[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

THE REACTION OF DIARYLFORMAMIDINES WITH ETHYL MALONATE[1]

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It has been reported previously (1) that the reaction of N,N'-*bis*-(3-chlorophenyl)formamidine with ethyl malonate may be controlled so that the predominant product is the substituted acrylate (II) rather than the anilide (IV) obtained by Dains (2). Compounds of type II are of interest because of the ease with which they may be cyclized to 4-hydroxyquinoline derivatives which are intermediates in the preparation of certain important antimalarial drugs (SN-7618 or Chloroquine, etc.). The present work was undertaken with the purpose of determining the general applicability of the reaction for the preparation of substituted 4-hydroxyquinoline derivatives. Substituted diphenylformamidines are easily obtained in good yield and we have shown that several of these react with ethyl malonate in the same way as the *m*-chloro derivative studied originally. We have encountered an interesting effect of an *ortho*-substituent on the rate of the reaction.

In order to facilitate the investigation of the reaction of ethyl malonate with the formamidines, the acrylates (II) were not isolated, but after removing unchanged formamidine,[3] the crude reaction mixture was subjected to cyclizing conditions, followed by saponification of the quinoline esters (VI) produced; the acids (VII) were precipitated by the addition of mineral acid and their weights taken as a measure of the extent of the first reaction. This is advantageous because it is difficult to separate quantitatively the low-melting acrylates (II) and anilides (IV). Both are cyclized by heating in an inert solvent, but the quinoline anilides (V) are not hydrolyzed by aqueous alkali and separate fairly completely from the alkaline solutions from which they may be removed before acidifying to precipitate the acids (VII). The yield of acrylate from the reaction of a formamidine with ethyl malonate is of course somewhat higher than the value implied by the weight of acid produced, since this figure includes the losses in the cyclization and saponification steps. That these losses are quite low and consistent, however, may be demonstrated by subjecting pure acrylates prepared from ethoxymethylene malonic ester (3) to cyclization followed by saponification under the same conditions employed with the crude acrylates. It is probable that the presence of anilide in the latter lowers the yield in the cyclization step

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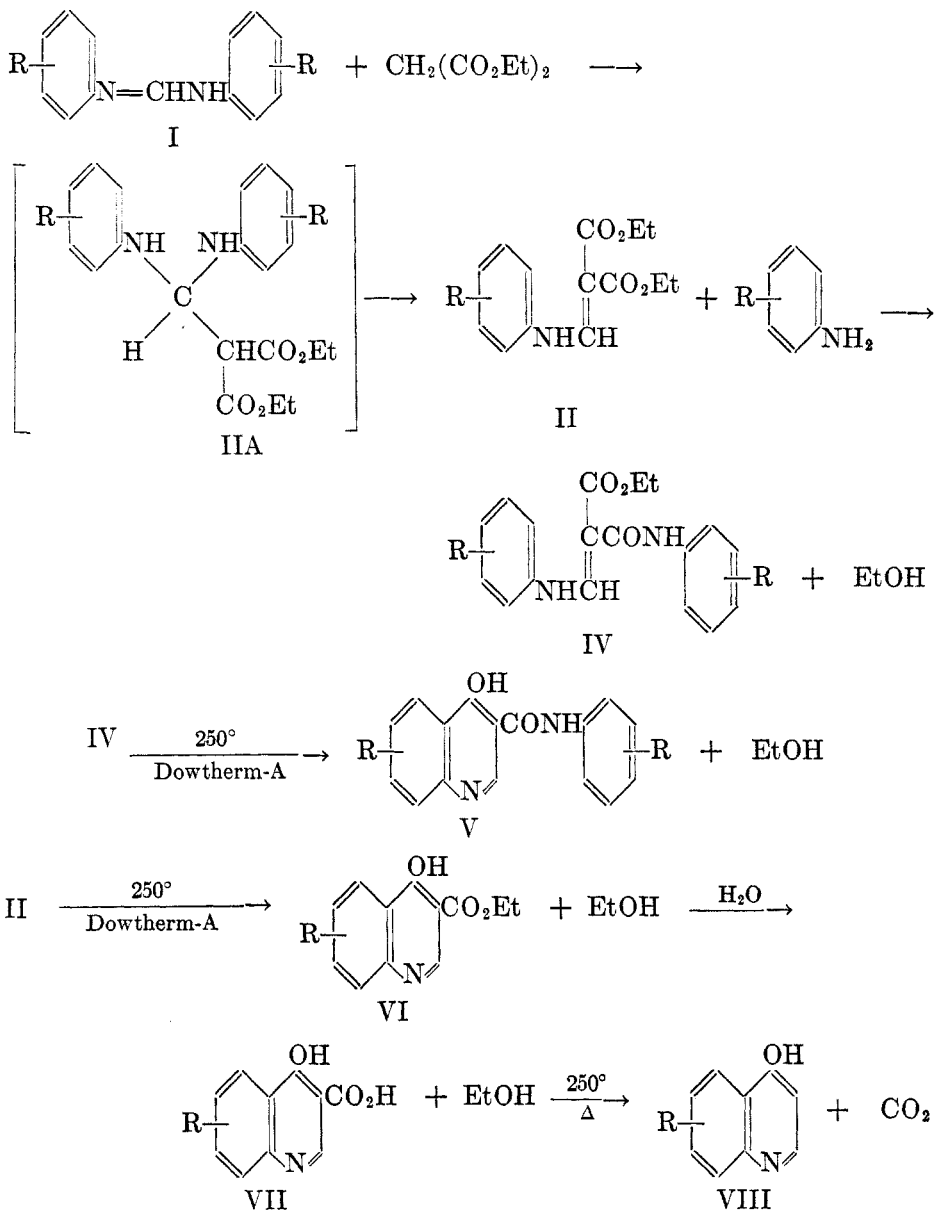
[3] The reaction is interrupted at about 40% conversion to (II) in order to prevent excessive aminolyzation of the ester group to produce the anilide (V). The unchanged formamidine may be recovered in good yield by precipitating its insoluble hydrochloride.



somewhat, another factor which makes the yield of the acid represent considerably less than the actual amount of acrylate produced in the first reaction.

The acrylates derived from *o*- and *p*-chloroaniline have been made and cyclized by Tarbell (4), who reported that the *p*-chloro derivative was cyclized under the same conditions as the *m*-chloro and, like it (3), in quantitative yield, but that the *o*-chloro derivative was difficult to cyclize in good yield and gave "by-products." We repeated this work and we found that the *o*- and *p*-chloro derivatives

were cyclized with equal ease under the conditions used previously (3) for the *m*-chloro derivative, giving almost quantitative conversion of the acrylates to 4-hydroxychloroquinoline-3-carboxylic acids. The acrylates derived from ethoxymethylene malonic ester and *o*-, *m*-, and *p*-toluidine were also prepared and converted in good yield to the corresponding 4-hydroxymethylquinoline-3-carboxylic acids.

The treatment of the formamidines with ethyl malonate was carried out at the same temperature for the same length of time as in the original experiment (3) and also at lower temperatures for longer periods in the hope that the rate of the secondary reaction (of the acrylate with aromatic amine) would be retarded more than that of the primary reaction. It was found, however, that the proportion of anilide (IV) to acrylate (II) produced was hardly enough different at the lower

TABLE I

REACTION OF DIARYLFORMAMIDINES WITH ETHYL MALONATE

SUBSTITUENTS ON AROMATIC RINGS	TEMP. (°C)	TIME (HOURS)	PRODUCTS OBTAINED (%)	
			Acid (VII)	Anilide (V)
m-Cl	118	4	36	10
	103	10	39	8
p-Cl	103	10	36	6
o-Cl	103	13	7	
	118	8	18	10
p-CH_3	118	4	31	5
o-CH_3	103	10	15	
	118	8	31	19
m-CH_3	118	4	25[a]	[a]

[a] The yield of acid was probably higher, and an appreciable amount of anilide was produced; but the formation of isomers led to greater solubility and incomplete precipitation of both acid and anilide.

temperatures to offset the inconvenience of a much longer reaction time (Table I); also some of the formamidines do not give homogeneous reaction mixtures at temperatures below 118°.

The yield of 7-chloro-4-hydroxyquinoline-3-carboxylic acid obtained corresponded quite satisfactorily with the results obtained previously when the acrylate was isolated. The behavior of the formamidines prepared from *p*-chloroaniline, *m*- and *p*-toluidine was comparable to that of the *m*-chloroaniline derivative (Table I), but the rate of reaction of the *o*-chloro and *o*-methyl derivatives was much slower. At 118°, twice as long a reaction time was required to give the same per cent yield of acid from the *o*-methyl as from the *p*-methyl derivative, and the rate of reaction of the *o*-chloro derivative was still slower. This is not surprising in view of the fact that the reaction probably proceeds by means of an intermediate addition compound (IIA). [Dains actually pictured such an intermediate in his original paper (2a).] In the formation of this intermediate from the *ortho*-substituted formamidines there would be considerable steric inter-

ference by the substituents on both aromatic rings with the approach of the malonic ester molecule, leading to a decreased rate in the formation of the acrylate (II). It will also be noted that a higher proportion of secondary reaction (producing anilide) occurred with the *o*-substituted formamidines; this is to be expected if the rate of the primary reaction is decreased and that of the secondary reaction remains about the same. The diarylformamidines derived from *o*- and *p*-nitroaniline were prepared but were so insoluble in ethyl malonate at 118° that no appreciable reaction occurred. This reaction seems to offer an interesting opportunity for the study of the effect of substituents on the benzene ring on a type of reaction which has received no attention as far as this aspect is concerned, and we plan to continue such an investigation. It will be more desirable for this work to use an active methylene compound other than ethyl malonate in order to avoid the complication of a secondary reaction.

The separation of the corresponding anilides (V) from the hydroxymethylquinolinecarboxylic acids was less complete than with the chloro derivatives due to the greater solubility of these anilides. Satisfactory separation was obtained in the case of the *o*- and *p*-methyl derivatives by using a smaller volume of aqueous alkali for saponification, but this modification gave no success with the *m*-methyl derivative. Decarboxylation of the crude acid obtained from this compound showed it to contain a mixture of isomers. Ring closure of this acrylate may produce 7-methyl- and 5-methyl-quinoline derivatives, so that a mixture of two anilides and two acids is formed. That this occurred was not surprising, since appreciable isomer formation was noted in the cyclization of the acrylate prepared from ethoxymethylene malonic ester and 3,4-dimethylaniline (6); the surprising thing is the lack of isomer production in the cyclization of the *m*-chloro acrylate. After decarboxylation it was possible to separate the unchanged anilides from the mixture of hydroxymethylquinolines, and the higher-melting 4-hydroxy-7-methylquinoline (5) was isolated easily in pure form. This is the predominant product. The more soluble 4-hydroxy-5-methylquinoline was isolated with difficulty from the mixture in an almost pure state.

The other acids were readily decarboxylated to the chloro- and methyl-hydroxyquinolines which were easily purified and characterized.

EXPERIMENTAL

All melting points are uncorrected. Microanalyses by Clark Microanalytical Laboratory.

Ethyl α-carbethoxy-β-toluidinoacrylates. These were prepared from ethoxymethylene malonic ester and *o*-, *m*-, and *p*-toluidine (3). They were recrystallized from petroleum ether (b.p. 28–38°); all three were obtained in the form of fine white needles. The melting points were: *o*-derivative, 63.5–65°; *m*-, 41–42°; *p*-, 46–47°.

Anal. Calc'd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91.

Found: (*o*-) C, 64.52; H, 6.74; (*m*-) C, 64.92; H, 6.65; (*p*-) C, 64.83; H, 6.93.

4-Hydroxymethylquinoline-3-carboxylic acids. The acrylates were cyclized in Dowtherm-A (kindly supplied by The Dow Chemical Co.) using a ratio of 200 ml. per 0.1 mole of acrylate. The mixture was heated to reflux for forty-five minutes in an open round-bottomed flask. The quinoline ester was saponified without removing the solvent, which was later separated from the aqueous salt solution with the aid of ether. The aqueous solu-

tion was heated to boiling to remove ether and dilute sulfuric acid was added to the hot solution to precipitate the quinoline acid. After allowing the mixture to cool to room temperature, the acid was collected on a filter and washed with several portions of water. The yield of crude 4-hydroxymethylquinoline-3-carboxylic acids from the *o*- and *m*-toluidino acrylates was practically quantitative (97%) while the *p*-derivative gave 83% conversion. This lower yield was undoubtedly due to the impurity of the *p*-toluidino acrylate used; the analytical sample prepared later had a melting point several degrees higher than that of the sample cyclized. It was found that cyclization of the *m*-toluidino acrylate produced a mixture of 7-methyl- and 5-methyl-4-hydroxyquinoline-3-carboxylic acids. Separation of the isomers was not feasible at this stage so the mixture of acids was submitted for analysis. The acids were best purified by recrystallization from glacial acetic acid, from which they were obtained in the form of fine, colorless needles.

4-Hydroxy-8-methylquinoline-3-carboxylic acid, m.p. 259°, dec.

Anal. Calc'd for $C_{11}H_9NO_3$: C, 65.00; H, 4.47.
Found: C, 65.04; H, 4.42.

4-Hydroxy-6-methylquinoline-3-carboxylic acid, m.p. 257°, dec.

Anal. Found: C, 64.75; H, 4.52.

4-Hydroxy-7(5)-methylquinoline-3-carboxylic acid (mixture), m.p. 246°, dec.

Anal. Found: C, 65.00; H, 4.53.

4-Hydroxy-7-methylquinoline and 4-hydroxy-5-methylquinoline. A 19.8-g. (0.098 mole) sample of the mixed acids (obtained from the cyclization of ethyl α-carbethoxy-β-*m*-toluidinoacrylate followed by saponification) was decarboxylated by heating in 100 ml. of diphenyl ether (kindly supplied by The Dow Chemical Co.) for one hour. The product crystallized slowly from the cool solvent; 100 ml. of petroleum ether (b.p. 28–38°) was added, the mixture was stirred well and filtered. The crude hydroxymethylquinoline was resuspended in petroleum ether and collected again on a filter; it weighed slightly more than the calculated amount (15.5 g.). It was dissolved in 200 ml. of 95% ethanol and the solution was boiled with 2 g. of activated charcoal for fifteen minutes. The charcoal was removed and the alcohol was distilled, leaving 14.1 g. of almost-white solid which was ground in a mortar. The powdered mixture was placed in the cup of a Soxhlet extractor and extracted with 300 ml. of benzene for four hours. Small samples of the undissolved solid were removed every hour, dried, and their melting points determined: after one hour, m.p. 205–215°, sint. 185°; after two hours, m.p. 209–219°, sint. 190°; after three hours, m.p. 214–218°, sint. 205°, after four hours, m.p. 214–218°, sint. 203°. The weight of the undissolved solid when dry was 7.2 g. After recrystallization from water three times there was obtained 5.4 g. of 4-hydroxy-7-methylquinoline, m.p. 223–225°, sint. 190° (5).

There were some crystals present in the benzene when the extraction was stopped. The mixture was allowed to cool and stand overnight and then was filtered; 5.1 g. of crystals were obtained, m p. 155–195°. This material was placed in a Soxhlet cup and extracted further with benzene for a short time. The melting point of the undissolved solid (4.7 g.) was not changed. Crystallization from water was next tried, but the material recovered (4.1 g.) was partially hydrated and still had essentially the same melting range (after drying). An attempt to dehydrate the crystals in boiling toluene was partially successful. A sample treated thus and then recrystallized from toluene melted at 157–160°. The analysis indicated that it still contained a small amount of water.

Anal. Calc'd for $C_{10}H_9NO$: C, 75.40; H, 5.70.
Found: C, 74.65; H, 5.76.
Calc'd for $C_{10}H_9NO \cdot 0.1\ H_2O$: C, 74.64; H, 5.76.

Cyclization of ethyl α-carbethoxy-β-o-chloroanilinoacrylate. Fifteen grams (0.05 mole) of pure acrylate (m.p. 91–92°) was cyclized in 100 ml. of Dowtherm-A (heating forty-five minutes) and the quinoline ester was filtered from the cool solvent and washed with petroleum ether; 12.1 g. (96%) of light tan crystalline 3-carbethoxy-8-chloro-4-hydroxyquinoline was obtained, m.p. 251–255°, sintering slightly from 195°. Recrystallization of the ester from glacial acetic acid, then from a mixture of pyridine and benzene gave 7.2 g. of fine white

leaflets, m.p. 253–255°, sintering from 240°. This was shown to be quite pure 3-carbethoxy-8-chloro-4-hydroxyquinoline by saponification to 8-chloro-4-hydroxyquinoline-3-carboxylic acid, 6.5 g. (100%), and decarboxylation to 8-chloro-4-hydroxyquinoline, 5.05 g. (97%), m.p. 206–212°. Two grams of the last compound were recrystallized from water, 1.5 g. of white needle-clusters being recovered, m.p. 211–213°.

The cyclization was repeated using diphenyl ether as solvent. A 5.1-g. (0.017 mole) sample of acrylate was dissolved in 36 ml. of diphenyl ether and heated to reflux for forty minutes. After the mixture had cooled to room temperature it was filtered and the crystalline product was washed with petroleum ether; when dry it weighed 4.0 g. (93%), m.p. 248–254°, sintering from 195°. One recrystallization from glacial acetic acid gave white leaflets, 3.5 g., m.p. 254–256°, sintering from 195°.

N,N'-bis-(2-chlorophenyl)formamidine. The procedure for the preparation of this compound is described in detail because it is illustrative of the preparation of all the formamidines used in this work and because no satisfactory description of the preparation of formamidines from aromatic amines and ethyl orthoformate was found in the literature.

In a 500-ml. round-bottomed flask was placed 104 g. (0.7 mole) of ethyl orthoformate and 179 g. (1.4 mole) of *o*-chloroaniline. The flask was connected to a 40-cm. Berl saddle-packed column equipped with an electrically heated jacket. The column was kept at 90–100° and the flask was heated in an oil-bath at 145° for about one and one-half hours while ethanol slowly distilled. At the end of this time the oil-bath temperature was raised to 180° and kept there for about one-half hour (or until distillation of ethanol stopped). The reaction mixture was poured out immediately into a porcelain dish because it solidified very quickly on cooling. The crude product (practically quantitative yield) melted at 137–141°; it was recrystallized from dry benzene (a mixture of dry benzene and petroleum ether was used in other runs) giving 150 g. (81%) of colorless prisms, m.p. 139–141°. The analytical sample melted at 141–142°. N,N'-*bis*-(2-chlorophenyl)formamidine has been mentioned in the literature before (6), but no melting point or analytical data are recorded.

Anal. Calc'd for $C_{13}H_{10}Cl_2N_2$: C, 58.90; H, 3.80.
Found: C, 59.25; H, 3.89.

Reaction of N,N'-bis-(3-chlorophenyl)formamidine with ethyl malonate at 118° and at 103°. In a 50-ml. Erlenmeyer flask was placed 13.3 g. (0.05 mole) of N,N'-*bis*-(3-chlorophenyl)-formamidine and 8.0 g. (0.05 mole) of ethyl malonate. The flask was immersed in an oil-bath heated by a thermostatically controlled electric coil (this heating bath was used in all the formamidine and ethyl malonate experiments) to 118° (± 1°) and kept there four hours. The mixture was homogeneous after a few minutes in the oil-bath. After cooling to room temperature, the reaction mixture was dissolved in 85 ml. of benzene and the solution was stirred mechanically while 20 ml. of 10% hydrochloric acid was added dropwise and for fifteen minutes thereafter. The precipitated formamidine hydrochloride was collected, resuspended in 25 ml. of benzene, collected again, and washed with five 15-ml. portions of benzene. All the benzene washings were combined with the first benzene filtrate and washed in a separatory funnel with four 25-ml. portions of water; the benzene solution was next dried over potassium carbonate and the benzene was then removed by distillation. To the residue (containing the acrylate) was added 50 ml. of Dowtherm-A and the mixture was heated to boiling in an open 500-ml. round-bottomed flask for thirty minutes. After cooling the mixture somewhat, 50 ml. of 10% sodium hydroxide was added and the mixture was heated under reflux with mechanical stirring for two hours. After standing for one and one-half hours, the three-phase mixture was filtered and 1.7 g. of solid, m.p. > 300°—undoubtedly 7-chloro-3-*m*-chlorocarbanilido-4-hydroxyquinoline (7)—was collected. The weight corresponded to a yield of 10%. To the filtrate was added 50 ml. of ether and the ether-Dowtherm-A and water layers were separated. The organic solution was washed with 25 ml. of water, this wash was added to the main aqueous solution and this solution was next washed with two 50-ml. portions of ether and then heated to boiling. After cooling slightly, the aqueous solution was made acid to Congo Red paper with 24 ml. of 18% hydrochloric acid. The precipitated 7-chloro-4-hydroxyquinoline-3-carboxylic acid was allowed to stand overnight and was then washed and dried; yield, 4.0 g. or 36%; m.p. 246–247°, dec.

The same amounts of reactants were heated in the oil-bath at 103° for ten hours and the reaction mixture was worked up in exactly the same way. This time 1.4 g. (8%) of the anilide (V) was obtained and 4.2 g. (39%) of the acid (VII) m.p. 254°, dec.

Reaction of N,N'-bis-(4-chlorophenyl)formamidine with ethyl malonate. These reactants (0.05 mole of each) were heated at 103° for ten hours; the formamidine never completely melted or dissolved. After addition of benzene as above, 3.2 g. of unchanged formamidine was recovered by filtration. The remainder of the reaction mixture was treated essentially as described above. One gram (6%) of anilide (V) was obtained and 4.0 g. (35%) of 6-chloro-4-hydroxyquinoline-3-carboxylic acid, m.p. 277°, dec. The acid was decarboxylated in boiling diphenyl ether, the product treated with charcoal and recrystallized from glacial acetic acid, giving 2.7 g. (84%) of 6-chloro-4-hydroxyquinoline, m.p. 262–268°. A second recrystallization gave 2.0 g. of fine white needles, m.p. 268–270° [reported by Tarbell (4) as 261–263°, by Bachmann and Cooper (8) as 269°].

Reaction of N,N'-bis-(2-chlorophenyl)formamidine with ethyl malonate. Equivalent amounts (0.05 mole) of these reactants were heated together at 103° for thirteen hours. As in the above experiment, the formamidine melted and dissolved only partially; this time the mixture was stirred mechanically during the entire heating period. The reaction mixture was worked up as in the preceding experiment. The unchanged formamidine recovered amounted to 7.2 g. The cyclization and saponification steps were also carried out exactly as in the preceding experiment and 0.8 g. (7%) of 8-chloro-4-hydroxyquinoline-3-carboxylic acid was obtained, m.p. 258°, dec. No anilide (V) was isolated.

The same amounts (0.05 mole) of the formamidine and ethyl malonate were heated together at 118° for eight hours; at this temperature the reaction mixture became homogeneous in a few minutes. When worked up in the usual way, no unchanged formamidine was recovered; after cyclization and saponification, 1.9 g. (18%) of 8-chloro-4-hydroxyquinoline-3-carboxylic acid and 1.6 g. (10%) of anilide (V) was obtained. The acid was decarboxylated to produce 8-chloro-4-hydroxyquinoline, m.p. 213–215°, sintering slightly from 205°.

Reaction of N,N'-bis-(4-methylphenyl)formamidine with ethyl malonate. In a small Erlenmeyer flask was placed 22.4 g. (0.10 mole) of the formamidine and 16.0 g. (0.10 mole) of ethyl malonate and the flask was immersed in the oil-bath at 118° for four hours; the mixture was homogeneous almost at once. The reaction mixture was worked up as before with the exception that only one-half the amount of 10% alkali solution used for the chloro derivatives was used in the saponification step. This allowed the separation of the more soluble anilide (V); 1.4 g. (5%), m.p. > 300° was obtained, and 6.3 g. (31%) of 4-hydroxy-6-methylquinoline-3-carboxylic acid, m.p. 257, dec. The acid was decarboxylated to give 4-hydroxy-6-methylquinoline in quantitative yield. One recrystallization from water gave 3 g. of colorless needles, m.p. 234–235°, sintering slightly at 210°. Robson (9) reported the melting point as 227°.

Anal. Calc'd for $C_{10}H_9NO$: C, 75.40; H, 5.70.
Found: C, 75.40; H, 5.71.

Reaction of N,N'-bis-(2-methylphenyl)formamidine with ethyl malonate. A mixture of 10.3 g. (0.046 mole) of the formamidine and 7.4 g. (0.046 mole) of ethyl malonate was heated in the oil-bath at 103° for ten hours. The mixture did not become homogeneous, so it was stirred mechanically during the entire heating period. The reaction mixture was worked up in the usual way; the crude acrylate was cyclized and the quinoline ester saponified to yield 1.4 g. (15%) of 4-hydroxy-8-methylquinoline-3-carboxylic acid, m.p. 259°, dec. This product probably contained some anilide (V) since none was separated.

When the reactants (0.05 mole of each) were heated at 118° the mixture became homogeneous at once. After eight hours, the reaction mixture was worked up as before; there was obtained 2.7 g. (19%) of anilide (V), m.p. 298–305° (not characterized further). The aqueous layer when subsequently acidified yielded 3.1 g. (31%) of 4-hydroxy-8-methylquinoline-3-carboxylic acid, m.p. 258.5°, dec.

The above acid (3.1 g.) was decarboxylated in 15 ml. of diphenyl ether. The crude 4-hydroxy-8-methylquinoline was boiled with 500 ml. of water; the hot mixture was filtered and 0.4 g. of insoluble solid, m.p. 291–> 300°, was collected. [This is evidently partly

anilide (V) but probably represents also some decomposition product of the acid because a water-insoluble substance is always encountered when recrystallizing even the hydroxyquinolines obtained *via* ethoxymethylenemalonic ester, *i.e.*, no possibility of anilide (V).] The aqueous filtrate was treated with charcoal, concentrated, and cooled. There was obtained 1.5 g. of 4-hydroxy-8-methylquinoline, colorless needles, m.p. 212–213°, sintering from 203°. A sample recrystallized for analysis melted at 212–213°, sintering from 206°.

Anal. Calc'd for $C_{10}H_9NO$: C, 75.40; H, 5.70.

Found: C, 75.70; H, 5.68.

Reaction of N,N'-bis-(3-methylphenyl)formamidine with ethyl malonate. One-tenth-mole quantities of the reactants were heated in the oil-bath at 118° for four hours (the mixture became homogeneous immediately). The reaction mixture was worked up exactly as were those from ethyl malonate and N,N'-*bis*-(3-chlorophenyl)formamidine. Only a negligible amount (0.1 g.) of anilide separated from the aqueous solution of the quinoline acid(s) even though the amount of alkali used was that which gave fair separation of the anilide in the case of the *o*- and *p*-toluidine derivatives. This is undoubtedly due to the formation of isomers in the cyclization step, a mixture of two anilides and two acids being produced. The crude mixture of 4-hydroxy-7-methylquinoline-3-carboxylic and 4-hydroxy-5-methylquinoline-3-carboxylic acids precipitated weighed 5.1 g. (25%), m.p. 244°, dec., and evidently contained an appreciable proportion of the mixed anilides, as is demonstrated below.

The crude acid mixture (5.1 g.) was suspended in 25 ml. of diphenyl ether and decarboxylated as before, giving 4.0 g. of crude product. When this material was boiled with 430 ml. of water and the hot mixture was filtered, 0.6 g. of insoluble solid, m.p. > 310°, was collected. Upon cooling, the filtrate deposited droplets of a brown oil, so activated charcoal was added and the mixture was boiled and then filtered. After cooling the filtrate thoroughly in ice, 2.5 g. of white crystals, m.p. 198–216°, sintering from 170°, were obtained. This weight corresponds to 62.5% of the amount of hydroxymethylquinoline calculated from 5.1 g. of acid. Fractional crystallization of this material from water and benzene gave 1.6 g. of 4-hydroxy-7-methylquinoline, m.p. 223–225°, sint. 190°. The isomeric 4-hydroxy-5-methylquinoline was not obtained in a pure state in this experiment.

SUMMARY

The reaction of substituted diphenylformamidines with ethyl malonate to produce acrylates which may be converted readily to 4-hydroxyquinoline derivatives has been shown to be of general applicability. Substituents in the *ortho*- position of the benzene ring were found to have a pronounced effect on the rate of the reaction.

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