[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Preparation of 4-Quinolinols by the Ethyl Ethoxalylacetate Method[1]

BY BYRON RIEGEL, CHARLES J. ALBISETTI, JR., GERALD R. LAPPIN AND ROBERT H. BAKER

After our pioneering work among the antimalarial contractors on the 4-aminoquinolines,[2] better methods for the synthesis of 4-quinolinols[3] were actively investigated. In a manner analogous to that used by Mueller and Hamilton[4] for the preparation of 1-chlorobenzo(f)quinolines, we applied the oxalacetic ester method to aniline and *p*-anisidine. Independently, Surrey and Hammer[5] have used this method on *meta*-substituted anilines.

An improved method is described which makes unnecessary the isolation of oxalacetic ester and which is more rapid than the method used by Musajo.[6] Acidification of a benzene–water suspension of the sodium salt of ethyl ethoxalylacetate gave the free ester which could react directly with aniline. Cyclization of the anilino compound by means of refluxing diphenyl ether was found to be more satisfactory than the use of mineral oil because of the ease of removal of solvent and of temperature regulation. Decarboxylation of the acid obtained after saponification was effected by heating in the same solvent. In the case of *p*-anisidine, however, mineral oil was used because the products were more soluble in diphenyl ether.

2-Carbethoxy-4-quinolinol was obtained in 61% yield from commercial (91%) ethyl sodio-ethoxalylacetate and this was converted to 4-quinolinol in 95% yield. In a similar fashion 6-methoxy-4-quinolinol was obtained in 42% yield.

Experimental

2-Carbethoxy-4-quinolinol.—To a cooled, stirred mixture of 105 g. (0.5 mole) of ethyl sodio-ethoxalylacetate, 250 ml. of water and 500 ml. of benzene was added 84 ml. of 6 *N* sulfuric acid over a period of ten minutes. If the mixture was allowed to stand for more than five minutes before the addition of the sulfuric acid, it had a tendency to set to a solid mass which was difficult to stir. The benzene layer was separated and was washed with two 300-ml. portions of water. To the organic layer was added 75 g. (0.8 mole) of aniline, and the mixture was refluxed for one hour. After cooling, the benzene solution was washed with dilute sulfuric acid followed by three 500-ml. portions of water to remove the excess aniline. The benzene was removed by distillation and the residual oil was carefully added to 700 ml. of refluxing diphenyl ether. The mixture was refluxed for ten minutes and cooled; the product, light yellow crystals, was isolated by filtration and was washed by trituration with 700 ml. of hexane. The product weighed 66 g. (61%) and melted at 213°. The reported m. p.[6] is 215°.

The reaction with free ethyl ethoxalylacetate and aniline in a similar fashion gave comparable results. Preliminary experiments involving the reaction of a water mixture of aniline hydrochloride and ethyl sodio-ethoxalylacetate for short periods of time gave erratic results.

4-Quinolinol.—Saponification of 43.4 g. (0.2 mole) of 2-carbethoxy-4-quinolinol with boiling dilute aqueous sodium hydroxide followed by acidification with 6 *N* hydrochloric acid produced 2-carboxy-4-quinolinol. Purified by crystallization from dilute acetic acid, the acid[6] decomposed at 277° with the evolution of carbon dioxide. The dry acid was decarboxylated by addition to 500 ml. of stirred, refluxing diphenyl ether. The mixture was refluxed for fifteen minutes or until the evolution of carbon dioxide ceased. After cooling, the product was isolated by filtration and was washed with 500 ml. of hexane to give 28.6 g. (95%) of 4-quinolinol, m. p. 185–188°. Crystallized from aqueous ethanol, the material melted at 200–201°.

Decarboxylation by direct pyrolysis using a salt-bath at 270–280° was effective only for several gram portions and was incomplete when larger quantities were used.

6-Methoxy-4-quinolinol.—Ethyl ethoxalylacetate was isolated from its sodium salt in the manner described above. The benzene solution obtained, after washing, was concentrated to remove the benzene and the residue was distilled *in vacuo*. The yield of the free ester was 65–70%, b. p. 85–87° at 1 mm.

It is unnecessary to dry the benzene solution and it should not be treated with alkaline agents such as sodium carbonate, which reduces the yield to 15–25%.

The anilino compound was formed from ethyl ethoxalylacetate and *p*-anisidine by allowing the mixture to stand twenty-four hours in a vacuum desiccator over calcium chloride. Cyclization was effected as described above except that stirred mineral oil, preheated to 255°, was used as the solvent. After heating for five minutes, the mixture was cooled and the product was separated by filtration and was washed with acetone. From 10.0 g. (0.053 mole) of ethyl ethoxalylacetate and 6.4 g. (0.052 mole) of *p*-anisidine, using 100 ml. of mineral oil, there was obtained 11.1 g. (85%) of 6-methoxy-2-carbethoxy-4-quinolinol. The product was a yellow crystalline solid, m. p. 215–216°. Saponification of the ester with 100 ml. of 15% aqueous sodium hydroxide at the reflux temperature followed by acidification with 6 *N* sulfuric acid produced 9.3 g. (96%) of 6-methoxy-2-carboxy-4-quinolinol, a brown solid, m. p. 305–308°. Two grams of the acid was heated at the melting point until the evolution of carbon dioxide ceased. The product was extracted with boiling ethanol, the solution was clarified with decolorizing carbon and the product was crystallized from aqueous ethanol. There was obtained 1.28 g. (80%) of 6-methoxy-4-quinolinol, white needles, m. p. 219–220°.

Chlorination of the hydroxy compound with phosphorous oxychloride in the usual manner produced 4-chloro-6-methoxyquinoline in 90.5% yield. This material melted at 75–76° and was identical with an authentic sample of 4-chloro-6-methoxyquinoline.

In dealing with larger quantities, decarboxylation of 6-methoxy-2-carboxy-4-quinolinol was carried out by addition of the dry acid to stirred mineral oil preheated to 255° followed by heating at this temperature for ten minutes or until the evolution of carbon dioxide ceased.

Summary

1. 4-Quinolinol and 6-methoxy-4-quinolinol have been prepared from the appropriate amines and crude ethyl ethoxalylacetate which is obtain-

(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 Northwestern University.

(2) B. Riegel, G. R. Lappin, C. J. Albisetti, Jr., B. H. Adelson, R. M. Dodson, L. G. Ginger and R. H. Baker, THIS JOURNAL, **68**, 1229 (1946).

(3) B. Riegel, G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson and R. H. Baker, *ibid.*, **68**, 1264 (1946).

(4) A. C. Mueller and C. S. Hamilton, *ibid.*, **65**, 1017 (1943).

(5) A. R. Surrey and H. F. Hammer, *ibid.*, **68**, 113 (1946).

(6) L. Musajo, *Gazz. chim. ital.*, **67**, 222 (1937).

able from commercial ethyl sodioethoxalylacetate.

2. The yield of the intermediate 2-carbethoxy-4-quinolinol is not appreciably raised by use of pure oxalacetic ester.

3. Variations in yield due to different methods of decarboxylating the 2-quinolinecarboxylic acids are noted.

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Synthesis of 7-Chloro-4-hydroxyquinoline Derivatives Employing Oxalacetic Ester[1]

BY GEORGE F. LISK AND GARDNER W. STACY[2]

Andersag, Breitner and Jung[3] prepared a number of 2-carbethoxy-4-hydroxyquinoline derivatives by thermal cyclization of β-carbethoxy-β′-anilinoacrylates, which themselves were obtained by the reaction of aromatic amines with oxalacetic ester. After removal of the carbethoxy group by hydrolysis and decarboxylation the 4-hydroxyquinolines were converted to 4-chloroquinolines which then could be condensed with basic side-chains yielding 4-dialkylaminoalkylaminoquinoline derivatives. Recently several workers[4] have elaborated on this synthesis and have prepared a number of substituted quinolines.

This synthesis is usually satisfactory; however, when cyclization of acrylates prepared from *meta*-substituted anilines is attempted, a mixture of 5- and 7-substituted quinolines results. For example, cyclization of β-carbethoxy-β-(*m*-chloroanilino)-acrylate yields both possible isomeric quinoline derivatives in about equal amounts. Since only the 7-isomer is desired in the preparation of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline, chloroquine, it seemed advisable to investigate the synthesis with the hope of finding conditions under which the tendency toward formation of the 5-isomer would be reduced. Therefore, a study was made of the variation of the ratio of isomers formed with the amount of diluent used in cyclization. The results of this series of experiments revealed that when limited amounts of diluent were employed, virtually all 5-isomer was obtained. When large amounts (thirty parts of diluent to one part of acrylate) were used, about 40% of the 5-isomer resulted. This trend is illustrated in Fig. 1. At the same time, however, the yields of combined dichloroquinolines, based on *m*-chloroaniline, varied from 17% at 2:1 (two parts of diluent to one part of acrylate) to 28% at 30:1, reaching a maximum of 32% at 15:1.

Since the ratio of isomers could not be altered

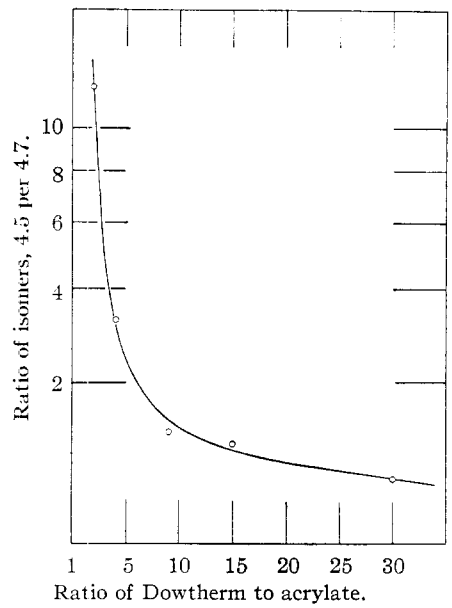
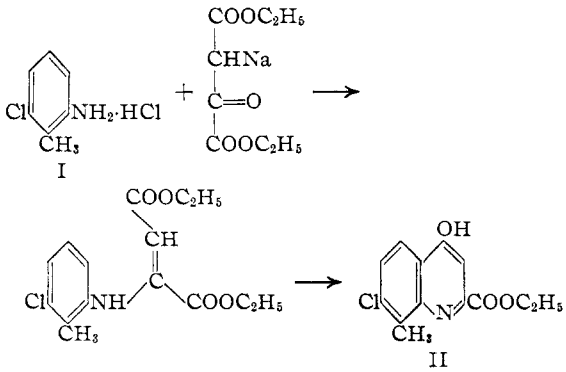


Fig. 1.—Curve showing changes in the composition of a mixture of isomeric dichloroquinolines, obtained by thermal cyclization of β-carbethoxy-β-(*m*-chloroanilino)-acrylate in varying amounts of Dowtherm. The melting points corresponding to the ratio of isomers indicated were: 2:1, 59.5–62.1°; 4:1, 58.8–64.2°; 8:1, 59.4–70.2°; 15:1, 59.4–71.0°; 30:1, 59.6–74.3°.



(1) The work described in this paper was done in part under contracts, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the National Aniline Division of the Allied Chemical and Dye Corporation and between the Office of Scientific Research and Development and the University of Illinois.

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(3) Andersag, Breitner and Jung, German Patent 683,692; *C. A.*, **36**, 4973 (1942); U. S. Patent 2,233,970; *C. A.*, **35**, 3771 (1941).

(4) (a) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946); (b) Steck, Hallock and Holland, *ibid.*, **68**, 132 (1946); (c) Steck, Hallock and Holland, *ibid.*, **68**, 380 (1946); (d) Surrey and Cutler, *ibid.*, **68**, 514 (1946).