[CONTRIBUTION FROM THE STEELE CHEMICAL LABORATORY OF DARTMOUTH COLLEGE]

2,4-Dihydroxy-3-quinolyl Methyl Ketones[1]

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The preparation of the substances described below was undertaken in order that they might be tested as antimalarials. Two of the compounds were submitted for testing: 6-methoxy-2,4-dihydroxy-3-quinolyl methyl ketone (SN 12,989)[2] and 7-chloro-2,4-dihydroxy-3-quinolyl methyl ketone (SN 12,990).[2] The results of these tests will be reported elsewhere.

In general the preparation of 2,4-dihydroxyquinolines has been carried out by four processes: one involves the reduction and simultaneous cyclization of an *o*-nitrobenzoylmalonic ester as described by Bischoff[3] and later modified by others[4]; a second process involves the cyclization of an anilide of malonic ester as described by several authors[5,6,7]; the third involves the condensation of an ester of anthranilic acid with malonic ester[8]; and the fourth is a relatively simple reaction between quinoline and anhydrous potassium hydroxide in the presence of barium oxide.[9] Preliminary tests showed that the first method was unpromising, and the third and fourth methods were set aside as unnecessarily cumbersome. Hence the second method, cyclization of an anilide of malonic ester, seemed most suitable. There was a precedent for using a substituted malonic ester,[7] and substitution by the acetyl group, if anything, facilitated the over-all reaction.

The procedure employed in the syntheses is in general that of Kämmerer,[6] but the concentration of reactants is particularly important since side reactions producing tars occur if too little solvent, nitrobenzene, is used. From this it would appear that the initial reaction between an amine and acetylmalonic ester is the formation of an ethyl malonanilate with the elimination of ethanol. Evidently the subsequent ring closure, with the elimination of another molecule of ethanol, is a slower process, probably first order; and the tar formation is of higher order since dilution has no apparent effect on the rate of cyclization but materially diminishes the tar formation.

The compounds which may be prepared in this manner constitute a new class, of which three members have been prepared in the present work. While 6 - methoxy - 2,4 - dihydroxy -3 - quinolyl methyl ketone (I) was prepared in good yield from 4-anisidine and acetylmalonic ester, the reaction between 3-chloroaniline and acetylmalonic ester yielded two isomeric substances as was expected: one in considerably greater quantity (84% of the product). Steric considerations indicated that the isomer formed in greater yield would be 7-chloro-2,4-dihydroxy-3-quinolyl methyl ketone (II), while the other isomer would be 5-chloro-2,4-dihydroxy-3-quinolyl methyl ketone (III). Various attempts at structure proof by synthesis or by degradation of II were unsuccessful until a chance attempt to convert the acetyl group to carboxyl by means of sodium hypobromite[10] yielded an unexpected substance which upon purification and analysis proved to be 4-chloroanthranilic acid. Evidently the sodium hypobromite acted to disrupt the hetero-ring yielding a primary amino group from the quinoline nitrogen and a carboxyl group from the 4-carbon atom. Obviously this acid could only have been formed from the 7-chloro isomer (II), since the 5-chloro isomer (III) would give 6-chloroanthranilic acid. Thus, predictions of the course of the cyclization were found to be correct.

The three 2,4-dihydroxy-3-quinolyl methyl ketones described proved to be very stable crystalline solids with relatively high decomposition points. As acids they are stronger than most phenols, although the solubility of the 7-chloro compound in 5% sodium carbonate solution is masked by the formation of a very insoluble sodium salt. All of the ketones are insoluble in 5% sodium bicarbonate solution and in 5% hydrochloric acid. They are insoluble in water and in absolute ethanol (<0.03 g. per 100 ml.), but they are conveniently recrystallizable from glacial acetic acid. All three give a characteristic orange-red color with ferric chloride in alcoholic solution.

Experimental[11,12]

6-Methoxy-2,4-dihydroxy-3-quinolyl Methyl Ketone (I) (SN 12,989).[2]—A solution of 3.0 g. (0.024 mole) of 4-anisidine and 10 g. (0.049 mole) of acetylmalonic ester[13] in 75 ml. of nitrobenzene[14] was heated in a metal bath at 230–235° for one hour[14] during which time the ethanol

(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 Dartmouth College.

(2) Number assigned to compound by the Survey of Antimalarial Drugs.

(3) Bischoff, *Ann.*, **251**, 360 (1889).

(4) Gabriel, *Ber.*, **51**, 1500 (1918); Asahina, *ibid.*, **63**, 2057 (1930).

(5) Baumgarten and Kärgel, *ibid.*, **60**, 832 (1927).

(6) Kämmerer, German Patent 505,798; *Chem. Zentr.*, **102**, I, 2679 (1931).

(7) Meyer and Heimann, *Compt. rend.*, **204**, 1204 (1937).

(8) Koller, *Ber.*, **60**, 1108 (1927).

(9) Tschitschibabin, *J. Russ. Phys.-Chem. Soc.*, **55**, 7 (1924).

(10) Homeyer, Whitmore and Wallingford, THIS JOURNAL, **55**, 4209 (1933).

(11) All melting points are corrected.

(12) Generous supplies of 4-anisidine, 3-chloroaniline and technical malonic ester were provided by Dr. R. C. Elderfield of Columbia University.

(13) Lund, *Ber.*, **67B**, 935 (1934).

(14) By adjustment of the reaction time and dilution, tar formation was minimized. A shorter time gave incomplete reaction, and the use of less nitrobenzene resulted in formation of tarry by-products (which remained dissolved) at the expense of the desired product.

formed in the reaction was allowed to distil over while the other liquids refluxed.[5,6] Upon cooling the reaction mixture, a heavy crystalline precipitate was formed. The precipitate was filtered off and washed thoroughly with ether to remove nitrobenzene. The product weighed 3.5 g. (63%) and recrystallization from glacial acetic acid yielded fine bright yellow needles, m. p. 287.0–289.3° with decomposition. A gradual darkening of the material in the capillary was observed above 270°.

Anal. Calcd. for $C_{12}H_{11}O_4N$: C, 61.79; H, 4.76; N, 6.01. Found: C, 61.90; H, 4.82; N, 6.31.

4,4′-Dimethoxymalonanilide.—In a preliminary attempt to prepare I, equimolecular quantities of 4-anisidine (30 g.) and malonic ester (40 g.) in 50 ml. of nitrobenzene were warmed in a metal bath at 230–235° for about three hours. Upon cooling, the reaction mixture yielded 15 g. of brown-orange crystals. A 1-g. sample was recrystallized from 100 ml. of alcohol (norite) and then further recrystallized for analysis to yield white flat needles, m. p. 232.4–233.0°. The formula deduced from the analysis showed the substance to be 4,4′-dimethoxymalonanilide.[15]

Anal. Calcd. for $C_{17}H_{18}O_4N_2$: C, 64.95; H, 5.77; N, 8.91. Found: C, 65.04; H, 5.90; N, 9.40.

7-Chloro-2,4-dihydroxy-3-quinolyl Methyl Ketone (II) (SN 12,990)[2] and 5-Chloro-2,4-dihydroxy-3-quinolyl Methyl Ketone (III).—A solution of 10.5 ml. (0.10 mole) of 3-chloroaniline and 40 ml. (0.21 mole) of acetylmalonic ester[13] in 300 ml. of nitrobenzene was heated in a metal bath at 230–235°, as in the preparation of I, for two hours.[5,6] Upon cooling, filtering and washing the precipitate well with ether there was obtained 14.3 g. of a crystalline product (60.4%). This was shown to be a mixture of two isomeric substances, II and III. It was dried and powdered and was then warmed on the steam-bath in 5% sodium carbonate solution with vigorous stirring for three hours, after which the mixture was cooled and filtered. The residue was thoroughly washed with water and the washings were added to the filtrate, the residue being pressed as nearly dry as possible. The moist residue was recrystallized directly from glacial acetic acid to yield 10 g. of a substance (II) melting at 280–283° with decomposition. Gradual darkening of the substance in the capillary was observed above 250°. Further recrystallization from glacial acetic acid yielded flat pale yellow or flesh-colored needles, m. p. 283.0–285.8° with decomposition and with gradual darkening above 260°.

Anal. Calcd. for $C_{11}H_8O_3NCl$: C, 55.62; H, 3.40; N, 5.90. Found: C, 55.89; H, 3.65; N, 6.05.

The sodium carbonate solution from which II had been removed by filtration was acidified with hydrochloric acid. After filtration and drying, the yellow precipitate (III) formed in this manner weighed 2.3 g. (16% of the product). It was recrystallized from glacial acetic acid to give a yellow crystalline powder which darkened above 250° and decomposed slowly above 295°.

Anal. Calcd. for $C_{11}H_8O_3NCl$: C, 55.62; H, 3.40; N, 5.90. Found: C, 55.89; H, 3.46; N, 6.18.

Reaction of Sodium Hypobromite with II.—To a mixture of 10 g. of ice in a cold solution of 5.3 g. of sodium hydroxide in 20 ml. of water there was added slowly 2.4 ml. of bromine.[16] The addition required about ten minutes during which time the mixture was well stirred with a wire stirrer.[16] To the resulting solution of sodium hypobromite, cooled in an ice–salt-bath, was added 3.9 g. (0.016 mole) of II. The stirring was continued, and the odor of bromoform was noticeable almost at once. After one hour all of the suspended II had dissolved,[17] but the stirring was continued overnight at room temperature. The solution was then extracted with ether to remove bromoform and carbon tetrabromide. After this treatment the clear, dark-colored aqueous layer was acidified with acetic acid whereupon there was a copious evolution of carbon dioxide. The solution was further acidified with concentrated hydrochloric acid and warmed on the steam-bath for one hour, and after cooling and filtering there was obtained 1.5 g. of a substance containing nitrogen and chlorine. It was soluble in 5% sodium bicarbonate solution but not in dilute hydrochloric acid. Upon recrystallization from glacial acetic acid it melted with the evolution of a gas at 227–229°. Repeated recrystallization from ethanol–water yielded pale yellow needles, m. p. 235.0–235.5° with the evolution of a gas. This corresponds to the melting point, with the evolution of carbon dioxide, of 4-chloroanthranilic acid; and the melting point of a mixture of authentic 4-chloroanthranilic acid with this substance showed no depression.

Anal. Calcd. for $C_7H_6O_2NCl$: C, 49.00; H, 3.53; N, 8.16. Found: C, 49.06; H, 3.64; N, 8.45.

Summary

6-Methoxy-, 7-chloro- and 5-chloro-2,4-dihydroxy-3-quinolyl methyl ketones have been prepared. These substances are stable compounds with relatively high decomposition points. They are more acidic than ordinary phenols and they give a characteristic color reaction with alcoholic ferric chloride. The structure of the 7-chloro compound has been demonstrated by degradation to 4-chloroanthranilic acid. 4,4′-Dimethoxymalonanilide has also been prepared.

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(15) *Cf.* Chattaway and Mason, *J. Chem. Soc.*, **97**, 339 (1910).

(16) Hershberg, *Ind. Eng. Chem., Anal. Ed.*, **8**, 313 (1936).

(17) In subsequent runs of this reaction there was invariably recovered a small quantity of unchanged II.