allow the solution to stand in a vacuum desiccator over sulfuric acid at 0°. After a few days a yellow solid, identical with the above, appeared.

N-(2'-Chlorophenyl)-5-methoxyanthranilic Acid (IIIb).—A mixture of 50 g. (0.268 mole) of 2-chloro-5-methoxybenzoic acid, 50 g. (0.392 mole) of *o*-chloroaniline, 50 g. (0.362 mole) of anhydrous potassium carbonate, 1 g. of copper powder,[15] and 250 cc. of isoamyl alcohol was condensed and processed as described above. The yellow precipitate obtained by acidification to a *p*H of 7 was recrystallized twice from aqueous ethanol. The yield was 8.5 g. (11.4%, 28.5% allowing for recovered acid), m. p. 189–190°.

Anal. Calcd. for $C_{14}H_{12}O_3NCl$: C, 60.54; H, 4.36; N, 5.04; Cl, 12.76. Found: C, 60.63; H, 4.32; N, 5.34; Cl, 12.92.

The white precipitate obtained at a *p*H of 5 yielded 30 g. of the starting acid. Further acidification of the mother liquor gave only a brown oil.

2-Methoxy-5,9-dichloroacridine (IVb).—The ring closure was conducted as described above employing 7.4 g. (0.027 mole) of N-(2-chlorophenyl)-5-methoxyanthranilic acid. The yield of pure product was 6.2 g. (83.8%), m. p. 157–158° (benzene).

Anal. Calcd. for $C_{14}H_9ONCl_2$: C, 60.45; H, 3.26; N, 5.04; Cl, 25.50. Found: C, 60.55; H, 3.28; N, 4.77; Cl, 26.01.

2-Methoxy-5-chloro-9-[(4-diethylamino-2-amyl)-amino]-acridine.—The condensation was carried out and worked up as described above using 1.1 g. (0.004 mole) of 2-methoxy-5,9-dichloroacridine. Upon removal of the ether, a mixture of a yellow solid and a brown sirup was obtained. The yellow solid was removed and recrystallized from benzene. The compound was 2-methoxy-5-chloro-9-phenoxyacridine, m. p. 189–190°, yield 0.55 g. (41%).

Anal. Calcd. for $C_{26}H_{14}O_2NCl$: C, 71.53; H, 4.20; N, 4.17. Found: C, 71.42; H, 4.22; N, 4.17.

The brown sirup was processed in a manner analogous to that used for the 8-chloro isomer but no crystalline hydrochloride was obtained. Attempts to distil the product led to decomposition.

(15) When copper bronze was used as the catalyst, it was found necessary to dissolve the coating of wax and stearic acid by heating with ethanol.

Summary

2-Methoxy-8,9-dichloroacridine and 2-methoxy-5,9-dichloroacridine have been prepared. The 8-chloro isomer of Quinacrine has been prepared and its antimalarial activity determined. The 5-chloro isomer has been made but was not obtained in a crystalline form.

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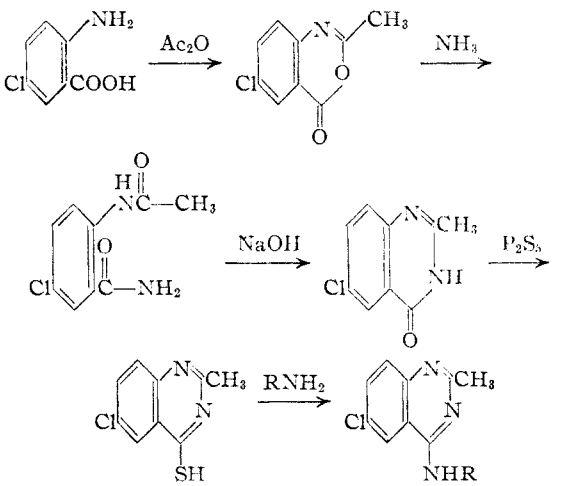
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Quinazolines. VI. Syntheses of Certain 2-Methyl-4-substituted Quinazolines[1]

BY ARTHUR J. TOMISEK AND BERT E. CHRISTENSEN

The study of the quinazoline compounds provides unusual interest, in view of the many novel[2] reactions and unpredictable[3] reaction products. During the course of nitration studies of 2,4-dimethylquinazoline, another unusual reaction was observed; instead of a nitro-2,4-dimethylquinazoline, the reaction product was 2-methyl-6-nitro-4-quinazolone. Even when equimolar quantities of reagents were used the nitrated quinazolone and unreacted quinazoline were the only compounds isolated from the reaction mixture, which fact indicates that the nitration of the quinazolone must have taken precedence over all other reactions. This reaction again illustrates the marked activity of a univalent substituent in the 4-position of the quinazoline nucleus.[4]

Another unpredictable reaction[5] of the quinazolines is illustrated in the chlorination of 2-methyl-4-quinazolone; in this instance benzenoid chlorination occurs along with the replacement of the 4-hydroxyl group. This makes it impossible to prepare 4-alkylaminoquinazolines with a methyl substituent in the 2-position by the usual procedures, *i. e.*, coupling of the 4-chloro derivative with desired amine. Recently Leonard and Curtin[6] have successfully employed the 4-mercaptoquinazolines in place of the usual chloro derivative as intermediates for synthesis of alkylamino compounds. This procedure has now been used to circumvent the problem of benzenoid chlorination in the preparation of 4-alkylamino-2-methylquinazolines; 2-methyl-4-quinazolone and 6-chloro-2-methyl-4-quinazolone were readily converted to the respective 4-mercaptoquinazolines by means of phos-



(1) Published with the approval of the Monographs Publication Committee, Oregon State College, as Research Paper No. 124.

(2) Leonard and Curtin, *J. Org. Chem.*, **11**, 341 (1946).

(3) Tomisek and Christensen, THIS JOURNAL, **70**, 874 (1948).

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

(5) Dehoff, *J. prakt. Chem.*, **2**, **42**, 352 (1890); Bogert and May, THIS JOURNAL, **31**, 511 (1909).

(6) Leonard and Curtin, *J. Org. Chem.*, **11**, 349 (1946).

phorus pentasulfide in refluxing xylene. 2-Methyl-6-nitro-4-quinazolone on the other hand gave no reaction with phosphorus pentasulfide, even upon twelve hours of heating in boiling *p*-cymene. This was probably due to its solubility characteristics.

The 6-chloro-2-methyl-4-quinazolone was prepared through a series of previously unreported intermediates. For purposes of characterization small amounts of each of these intermediates were purified after each stage of the synthesis. The diagram illustrating this series of reactions is also representative of the synthesis and reaction of 2-methyl-4-quinazolone.

Experimental[7]

6-Chloro-2-methyl-4-quinazolone.—A solution consisting of 25 g. of 5-chloroanthranilic acid[8] and 75 ml. of pure acetic anhydride was refluxed one hour, then cooled to about 0° and filtered. The crystalline product (21.8 g. of crude benzoxazine) was converted to N-acetyl-5-chloroanthranilamide after standing four hours in concentrated ammonia. Ten ml. of 10% sodium hydroxide was added to the unisolated product and the mixture was heated for several minutes; then the quinazolone was brought into solution by addition of an excess of hot 10% sodium hydroxide. The basic solution was decolorized with charcoal, adjusted to *p*H 8 and filtered (5.4 g. of crude N-acetyl-5-chloroanthranilic acid was recovered from the filtrate). The product was recrystallized from alcohol, and residues from the alcoholic liquors were recrystallized (with charcoal treatment) from aqueous acetic acid. The combined quinazolone fractions, 10.45 g., m. p. 283–286°, corresponds to an over-all yield of 37%. An additional recrystallization from the acetic acid raised the m. p. to 287°.

Anal. Calcd. for $C_9H_7N_2OCl$: C, 55.54; H, 3.63; N, 14.40. Found: C, 55.30; H, 3.91; N, 14.55.

6-Chloro-2-methyl-3,1,4-benzoxaz-4-one.—A small amount of the crude benzoxazone[9] was removed at the point indicated above, decolorized and recrystallized from hot acetic anhydride solution. The colorless plates melted at 124–125°.

Anal. Calcd. for $C_9H_6NO_2Cl$: C, 55.26; H, 3.09. Found: C, 55.17; H, 2.84.

N-Acetyl-5-chloroanthranilamide.—A sample of the crude N-acetyl-5-chloroanthranilamide which occurred as an intermediate in the above synthesis of 6-chloro-2-methyl-4-quinazolone was recrystallized from alcohol to yield white crystals of m. p. 183°.

Anal. Calcd. for $C_9H_9N_2O_2Cl$: C, 50.83; H, 4.27. Found: C, 50.88; H, 4.16.

N-Acetyl-5-chloroanthranilic Acid.—The crude N-acetyl-5-chloroanthranilic acid which occurred as a result of incomplete and/or side reaction in the above synthesis of 6-chloro-2-methyl-4-quinazolone was decolorized from hot aqueous alcohol and crystallized. The flat white needles melted at 204°. This compound is not to be confused with 5-chloroanthranilic acid (m. p. 210–212°)[10] the melting point of which in the earlier literature[11] is given as 204°.

Anal. Calcd. for $C_9H_8NO_3Cl$: C, 50.60; H, 3.77. Found: C, 50.71; H, 3.67.

2-Methyl-4-mercaptoquinazoline.—Sixteen grams (0.1 mole) of 2-methyl-4-quinazolone and 21.6 g. (0.1 mole) of phosphorus pentasulfide were mixed dry. One hundred ml. of xylene was added and mixture was refluxed two hours. The heating was interrupted at the end of the first hour to permit repulverizing of the solids in the mixture. The mixture was shaken with 100 ml. of 10% sodium hydroxide and filtered. The solid material from the filtration was thoroughly dried, then extracted with 100 ml. of hot 10% sodium hydroxide. The combined basic solutions after treatment with charcoal were precipitated with acetic acid. The solid material was removed by filtration and reprecipitated from sodium hydroxide solution.

This crude mercaptoquinazoline was recrystallized from aqueous alcohol to yield 8.55 g. (49%) of yellow needles, m. p. 217–219°. The melting point recorded for 2-methyl-4-mercaptoquinazoline as prepared from acetylanthranilic-nitrile is 218–219° (dec.).[12]

6-Chloro-2-methyl-4-mercaptoquinazoline.—The synthesis and isolation were as given for 2-methyl-4-mercaptoquinazoline. The crude 6-chloro-2-methyl-4-mercaptoquinazoline was decolorized and recrystallized from hot aqueous alcohol solution. The yield from 19.5 g. (0.1 mole) of 6-chloro-2-methyl-4-quinazoline was 11.6 g. (55%). An additional recrystallization from aqueous acetic acid gave yellow needles of m. p. (dec.) 276–278°.

Anal. Calcd. for $C_9H_7N_2SCl$: C, 51.30; H, 3.35; Cl, 16.83. Found: C, 51.53; H, 3.21; Cl, 16.78.

4-(β-Hydroxyethylamino)-2-methylquinazoline.—A mixture of 5 ml. of ethanolamine and 1.47 g. of 2-methyl-4-mercaptoquinazoline was heated for seven hours at 80°. The suspension which resulted on cooling was diluted with a small amount of water. This product was recrystallized (preferably by seeding from a previous preparation) yielding rosettes of thick, yellow needles. The product (1.5 g., 88%) was dissolved in hot dioxane, in order to remove a trace of insoluble oil. This solution was then evaporated to dryness, and the residue was recrystallized from the minimum amount of water. The pure 4-(β-hydroxyethylamino)-2-methylquinazoline crystallized from water as yellow prisms and spherulites. When dropped upon a hot melting point block the crystals appeared to melt at 164–166° resolidifying to white needles which melted (with sublimation) at 174.5–176°. Since both forms recrystallized from water to yield a mixture of highly birefringent spherulites and prisms one cannot attribute the behavior to crystal habit or to a monotropic transformation on the basis of the present information.

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 64.83; H, 6.69; N, 20.69.

6-Chloro-4-(*p*-methoxyanilino)-2-methylquinazoline.—A mixture of 4 g. of *p*-anisidine and 1.75 g. of 6-chloro-2-methyl-4-mercaptoquinazoline was heated for six hours at 190°. The resulting dark yellow solid was triturated first with acid and then with sodium hydroxide. The solid was decolorized and recrystallized from 0.5 *N* hydrochloric acid to yield 0.59 g. of fine, yellow needles of 6-chloro-4-(*p*-methoxyanilino)-2-methylquinazoline hydrochloride. The m. p. in a capillary block preheated to 319° was 321° (dec.).

Anal. Calcd. for $C_{16}H_{15}N_3OCl_2$: C, 57.15; H, 4.50. Found: C, 57.41; H, 4.42.

Nitration of 2,4-Dimethylquinazoline.—Two and one-half grams of 2,4-dimethylquinazoline was dissolved in 20 ml. of concentrated sulfuric acid and 10 ml. of fuming nitric acid (sp. gr. 1.5) was added in one portion. In order to keep the initial temperature below 75°, it was necessary to cool the reaction mixture which was then maintained at 75° for one hour, and then poured on 200 g. of ice; tiny white needles (0.61 g.) separated on standing overnight. The liquors were neutralized to yield more product which was recrystallized from glacial acetic acid; yield 1.84 g. Several recrystallizations from glacial acetic acid and pyridine gave a product with m. p. (dec.) 302–304°, which did not depress the melting point of the 2-methyl-6-nitro-4-quinazolone prepared later by nitration of 2-methyl-4-quinazolone.

Anal. Calcd. for $C_9H_7N_3O_3$: N, 20.48. Found: N, 20.44.

(7) All melting points are corrected.

(8) Eastman Kodak Company, technical grade (blue label).

(9) Wegscheider and Faltis, *Monatsh.*, **33**, 185 (1911).

(10) Magidson and Golovchinskaya, *J. Gen. Chem.* (*USSR*), **8**, 1801 (1938).

(11) Eller and Klemm, *Ber.*, **55**, 222 (1922).

(12) Bogert, Breneman and Hand, THIS JOURNAL, **25**, 377 (1903).

Nitration of 2-Methyl-4-quinazolone.—Two and one-half grams of 2-methyl-4-quinazolone was nitrated according to the directions given for the nitration of 2,4-dimethylquinazoline. The yield of crude product was 2.8 g. The m. p. after several recrystallizations was 298–300° (dec.) Bogert and Geiger reported[13] a melting point of 299° (uncor.) for 2-methyl-6-nitro-4-quinazolone obtained by a similar nitration.

(13) Bogert and Geiger, THIS JOURNAL, **34**, 529 (1912).

Summary

4-Mercapto-2-methylquinazoline can be used as an intermediate for synthesis of 4-(β-hydroxyethylamino)-2-methylquinazoline and 6-chloro-4-(*p*-methoxyanilino)-2-methylquinazoline.

The nitration of 2,4-dimethylquinazoline yields 2-methyl-6-nitro-4-quinazolone.

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[CONTRIBUTION NO. 80 FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF UTAH]

The Willgerodt Reaction on α-Tetralone

BY W. J. HORTON AND J. VAN DEN BERGHE[1]

The reaction of aliphatic aromatic ketones with aqueous ammonium polysulfide to produce ω-aryl aliphatic amides, first reported by Willgerodt,[2] has been shown to be applicable to olefins, acetylenes, aldehydes, alcohols and mercaptans.[3,4] It is apparent that a rearrangement is not involved.[5] This confirms Willgerodt's experiment[6] in which isovalerophenone was converted to α-methyl-γ-phenylbutyramide rather than the β-methyl-γ-phenylbutyramide expected by rearrangement. This reaction has been successfully repeated in several laboratories.[4,7,8]

The most important suggestions as to the mechanism of the reaction[4,8] have postulated a group which migrates along the chain by reversible steps, the process being terminated by irreversible changes which yield the amide. These ideas have been supported by the fact that the proposed intermediates, olefins, acetylenes, mercaptans, will yield amides if they are submitted to the conditions of the reaction. No intermediates have been isolated from the reaction mixture.

In the hope of interrupting the progression of a functional group along the aliphatic chain, we proposed to terminate the aliphatic chain of the aliphatic aromatic ketone with a second aryl group, or to use α-tetralone in the reaction[9] so that the aryl group of the ketone would also be the terminal group on the chain. We employed for convenience the modification suggested by Schwenk and Bloch[10] which avoids the use of sealed tubes.[11] The principal product of the reaction was a tertiary aromatic amine. When this was hydrolyzed using dilute sulfuric acid in a sealed tube,[12] β-naphthol was obtained and further identified by conversion to β-naphthyl methyl ether. That the amine is 4-(2-naphthyl)-morpholine was fully confirmed by independent syntheses from β-naphthol and morpholine in the presence of aqueous sodium bisulfite, and from β-naphthylamine and β,β′-dichlorodiethyl ether.[13]

The reaction of α-tetralone, morpholine and sulfur gives, in addition to the above amine, small amounts of at least one other product which has not been fully investigated.

When α- or β-naphthol replaced α-tetralone in this reaction, no amines could be found. Thus the conversion of α-tetralone to α-naphthol by means of sulfur cannot be the initial step in the reaction.

We have also investigated the behavior of morpholine and sulfur without the addition of any other material. Several reports in which the Schwenk and Bloch modification of the Willgerodt reaction was used have appeared[14,15] but products of a reaction between morpholine and sulfur have not been noted.[16] At a temperature just above that used to produce 4-(2-naphthyl)-morpholine from α-tetralone, morpholine and sulfur, the latter two components alone gave a high melting compound which resembled that isolated in the reaction of commercial diisobutylene, two styrene homologs, or certain mercaptans with morpholine and sulfur and shown to be dithiooxalodimorpholide.[15] When our product was mixed with known dithioöxalodimorpholide, no depression of the melting point was obtained. Hydrolysis of the high melting material with aqueous hydrobromic acid produced the hydrobromide of β,β′-dibromodiethylamine. It is apparent then that sulfur attacks the morpholine molecule to give hydrogen sulfide and a dithioöxalyl fragment

(1) In part from the Master's Dissertation of J. Van Den Berghe.

(2) Willgerodt, *Ber.*, **20**, 2467 (1887).

(3) For a recent review of this reaction, see Carmack and Spielman, "Organic Reactions," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 83.

(4) King and McMillan, THIS JOURNAL, **68**, 525, 632 (1946).

(5) Shantz and Rittenberg, *ibid.*, **68**, 2109 (1946). Calvin, *et al.*, *ibid.*, **68**, 2117 (1946), have shown that the acid produced is not formed by the same mechanism as the amide.

(6) Willgerodt and Merck, *J. prakt. Chem.*, **80**, 192 (1909).

(7) Fieser and Kilmer, THIS JOURNAL, **62**, 1354 (1940).

(8) Carmack and De Tar, *ibid.*, **68**, 2029 (1946).

(9) This is the first recorded example of a cyclic ketone in the Willgerodt reaction.

(10) Schwenk and Bloch, THIS JOURNAL, **64**, 3051 (1942).

(11) Preliminary work by one of us on α-tetralone and aqueous ammonium polysulfide in a sealed tube gave crystals melting at 139–140° which contain sulfur but no nitrogen.

(12) *Cf.* Arnold, Buckley and Richter, THIS JOURNAL, **69**, 2322 (1947), who treated 1-acetamido-3,4-dimethylnaphthalene in this manner.

(13) Cretcher and Pittenger, *ibid.*, **47**, 163 (1925).

(14) Campaigne and Rutan, *ibid.*, **69**, 1211 (1947); Arnold and Rondestvedt, *ibid.*, **67**, 1265 (1945).

(15) McMillan and King, *ibid.*, **69**, 1207 (1947).

(16) Carmack has reported (ref. 8) a high melting material in the reaction of phenylacetylene with morpholine and sulfur.