orthoformate react directly under the influence of heat to form α-substituted β-anilinoacrylates through elimination of ethyl alcohol. The generality of the reaction has been shown by application to several substituted anilines and to various active methylene reagents. The yields of acrylates in the reaction have been shown to be strongly dependent upon the activity of the methylene group of the reagent used. The products of the reaction are of value in the synthesis of 4-hydroxyquinolines.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

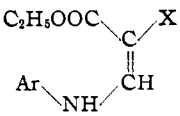
Synthesis of 4-Hydroxyquinolines. IV. A Modified Preparation through *bis*-(*m*-Chlorophenyl)-formamidine[1]

BY CHARLES C. PRICE[2] AND ROYSTON M. ROBERTS[3]

The advantages of the synthesis of 4-hydroxyquinolines through the β-arylamino-α-carbethoxyacrylates (I) formed from ethoxymethylenemalonic ester have been outlined in the first paper of this series.[4] The principal disadvantage for large-scale production is the expense of the starting material. This is due in part to the reagents needed for its preparation, especially ethyl orthoformate, and in part to the maximum 60% yield in the conversion of the latter to ethoxymethylenemalonic ester.

In the second paper[5] a procedure was outlined for the preparation of the α-carbanilido (II) analog of I and in the third[6] for the simple, direct preparation of II and the α-cyano- (III) analogs of I. For each of these, it was possible to eliminate the preparation of ethoxymethylenemalonic ester. A disadvantage of the syntheses utilizing II or III was the high dilution necessary for successful cyclization to the 4-hydroxyquinoline.

The purpose of the present investigation was to see whether I, which can be readily cyclized in high concentration, could be prepared by a synthesis avoiding ethoxymethylenemalonic ester and, preferably, ethyl orthoformate as well.



I, X = $COOC_2H_5$
II, X = CONHAr
III, X = CN

Dains[7] had reported that acrylates of type III could be prepared by heating cyanoacetic ester with arylformamidines.

$$C_6H_5NHC{=}NC_6H_5 + CH_2(CN)CO_2Et \xrightarrow{150^\circ} III + C_6H_5NH_2$$

When this reaction was carried out with malonic ester, a higher temperature was used and the aniline formed aminolyzed an ester group.

$$C_6H_5NHC{=}NC_6H_4 + CH_2(CO_2Et)_2 \longrightarrow [I + C_6H_5NH_2] \xrightarrow{180^\circ} II + C_2H_5OH$$

A reinvestigation of this latter reaction, using *bis*-(*m*-chlorophenyl)-formamidine (IV), led to the discovery that, by operating at 115 to 120° for a few hours, the principal products of the reaction were I and *m*-chloroaniline. If the reaction is interrupted at about 40% conversion to I, the yield is over 90%. Longer times for reaction or higher temperatures led to increased conversion to II.

Since IV is readily formed from *m*-chloroaniline and formic acid, in virtually quantitative yield, the synthesis offers a convenient and economical route to 4,7-dichloroquinoline.

Experimental

***bis*-(*m*-Chlorophenyl)-formamidine.**—A mixture of 31 g. (0.20 mole) of crude *m*-chloroformanilide[8] and 33 g. (0.20 mole) of *m*-chloroaniline hydrochloride was heated in an oil-bath at 160° under reduced pressure for two hours.[9] The solid reaction mixture was allowed to cool and 100 cc. of water, 20 cc. of concentrated ammonium hydroxide and 200 cc. of benzene were added and the contents were stirred vigorously at 50° until all the solid dissolved (one hour). The layers were separated and the aqueous layer was extracted with two 75-cc. portions of benzene. The combined benzene extracts were dried over magnesium sulfate and the benzene was distilled. The residue, which crystallized immediately upon cooling, weighed 50.8 g. or 96% of the theoretical amount of *bis*-(*m*-chlorophenyl)-formamidine, m. p. 99–109°. This product was used without purification in the experiment described below. The pure amidine, melting at 115–117°,[5] was obtained by recrystallization from methanol.

Ethyl α-Carbethoxy-β-*m*-chloroanilinoacrylate (I).—A mixture of 13.3 g. (0.05 mole) of the amidine and 8.0 g. (0.05 mole) of diethyl malonate was heated in an oil-bath at 116–120° (inside temperature) for three and one-half hours. To the reaction mixture was then added 20 cc. of 10% hydrochloric acid and 10 cc. of benzene. The insoluble hydrochloride of unchanged *bis*-(*m*-chlorophenyl)-

(1) The work reported in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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(4) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946).

(5) Price, Leonard and Herbrandson, *ibid.*, **68**, 1251 (1946).

(6) Snyder and Jones, *ibid.*, **68**, 1253 (1946).

(7) Dains, *Ber.*, **35**, 2507 (1902); *University of Kansas Sci. Bull.*, **19**, 215 (1930).

(8) Davis, *J. Chem. Soc.*, **95**, 1398 (1909).

(9) The procedure is similar to that used by Tobias (*Ber.*, **15**, 2449 (1882)) for the preparation of diphenylformamidine.

formamidine which precipitated was collected. An additional 25-cc. of benzene was added to the filtrate and the aqueous layer was extracted with an additional 25-cc. portion of benzene. The combined benzene extracts were washed with 20 cc. of water, which was then added to the main aqueous acid solution. *m*-Chloroaniline (*ca.* 2.6 g.) was isolated from the aqueous solution and identified by conversion to the benzenesulfonamide, m. p. 118–119° (lit., 121°).[10]

The benzene solution was distilled at atmospheric pressure and finally at reduced pressure to remove the unchanged malonic ester. To the residue was added 10 cc. of ether and 25 cc. of low-boiling petroleum ether and the solution was cooled in an acetone–Dry Ice mixture. After one and one-half hours the mixture was filtered and 6.3 g. of very fine white needles were collected, m. p. 48–49°.

This product was shown to be ethyl α-carbethoxy-β-*m*-chloroanilinoacrylate (I), containing about 10% ethyl α-*m*-chlorocarbanilido-β-*m*-chloroanilinoacrylate (II), both by recrystallization (a) and by cyclization (b). Hence the conversion to the former (I) was about 38% neglecting the starting materials recovered. (In other experiments it was shown that the unreacted amidine could be recovered in good yield.)

A series of experiments indicated that the conditions above were about optimum. At shorter times, the conversion was considerably less. At longer times or higher temperatures, the yield of anilide (II) increased rapidly.

(a) **Recrystallization.**—A 1.0-g. sample of the product above was recrystallized from 12 cc. of ethanol. The crystals recovered amounted to 0.10 g. and melted at 102–103°. A second recrystallization from 5 cc. of ethanol brought the melting point to 112–113°; a mixed melting point with an authentic sample of ethyl α-*m*-chlorocarbanilido-β-*m*-chloroanilinoacrylate[5] (II) was 112–113°. The filtrate from the first recrystallization was evaporated to dryness at room temperature and the residue was recrystallized from 10 cc. of low-boiling petroleum ether to give fine white needles, m. p. 53–54°. A mixed melting point with an authentic sample of ethyl α-carbethoxy-β-*m*-chloroanilinoacrylate[4] (I) was 53–55°.

(b) **Cyclization.**—A 3.0-g. sample of the product was melted, added to 9 cc. of boiling "Dowtherm-A" and washed in with another cubic centimeter of hot solvent. The crystals which separated after three or four minutes soon filled the mixture, and the heating was continued for only fifteen minutes. The reaction mixture set to a solid light yellow mass on cooling. To this was added 10 cc. of 10% sodium hydroxide solution and the mixture was heated under reflux for twenty minutes. When the two-phase liquid mixture cooled, a precipitate appeared in the aqueous layer; this was collected by filtration and amounted to 0.3 g., m. p. 290–305° (uncor.). It was evidently 7-chloro-3-*m*-chlorocarbanilido-4-hydroxyquinoline.[5] Ether was added to the filtrate and the layers were separated. The aqueous layer was extracted with another 10-cc. portion of ether and then neutralized with 10% hydrochloric acid. The white precipitate was digested by heating to boiling, cooled and collected on a filter. After drying *in vacuo* the weight of the acid was 1.6 g. (79% of the theoretical amount, assuming the starting material to be 90% pure), m. p. 253° (uncor.) with loss of carbon dioxide. One gram of this acid was decarboxylated to 7-chloro-4-hydroxyquinoline in the usual way, and the recrystallized product was found to be identical with a sample prepared from ethoxymethylenemalonic ester.[4]

(10) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 195.

Summary

It has been found that, under the proper conditions, *bis*-(*m*-chlorophenyl)-formamidine will condense with malonic ester to produce ethyl β-(*m*-chloroanilino)-α-carbethoxyacrylate in excellent yield.

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Synthesis of 4-Hydroxyquinolines. V. A Direct Synthesis from β-Anilinoacrylates[1]

BY CHARLES C. PRICE,[2] NELSON J. LEONARD AND ROBERT H. REITSEMA

In spite of the report that ethyl β-*p*-anisidinoacrylate could not be cyclized to 6-methoxy-4-hydroxyquinoline,[3] the desirability of such a simple, direct synthesis of 4-hydroxyquinolines, coupled with the successful application to α-carbethoxy analogs,[4] has led to a careful reëxamination of this possibility.

After many preliminary experiments, the observation that the α-cyano- or α-carbanilidoacrylates would cyclize only at very high dilution[5] was applied successfully to the cyclization of methyl or ethyl β-anilino- and β-*m*-chloroanilinoacrylates. When the β-*m*-chloroanilinoacrylates (I) are boiled in relatively concentrated diphenyl ether solution the only crystalline product isolated was *bis*-(*m*-chlorophenyl)-urea (II). An acrid odor resembling acetaldehyde was noticed. At high dilution, three crystalline products were isolated. Two were identified as chlorohydroxyquinolines. The one formed in greater yield was identical with that obtained in the synthesis through ethoxymethylenemalonic ester, 7-chloro-4-hydroxyquinoline (III). Since no proof that this substance had the chlorine in the 7-position has appeared in the literature, its structure was established by conversion to 7-chloro-8-nitroquinoline.[6] The isomer was presumed to be 5-chloro-4-hydroxyquinoline, IV.

The third product from the cyclization had the correct analysis for 1,1-*bis*-(7-chloro-4-hydroxy-3-quinolyl)-ethane, V, which could conceivably be formed by condensation of III with acetaldehyde.

(1) The work described in this paper was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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(3) Rubtsov, *J. Gen. Chem.* (USSR), **7**, 1885 (1937); *C. A.*, **32**, 526 (1938).

(4) Price and Roberts, THIS JOURNAL, **68**, 1204 (1946).

(5) Price, Leonard and Herbrandson, *ibid.*, **68**, 1251 (1946).

(6) Price and Guthrie, *ibid.*, **68**, in press (1946).