, **66**, 1127 (1944).

(5) All melting points are corrected.

(6) C. C. Price and D. Y. Curtin, unpublished work.

TABLE I

ANALYSES

| Compound | Formula | Calcd., % C | H | N | Cl[a] | Found, % C | H | N[b] | Cl[a] |
|---|---|---|---|---|---|---|---|---|---|
| 4-(1-Piperidyl)-quinazoline | $C_{13}H_{15}N_3$ | | | 19.70 | | | | 19.82 | |
| | $C_{13}H_{15}N_3 \cdot HCl$ | 62.52 | 6.32 | 16.83 | 14.20 | 62.29 | 6.31 | 16.56 | 14.33 |
| 4-(1-Morpholinyl)-quinazoline | $C_{12}H_{13}N_3O$ | 66.95 | 6.09 | 19.52 | | 66.70 | 6.23 | 19.52 | |
| 4-*n*-Butylaminoquinazoline | $C_{12}H_{15}N_3$ | 71.61 | 7.51 | 20.88 | | 71.53 | 7.53 | 20.84 | |
| 4-(β-Hydroxyethylamino)-quinazoline | $C_{10}H_{11}N_3O$ | 63.46 | 5.86 | 22.21 | | 63.19 | 5.75 | 21.95 | |
| | $C_{10}H_{11}N_3O \cdot H_2O$ | | | 20.28 | | | | 20.21 | |
| 4-(β,γ-Dihydroxypropylamino)-quinazoline | $C_{11}H_{13}N_3O_2$ | 60.26 | 5.98 | 19.17 | | 60.10 | 5.98 | 19.24 | |
| | $C_{11}H_{13}N_3O_2 \cdot HCl$ | | | | 13.87 | | | | 13.96 |
| 4-(β-Hydroxyethylamino)-7-chloroquinazoline | $C_{10}H_{10}N_3OCl \cdot HCl$ | 46.17 | 4.26 | 16.15 | 13.63i | 46.12 | 4.41 | 16.17 | 13.53i |
| | $C_{10}H_{10}N_3OCl \cdot H_2O$ | | | 17.39 | | | | 17.48 | |
| 4-(β,γ-Dihydroxypropylamino)-7-chloroquinazoline | $C_{11}H_{12}N_3O_2Cl$ | | | 16.57 | | | | 16.82 | |
| | $C_{11}H_{12}N_3O_2Cl \cdot HCl$ | 45.53 | 4.52 | 14.48 | 24.44t | 45.76 | 4.82 | 14.59 | 24.60t |
| 4-(β,γ-Dihydroxypropylamino)-6-chloroquinazoline | $C_{11}H_{13}N_3O_2Cl \cdot H_2O$ | 48.62 | 5.19 | 15.47 | 13.05 | 48.46 | 5.35 | 15.49 | 13.03 |
| 4-(β(β′-hydroxyethoxy)-ethylamino)-7-chloroquinazoline | $C_{12}H_{14}N_3O_2Cl$ | 53.83 | 5.27 | 15.70 | 13.24 | 53.96 | 5.51 | 15.63 | 13.18 |
| 4-(Dihydroxy-tertiary-butylamino)-quinazoline | $C_{12}H_{15}N_3O_2$ | 61.78 | 6.48 | 18.02 | | 62.08 | 6.38 | 17.91 | |
| 4-(ω-Hydroxyhexylamino)-7-chloroquinazoline | $C_{14}H_{18}N_3OCl$ | 60.10 | 6.48 | 15.02 | 12.68 | 59.88 | 6.44 | 15.22 | 12.48 |
| | $C_{14}H_{18}N_3OCl \cdot HCl$ | | | 13.29 | 22.43t | | | 13.49 | 22.30t |
| 4-(ω-Hydroxyhexylamino)-6-chloroquinazoline | $C_{14}H_{18}N_3OCl$ | | | 15.02 | | | | 15.02 | |
| | $C_{14}H_{18}N_3OCl \cdot H_2O$ | 56.47 | 6.77 | 14.11 | 11.91 | 56.24 | 6.80 | 14.23 | 11.91 |
| | $C_{14}H_{18}N_3OCl \cdot HCl$ | | | | 22.43t | | | | 22.27t |

[a] The letter *i* or *t* designates the chloride content as ionizable or total. [b] All nitrogen analyses are by the Dumas method.

hydrochloride was removed and the combined filtrate and washings were evaporated. The residue when dissolved in hot heptane, treated with charcoal, and recrystallized gave 5.87 g. (88% yield) of white plates. This material was purified for analysis by crystallization as its hydrochloride from a small amount of hot absolute alcoholic hydrogen chloride. The hydrochloride was then converted to the free base with a minimum amount of sodium hydroxide solution and extracted with benzene, m. p. 95–96°; very soluble in water, alcohol, or benzene; moderately soluble in ether or carbon tetrachloride.

**4-*n*-Butylaminoquinazoline**—Two and five-tenths grams (0.035 mole) of butylamine and 2.81 g. (0.017 mole) 4-chloroquinazoline were each dissolved in dry benzene. On mixing, the reaction was complete within two or three minutes, in contrast to the previous instantaneous reactions. The precipitate in this case was a gummy mixture of hydrochlorides. The product was isolated by evaporating the benzene and dissolving the residue in warm dilute hydrochloric acid. The solution was then made basic with potassium hydroxide and allowed to stand until the oily layer solidified. The solid was filtered, washed with water and dried. After solution in heptane, treatment with charcoal, and recrystallization 2.84 g. (83%) of white needles, m. p. 116–116.5°, were obtained.

**4-(β-Hydroxyethylamino)-quinazoline** (SN 13268).—Five grams (0.030 mole) of 4-chloroquinazoline was dissolved in 25 cc. of warm absolute ethanol containing 2 g. (0.033 mole) of ethanolamine and 0.3 cc. of concd. hydrochloric acid (0.0036 mole) was then added. After standing for several hours, the mixture was made basic, and solvents were removed by evaporation *in vacuo*. Recrystallization of the residue from water gave 5.90 g. (94%) of 4-(β-hydroxyethanolamino)-quinazoline monohydrate. The white plates melted with the evolution of water, resolidifying in the anhydrous form. Recrystallization of the hydrate from absolute alcohol gave anhydrous, rectangular crystals melting at 174–175°. Although the yields on runs with no hydrochloric acid were the same, the reaction time was longer.

**4-(β,γ-Dihydroxypropylamino)-quinazoline** (SN 13265).—Eleven and one-tenth grams (0.068 mole) of powdered 4-chloroquinazoline was added to a solution of 6.45 g. (0.071 mole) of 1-amino-2,3-propanediol in 25 cc. of absolute alcohol. After the reaction had subsided the remaining chloroquinazoline was dissolved by warming and stirring. Six-tenths cc. (0.0072 mole) of concd. hydrochloric acid was added and the mixture allowed to stand for twenty-four hours. The crude monohydrochloride of the product was removed by filtration of the cooled mixture. The product was dissolved in boiling water and then converted to the free base with excess sodium hydroxide. The compound slowly crystallized in about two days yielding 11.97 g. (81%) of pale tan crystals. By recrystallizing the free base and the hydrochloride alternately several times from water, the anhydrous free base, m. p. 187–188°, and the monohydrochloride, m. p. 209–210°, were obtained.

**4-(β-Hydroxyethylamino)-7-chloroquinazoline** (SN 13266).—The reaction was carried out as described for the preceding compound, using 5 g. (0.025 mole) of dichloroquinazoline, 2 g. (0.033 mole) of ethanolamine, 25 cc. of absolute alcohol and 0.3 cc. of concd. hydrochloric acid. After standing 24 hours, the alcohol was removed. The residue was dissolved in hot 30% alcohol, treated with charcoal and then made basic with an excess of 50% potassium hydroxide solution. The product separated out as the monohydrate on cooling; by concentration of the mother liquors an additional amount was obtained. The combined fractions of crude material represented a total yield of 91%. The product after several recrystallizations from small amounts of dilute hydrochloric acid gave white needles of the monohydrochloride which decomposed on the melting point block with the evolution of a distillate. The free base was recrystallized from 30% alcohol yielding white crystals of monohydrate m. p. 179° (with preliminary evolution of water).

**4-(β,γ-Dihydroxypropylamino)-7-chloroquinazoline** (SN 13267).—To a solution containing 5.0 g. (0.055 mole) of 3-amino-1,2-propanediol and 75 cc. of absolute alcohol was added 10.8 g. (0.055 mole) of 4,7-dichloroquinazoline.

The mixture was warmed gently to effect solution and then acidified with 0.5 cc. of concd. hydrochloric acid. After standing twenty-four hours at 45°, the mixture was cooled to 0° and filtered. The crude hydrochloride was dissolved in 75 cc. of cold water, a small amount of impurity was removed by filtration, and the compound was then converted to the free base with 10 cc. of 40% sodium hydroxide. After standing two days the product was removed by filtration, washed with water and dried. This material was purified for analysis by recrystallization from 30 cc. of 6 *N* hydrochloric acid. A yield of 10.0 g. (63%) of pale yellow crystals of the monohydrochloride was obtained.

The pure anhydrous product was prepared by converting the salt to the free base which was then recrystallized from water yielding an amorphous white powder, m. p. 210–212°.

**4-(β,γ-Dihydroxypropylamino)-6-chloroquinazoline.**—The reactants [2.42 g. (0.027 mole) of 3-amino-1,2-propanediol, and 4.82 g. (0.024 mole) of 4,6-dichloroquinazoline[1] were added in the usual order and allowed to stand with occasional stirring for thirty-six hours at 45° in absolute alcohol (40 cc.). Following the addition of 0.27 cc. of concd. hydrochloric acid, the mixture was cooled at 0° and filtered. The solid material was dissolved in hot dilute sodium hydroxide and filtered to remove a small amount of amorphous precipitate. The crude product (4.82 g.) which separated out during the course of twenty-four hours was filtered and washed with water. Further purification, by solution in water, treatment with charcoal and recrystallization gave 4.12 g. (63%) m. p. 188–189.5°.

**4-(β(β′-Hydroxyethoxy)-ethylamino)-7-chloroquinazoline** (SN 14551).—Nineteen and nine-tenths grams (0.1 mole) of 4,7-dichloroquinazoline was added to a solution of 17.8 g. (0.17 mole) of 2-amino-2′-hydroxydiethyl ether in 200 cc. of absolute alcohol. After standing for twenty-four hours at 45°, the solvent was removed by evaporation and the residue dried in a current of warm air until it solidified. The resulting solid was dissolved in 50 cc. of water. The solution was filtered and then treated with 17 cc. of 6 *N* sodium hydroxide. Twelve hours later the precipitate was removed, washed with water, and dried. The pure compound was then obtained by recrystallization from a minimum amount of ligroin (several hundred cc.); yield, 17.0 g. (64%), m. p. 127°.

**4-(Dihydroxy-*t*-butylamino)-quinazoline** (SN 14552).—A solution containing 21.0 g. (0.20 mole) of 2-amino-2-methyl-1,3-propanediol in 200 cc. of absolute alcohol was prepared. To this solution was added 16.5 g. (0.10 mole) of 4-chloroquinazoline. The solvent was removed after standing at 45° for twenty-four hours and resulting residue was redissolved in 250 cc. of very dilute hydrochloric acid. The solution was then made alkaline with sodium hydroxide. Several hours later the precipitate was removed, washed with water, and dried. This material was further purified by recrystallization from 300 cc. of alcohol yielding 15.7 g. (67%) of white needles, m. p. (dec.) 213–215°. In one instance, the recrystallized product consisted of granular crystals. This allotropic form, if slowly heated, sublimed to the needle-like form without melting, but if dropped on a hot block, it melted at 197°, resolidified, then melted again 210–215°.

**4-(ω-Hydroxyhexylamino)-7-chloroquinazoline** (SN 14499).—Five and two-tenths grams (0.044 mole) of 6-aminohexan-1-ol was dissolved in 40 cc. of absolute alcohol and 8.86 g. (0.044 mole) of 4,7-dichloroquinazoline was then added. The reaction, which proceeded rapidly at first, stopped before all the dichloroquinazoline had dissolved. After cooling to room temperature, 2.54 g. (0.04 mole) of 85% potassium hydroxide pellets was dissolved in the mixture by stirring. It was then set aside for ten hours. The solvent was removed by vacuum distillation and the residue boiled briefly with aqueous alkali, cooled and filtered. The product was dissolved in a small amount of boiling 1:4 hydrochloric acid, cooled, then reprecipitated with sodium hydroxide, filtered, washed and dried. Recrystallization from 5:3 di-*n*-butyl ether–absolute alcohol, with charcoal treatment, gave colorless crystals, m. p. 140°; yield 8.91 g. (72%). Solubility in absolute alcohol at 25° was 6.6 g. per 100 g. of alcohol. The pure monohydrochloride of the product melted at 183–185°.

**4-(ω-Hydroxyhexylamino)-6-chloroquinazoline.**—The procedure for the previous compound was followed, using 4.44 g. (0.038 mole) of hexanolamine, 7.5 g. (0.038 mole) of dichloroquinazoline, 40 cc. of absolute alcohol and 2.5 g. (0.038 mole) of 85% potassium hydroxide pellets. The product was recrystallized from 50 cc. of 1:4 hydrochloric acid with charcoal treatment, yielding 10.07 g. of yellow monohydrochloride. This material was dissolved in hot water and then converted to the free base with 40% sodium hydroxide and cooled. The solidified oil was removed by filtration and recrystallized from 140 cc. of 50% alcohol with another charcoal treatment; yield, 8.48 g. (76%) of white, crystalline monohydrate, m. p. 137–138°. Recrystallization from di-*n*-butyl ether–absolute alcohol did not remove the water of hydration, but left a hydrate which melted 139–140°. These melting points are those of the anhydrous compounds: in each case the compounds melted at 115–117°, with evolution of gas, then resolidified. Pure monohydrochloride, had m. p. (dec.) 173–177–179°, first softening, first meniscus, and complete liquefaction, respectively, sample being heated at five degrees per minute on a calibrated Fischer–Johns block.

## Summary

4,6-Dichloroquinazoline was prepared in improved yields by the method of Price and Curtin.

The following compounds were prepared by coupling of 4-chloroquinazoline with the appropriate amine in benzene medium: 4-piperidylquinazoline, 4-morpholinylquinazoline, 4-butylaminoquinazoline.

The following were prepared in a similar manner in an alcohol medium: 4-(β-hydroxyethylamino)-quinazoline, 4-(β,γ-dihydroxypropylamino)-quinazoline, 4-(dihydroxytertiarybutylamino)-quinazoline, 4-(β-hydroxyethylamino)-7-chloroquinazoline, 4-(β,γ-dihydroxypropylamino)-7-chloroquinazoline, 4-(ω-hydroxyhexylamino)-7-chloroquinazoline, 4-)β-(β′-hydroxyethoxy)-ethylamino)-7-chloroquinazoline, 4-(β,γ-dihydroxypropylamino)-6-chloroquinazoline, and 4-(ω-hydroxyhexylamino)-6-chloroquinazoline.

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