TABLE I

Reagents	Glucose, g.	Formaldimethone, mg.	Furfural 2,4-dinitrophenylhydrazone, mg.	Aloin, g.	Formaldimethone, mg.	Furfural
$NaBO_3$	10	10	None	80	Found	None
$NaBO_3$ + HCl to 12%	10	65	365	80	60	2 cc.
Borax	20	1	None	60	0	0
Borax + HCl to 12%	60	35	215	60	15	0 to trace
12% HCl	50	Some	105	3[a]		0.0134 g. phloroglucide

[a] L. Joseph, unpublished results. Compare Goldner, *J. Am. Pharm. Assoc.*, **21**, 658 (1932).

Discussion

The majority of investigators who have suggested possible structures for barbaloin and isobarbaloin have postulated that the substances are either D-arabinosides or D-arabinose ethers of aloe-emodin or its anthranol,[7,8,9] despite the fact that no published analyses agree with such a formula. The main support for these postulations has been Léger's[7] demonstration of the formation of D-arabinose and aloe-emodin by slow acid hydrolysis of barbaloin and the discovery by Hauser that aloe-emodin anthrone is produced when borax is used. Earlier papers from this Laboratory have indicated that the aloins are not glycosides,[10] and Rosenthaler[9] has presented convincing arguments against the D-arabinose formula based upon the absence of aldehyde reactions.

Recently, Owen and Simonsen[11] have presented evidence that the molecular formula for barbaloin is $C_{21}H_{24}O_9$, in agreement with analyses carried out in this Laboratory by Joseph and with many published analyses. This is consistent with a carbon skeleton having a β-methylanthracene ring structure with a six carbon side chain.

(7) E. Léger, *Ann. chim.*, [9] **6**, 339 (1916).
(8) F. Hauser, *Pharm. Acta Helv.*, **6**, 79 (1931).
(9) L. Rosenthaler, *ibid.*, **7**, 19 (1932).
(10) J. H. Gardner and T. F. McDonnell, THIS JOURNAL, **59**, 857 (1937), and earlier papers.
(11) L. N. Owen and J. L. Simonsen, THIS JOURNAL, **64**, 2516 (1942).

The formation of furfural and formaldehyde is not specific for glucose as preliminary experiments have shown that D-fructose behaves similarly and presumably other hexoses and pentoses yield the same products. We may then conclude that the formation of furfural under the conditions described in this paper is characteristic of a five or six carbon sugar or sugar-like molecule, and the formation of formaldehyde presumably of a polyhydroxy alcohol. By analogy, we may now assign to the aloins either a five or a six carbon side chain, but can not determine which is correct until further evidence is available. Obviously, a five carbon side chain leaves one carbon atom to be accounted for in an additional group. This problem will be considered further in a subsequent paper.

Summary

It has been shown that D-glucose yields furfural and formaldehyde under the same conditions as do the aloins. This makes possible the consideration of a six carbon chain as a part of the aloin molecule instead of the five carbon atom chain hitherto being considered as necessary to explain the results obtained with these compounds.

PHILLIPSBURG, NEW JERSEY
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(12) Original manuscript received May 4, 1945.

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

Quinazolines. II. Properties of 4-Substituted Quinazolines[1]

BY ARTHUR J. TOMISEK AND BERT E. CHRISTENSEN

In the attempted synthesis of 4-acetylquinazoline, 4-chloroquinazoline was used as a synthetic intermediate. During the course of this work certain interesting properties of the latter compound were observed which have not been previously recorded. In particular, it was noted that the *p*H had a marked influence on the stability of this compound. For this reason the work was extended to include a study of acid activation of 4-substituted quinazolines in general.

The reactivity of 4-chloroquinazoline has been demonstrated by the ability of 4-chloroquinazoline to give active halide condensations with Grignard reagents[2] and of 2,4-dichloroquinazoline to react with atmospheric moisture.[3] These observations were augmented by the discovery in this Laboratory that pure 4-chloroquinazoline reacts spontaneously with absolute methanol at room temperature, evolving considerable heat,[4,5] and yield-

(1) Published with the approval of the Monographs Publication Committee, Oregon State College, as Research Paper No. 96, School of Science, Dept. of Chemistry.

(2) Hentrich, Hardtman and Knoche, U. S. Patent 1,780,879 (Nov. 1930).
(3) Abt, *J. prakt. Chem.*, [2] **39**, 150 (1889).
(4) This phenomenon was first observed by Bruce Graham, of this Laboratory.
(5) Lange and Sheibley[6] did find that 4-alkoxy quinazolines could be prepared by using potassium cyanide, sodium carbonate or sodium acetate in place of sodium alkoxide, and on these grounds postulated an alkoxy-chloro equilibrium, which proceeded to completion only

ing 4-methoxyquinazoline hydrochloride containing a small amount of 4-hydroxyquinazoline (Fig. 1). However, in the course of further work with 4-chloroquinazoline several observations were made which appeared anomalous to the extreme halogen activity necessary to explain the above reactions. Among these were (1) the remarkable

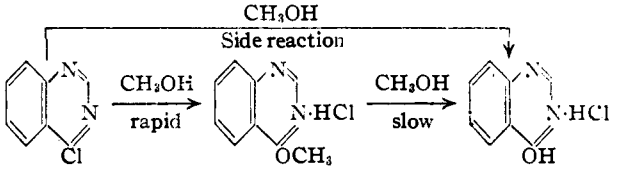

Fig. 1.

stability of 4-chloroquinazoline to aqueous base, (2) the successful recrystallization of 4-chloroquinazoline from alcohol containing traces of sodium hydroxide and (3) the fact that it reacts only slowly with alcoholic silver nitrate in the absence of nitric acid. From this behavior it was concluded that 4-chloroquinazoline was activated by the hydrogen ion. The mechanism for this activation (Fig. 2) is, except that it involves the principle of autocatalysis, essentially that suggested by Banks[7] for the activation of halonitrogen heterocycles. This mechanism also explains the acid catalyzed reactions of the other quinazolines which were studied.

Acid catalysis was again demonstrated in the hydrolysis of alkoxyquinazolines. 2,4-Dihydroxyquinazoline was produced very rapidly by the hydrolysis of 2,4-dimethoxyquinazoline in dilute acid,[8] and even by refluxing 2-chloro-4-methoxyquinazoline in water.[9] The fact that sodium alkoxides are themselves incapable of causing hydrolysis[10] while they give alkoxy-exchange reactions very readily,[12] indicates that the latter reaction is one of direct replacement without catalysis. On the other hand, the slow reaction of 4-methoxyquinazoline hydrochloride in absolute methanol (Fig. 1) indicates an acid catalyzed mechanism; because if preliminary activation by the formation of an acid complex were not necessary for this reaction with alcoholic solvent, the same reaction would also occur in the sodium alkoxide–alcohol solution. The slow formation of hydroxyquinazoline *hydrochloride* as the principal product (56% yield) of this reaction can readily be explained by the mechanism illustrated in Fig. 2 (reactions A to D). This reaction probably consists of a very rapid exchange of alkoxy groups with the solvent (A, B, C). Because the alcoholic solvent contains no water the accumulation of 4-hydroxyquinazoline hydrochloride can result only from that side reaction in which the methyl, rather than the hydrogen, splits away from the entering solvent molecule (side reaction D). The disappearance of some chloride, coupled with the isolation of part of the hydroxyquinazoline as the free base, suggests that some cleavage occurred by the conventional method.

Aminoquinazolines have not been previously reported as susceptible to hydrolysis. However, one would predict such properties on the basis of

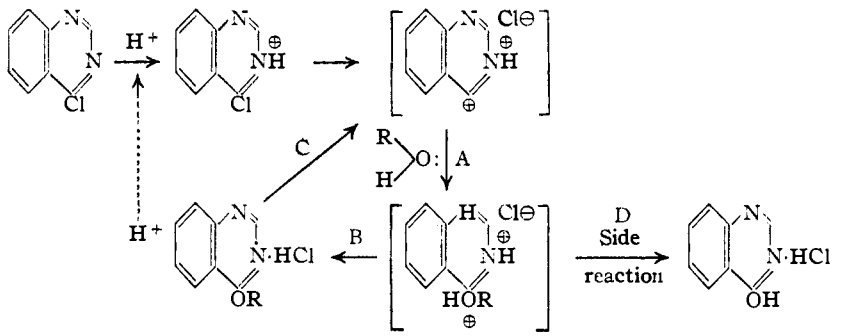

Fig. 2.

the reactions of the aminopyrimidines. Four alkylaminoquinazolines were tested and all hydrolyzed in dilute acid. The three dialkylamino quinazolines tested, hydrolyzed much more readily. 4-Piperidylquinazoline, moreover, had an activity comparable to that of 4-chloroquinazoline. The 4-piperidylquinazoline hydrochloride as in the case of 4-methoxyquinazoline hydrochloride was also converted to hydroxyquinazoline *hydrochloride* by refluxing in absolute methanol. The first step in this reaction may be a replacement of the piperidyl group by a methoxy group by the same mechanism as suggested for the chloroquinazoline–methanol reaction (Fig. 2). The 4-substituted quinazolines which are capable of tautomerizing to their more stable keto or imino

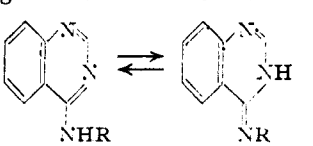

Fig. 3

because of the added dehydrohalogenating agents. However, the reaction reported here proceeded to the formation of 4-methoxy quinazoline hydrochloride in the absence of a dehydrohalogenating agent other than the quinazoline ring itself.

(6) Lange and Sheibley, THIS JOURNAL, **53**, 3867 (1931).

(7) Banks, *ibid.*, **66**, 1127 (1944).

(8) Bogert and May, *ibid.*, **31**, 509 (1909).

(9) Lange, Rousch and Asbeck, *ibid.*, **52**, 3701 (1930).

(10) Although it is known that 2,4-dimethoxyquinazoline is hydrolyzed fairly rapidly by alcoholic sodium hydroxide ($NaOCH_3$ in 95% methanol), when the sodium methoxide was used in better grades of absolute alcohol, the hydrolysis proceeded only to a slight extent (ref. 11).

(11) Lange and Sheibley, THIS JOURNAL, **55**, 1189 (1933).

(12) Lange and Sheibley, *ibid.*, **54**, 4306 (1932).

structures (Fig. 3) appear to lose some of the reactivity which is characteristic of the true quinazoline structure.

The only other described 4-functional derivatives of quinazoline are the sulfhydryl and carboxyl. While the former has not been tested, the latter class of compounds are known to be unstable to acid.[13]

In a recent article Banks[7] has studied the effect of acid on the condensation of amines with certain chloropyrimidines and on the basis of his data postulated a mechanism for the activation of halogen-substituted heterocycles. The data presented here, particularly in regard to the reactions of methanol with 4-chloroquinazoline, confirm the prediction of Banks. Furthermore it extends the application of acid activation to other 4-substituted quinazolines.

Certain other reactions of the quinazolines involved in these studies are worthy of recording although they have no direct bearing on acid catalysis. Experiments involving the fusion of 4-chloroquinazoline with silver or cuprous cyanides gave no trace of cyanoquinazoline. The 4-chloroquinazoline would not react with magnesium in either boiling diethyl or di-*n*-butyl ethers. 4-Aminoquinazoline was prepared from 4-chloroquinazoline with concentrated aqueous ammonia. The 4-aminoquinazoline formed a dihydrobromide and was difficult to acetylate. The finely divided salts of aminoquinazoline suspended in dilute hydrochloric or sulfuric acid proved to be passive to diazotization both at 0° and room temperature, probably due to its existing in the imino form. For purposes of comparison the aromatically aminated 5-amino-4-hydroxy-2-methylquinazoline was prepared. The amino group in the five position was found to undergo the Sandmeyer reaction fairly readily.

Experimental[14,15]

4-Chloroquinazoline.—The 4-chloroquinazoline[8] used in this investigation was purified by two Soxhlet extractions with low boiling petroleum ether. 4-Chloroquinazoline reacted slowly with boiling alcoholic sodium hydroxide. It was fairly soluble in ethanol, but by partial evaporation of the solvent its recrystallization from basic ethanol could be completed with reasonable yield. It was stable to cold aqueous base over long periods (due in part to its insolubility) but reacted slowly with the boiling base. By pouring the crude melt[8] into iced sodium hydroxide solution pure 4-chloroquinazoline was also obtained in good yield.

4-Methoxyquinazoline Hydrochloride.—To 1.00 g. of 4-chloroquinazoline was added 5 cc. of specially dried methanol, and the mixture shaken until the crystals dissolved. After fifteen minutes, 1.09 g. (91%) of the white crystalline product was precipitated by the addition of 30 cc. of dry ether, filtered and vacuum dried. It melted at 129° with evolution of gas and conversion to 4-hydroxyquinazoline, the conversion being shown by mixed melting point with sublimate from the conversion product. *Anal.* Calcd. for $C_9H_8N_2O\cdot HCl$: Cl, 18.03; N, 14.25; OCH_3, 15.78. Found: Cl, 17.9, 18.3; N, 14.26; OCH_3, 14.5, 14.7.

The deviation of the methoxyl content from the theoretical was probably due to the formation of hydroxyquinazoline hydrochloride, both direct and via the ether (Fig. 1). Several weeks of exposure to atmospheric moisture caused a marked decrease in methoxyl content.

4-Hydroxyquinazoline Hydrochloride.—Runs were similar to those for the methoxyquinazoline, except that twenty-four hours of reflux in the methanol (with exclusion of atmospheric moisture) were necessary. The yield was 0.60 g. (54%) of hydroxyquinazoline hydrochloride.

Anal. Calcd. for $C_8H_6N_2O\cdot HCl$: Cl, 19.42; OCH_3, none. Found: Cl, 19.03; OCH_3, 0.14, 0.21.

The melting behavior consisted of subliming to the needle-like form of 4-hydroxyquinazoline (as shown by mixed melting point) at about 150°, partially liquefying and then resolidifying at 200°, and finally melting as 4-hydroxyquinazoline, 212–215°. This melting behavior was identical to that observed with the hydrochloride obtained by dissolving 4-hydroxyquinazoline in boiling absolute alcohol, passing in dry hydrogen chloride, cooling and filtering. A mixture of the two samples showed no melting point depression.

A check run, diluted to volume with water after the reflux period, yielded 0.25 g. of free hydroxyquinazoline. The chloride analyses on filtrate aliquots were 48% of the maximum possible chloride.

4-Aminoquinazoline.—Finely powdered 4-chloroquinazoline was allowed to stand a day with an excess of concentrated ammonia. The suspension was evaporated almost to dryness, extracted twice with sodium hydroxide and washed with a little water. The yield of 70% was quite pure. Decomposition range[16] is 231–245–260° (sublimes about 150°). It was recrystallizable from alcohol, insoluble in acetone or benzene and slightly soluble in pyridine. *Anal.* Calcd. for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.36; H, 4.76; N, 28.91.

The dihydrobromide was prepared from pure aminoquinazoline by adding an absolute alcoholic solution of dry hydrogen bromide, and removing volatile material by vacuum evaporation. The monohydrobromide was prepared from the dihydrobromide by recrystallization from anhydrous acetone–alcohol. Both salts sublime to the same crystalline form, which begins to melt (dec.) at 292°. *Anal.* Calcd. for $C_8H_7N_3\cdot 2HBr$: Br, 52.1. Found: Br, 49.8, 49.9. Calcd. for $C_8H_7N_3\cdot HBr$: Br, 35.3. Found: Br, 34.9.

4-Acetaminoquinazoline.—The 4-aminoquinazoline was not acylated by prolonged boiling in acetic anhydride or acetyl bromide, or by the Schotten–Baumann method. The amine (0.70 g.) was refluxed eighteen hours with 3 cc. of acetic anhydride and 6 cc. of dry pyridine. The pyridine was removed by vacuum distillation. The remaining solid was purified by washing with ether and water, followed by treatment of its hot alcoholic solution with charcoal. The yield of pure acetaminoquinazoline was 0.35 g.: white crystals, m. p. 172° (sublimes 135°). *Anal.* Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.07; H, 5.09; N, 22.50.

Hydrolysis of 4-Aminoquinazolines.—All hydrolyses were conducted by heating 1 g. of amine at 85° in 10 cc. of dilute acid. Alkylaminoquinazolines listed in the order of their susceptibility to acid hydrolysis are: 2-methyl-1,3-propanediol-2-amino,[17] anilino,[6] amino, butylamino.[17] Conditions necessary for 50% hydrolysis within twenty-four hours ranged from 2 to 3 equiv. of acid per mole of amine. The dialkylaminoquinazolines (morpholino,[17] piperidyl[17] and diethylamino[17]) all hydrolyzed from ten to fifty times the above rate.

5-Amino-4-hydroxy-2-methylquinazoline.—The 5-nitro-4-hydroxy-2-methylquinazoline[18,19] was reduced using Pd–C at 60° and two to three atmospheres of hydrogen for twenty-four hours. Under these conditions the solubility

(13) Bogert and Gortner, THIS JOURNAL, **32**, 123 (1910).

(14) All melting points are corrected.

(15) All nitrogen analyses by the Dumas method.

(16) Decomposition ranges; first softening, first meniscus, and complete liquefaction, respectively. Sample heated at five degrees per minute on a calibrated Fischer–Johns block.

(17) Unpublished work.

(18) Bogert and Chambers, THIS JOURNAL, **27**, 656 (1905).

(19) Bogert and Seil, *ibid.*, **27**, 1307 (1905).

of the compounds limited the amount which could be reduced at one time to 2 g. per 200 cc. of 95% alcohol. No reaction was obtained in absolute alcohol. The white product was in quantitive yield (in contrast to the poor yield of red product reported[20] for stannous chloride reduction). It sublimed and decomposed over a wide range without melting. *Anal.* Calcd. for $C_9H_9N_3O$: N, 24.00. Found: N, 24.29. The dihydrobromide was formed from absolute alcoholic HBr. *Anal.* Calcd. for $C_9H_9N_3O.2HBr$: Br, 47.4. Found: Br, 47.7, 47.1.

5-Acetamino-4-hydroxy-2-methylquinazoline.—The amine (0.60 g.) was refluxed twenty-four hours with 3 cc. acetic anhydride and 6 cc. dry pyridine. The product was isolated and purified in the same manner as 4-acetaminoquinazoline. The yield was 0.48 g. of white crystals, which sublimed about 180° but did not melt below 300°. *Anal.* Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.11; N, 19.35. Found: C, 60.84; H, 5.32; N, 19.64.

5-Cyano-4-hydroxy-2-methylquinazoline.—Pure amine (1.75 g.) was dissolved in 13 cc. hot 21% hydrochloric acid and diazotized at 0° by adding during a period of one hour a solution of 0.81 g. of sodium nitrite in 2 cc. of water. The diazonium solution was neutralized with sodium carbonate to *p*H 7, poured into 11 cc. of cold cuprous cyanide solution,[21] warmed, recooled, strongly acidified with concentrated hydrochloric acid and filtered. The precipitate suspended in a little water was neutralized to *p*H 7 and filtered. Extracting this several times with boiling alcohol removed 1.30 g. (70%) of the crude 5-cyano-4-hydroxy-2-methylquinazoline. Recrystallization from alcohol or water yielded rosets of long, very thin, white needles, which sublimed about 200° but did not melt below 300°. The hydrochloride salt had a similar melting behavior. *Anal.* Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.57; H, 3.52; N, 22.58.

4-Hydroxy-2-methylquinazoline-5-carboxylic Acid Hydrochloride.—The nitrile was sealed in a tube with concentrated hydrochloric acid and heated at 160° for twenty hours. After cooling, some acid hydrochloride was filtered out as white, frequently triangular plates. *Anal.* Calcd. for $C_{10}H_8N_2O_3.HCl$: C, 49.90; H, 3.77; N, 11.64. Found: C, 49.24, 49.25; H, 3.80, 3.88; N, 11.46.

The free base obtained by neutralization of the liquors, evaporating to dryness, and extracting with absolute alcohol was not free of sodium chloride. It sublimed about 235° but did not melt below 300°.

(20) Bogert and Chambers, THIS JOURNAL, **28**, 212 (1906).

(21) Clarke and Read, "Organic Syntheses," 2nd ed. Coll. Vol. I, 1941, p. 514.

Summary

1. Evidence is presented that acid, acting catalytically, increased the reactivity of 4-chloro-4-alkoxy- and 4-aminoquinazolines.

2. Experimental support is provided for the mechanism suggested by Banks.

3. Several previously undescribed compounds of the 4-quinazoline amine and ether series are reported; but the use of 4-chloroquinazoline as an intermediate for other derivatives was not successful.

CORVALLIS, OREGON RECEIVED MAY 14, 1945

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF WASHINGTON]

The Determination of Surface Tension by the Sessile Bubble Method

BY O. L. WHEELER,[1] H. V. TARTAR AND E. C. LINGAFELTER

The surface tensions of solutions of paraffin-chain colloidal electrolytes have become of considerable theoretical interest in the past few years; their determination has, however, been handicapped by the lack of suitable experimental procedures. The more conventional methods are not applicable because the surfaces of these solutions age so slowly that equilibrium values cannot be obtained. It is the purpose of this paper to describe some of the newer procedures that permit unlimited aging of the surfaces so that equilibrium values may be obtained.

Recent workers[1a,2] have shown the practicability of the sessile bubble method but they have not developed thoroughly reliable apparatus nor explained some apparent theoretical anomalies. Consequently work was undertaken to perfect the method to give reproducible and accurate experimental results.

Bashforth and Adams[3] have shown that the shape of a drop of liquid, resting on a level surface and acted upon only by static forces, is a surface of revolution about a vertical axis, the shape being determined by the static forces and the surface tension of the liquid. A bubble of gas in a liquid, when resting underneath a horizontal plane, is analogous and subject to the same theoretical treatment. The shape of this sessile bubble can be given in terms of the diameter at a selected horizontal plane, and the vertical distance from this plane to the apex. Therefore the determination of surface tension requires a suitable apparatus to form and maintain the bubble and to measure the appropriate dimensions. When these have been precisely determined, the calculation of the surface tension can best be made by using the tables given by Bashforth and Adams or, for certain bubble shapes where these tables are not applicable, by the equation developed by Porter.[4] When the selected plane coincides with the equatorial plane, the Bashforth and Adams tables cover the range of h^2/r^2 from 0.2 to 1.0, where h is the vertical distance from the apex of the bubble to the equatorial plane and r is the radius of the bubble in this plane.

To permit the calculation of surface tensions of bubbles for all values of h^2/r^2 Porter[4] undertook the task of extending the application of the theory

(1) Standard Oil Company of California Fellow, 1941-1942.

(1a) Tartar, Sivertz and Reitmeier, THIS JOURNAL **62**, 2375 (1940).

(2) Nutting and Long, *ibid.*, **63**, 84 (1941).

(3) Bashforth and Adams, "An Attempt to Test the Theories of Capillary Action," Cambridge, 1883.

(4) Porter, *Phil. Mag.*, [7] **15**, 163 (1933); [7] **24**, 823 (1937).