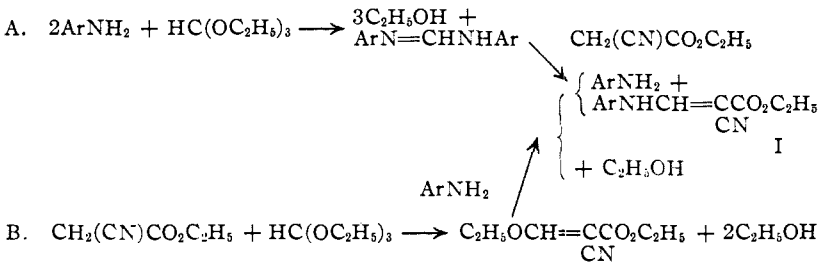
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Synthesis of 4-Hydroxyquinolines. III. A Direct Synthesis of β-Substituted Acrylic Esters[1]

BY H. R. SNYDER AND ROBERT E. JONES

The recently developed synthesis of 4-hydroxyquinolines[1a] makes use of ethyl orthoformate, an active methylene compound and an aromatic amine as the raw materials. The first two reagents are brought into reaction to give an ethoxymethylene compound which is isolated and allowed to react with the amine, forming a derivative of β-aminoacrylic acid which can cyclize to a quinoline. It occurred to us that the first two steps of the process might be combined, so that the acrylic acid derivative might be obtained directly by heating a mixture of the active methylene compound, the orthoformate and the amine. Two plausible paths, one through the amidine (scheme A) and one through the ethoxymethylene derivative (scheme B), are shown for the direct synthesis from cyanoacetic ester.

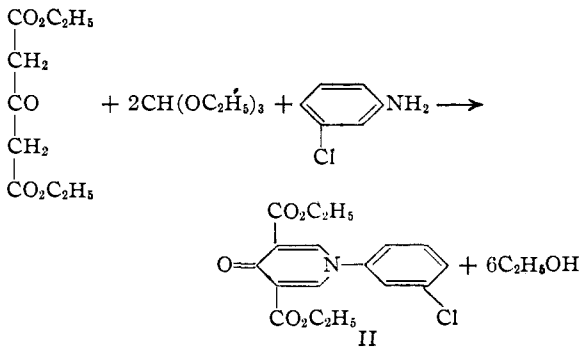


The two reactions of scheme A are well known[2,3] as individual processes; their combination into a single process should have the advantage that the amine liberated in the second step is formed in the presence of the orthoformate and hence is reconverted to the amidine, with the result that one mole of amine should give one mole of the acrylate. The individual reactions of scheme B are those of the previously described process.[1a]

When equimolar quantities of *m*-chloroaniline, ethyl orthoformate and cyanoacetic ester were heated at about 160° in an apparatus fitted for distillation, an amount of alcohol corresponding to complete reaction distilled and the residue consisted of the acrylate I in nearly pure state. Excellent yields of the anilinoacrylates were obtained also with *p*-anisidine and *m*-trifluoromethylaniline. 4,7-Dichloroquinoline was prepared from the *m*-chloroaniline condensation product by the method already described[1a] in a yield of 42%, based on ethyl orhoformate.

The direct synthesis of ethyl α-acetyl-β-(*m*-chloroanilino)-acrylate from *m*-chloroaniline, ethyl orthoformate and acetoacetic ester likewise proceeded smoothly and in excellent yield. The reaction with malonic ester occurred readily, but the product was not the expected dicarboxylic ester [*m*-ClC$_6$H$_4$NHCH=C(CO$_2$C$_2$H$_5$)$_2$] but rather the corresponding mono-*m*-chloroanilide; it was obtained in yields of about 80% when two moles of the amine were employed. The replacement of the ethoxyl group by the amine residue may have occurred before, during or after the other reactions, for α-carbethoxy-β-(*m*-chloroanilino)-acrylanilide [*m*-ClC$_6$H$_4$NHCH=C(CO$_2$C$_2$H$_5$)CONHC$_6$H$_5$] was obtained both from the reaction of ethyl N-phenylmalonamidate with ethyl orthoformate and *m*-chloroaniline and from ethyl α-carbethoxy-β-(*m*-chloroanilino)-acrylate and aniline.

Acetylacetone condensed with *m*-chloroaniline and ethyl orthoformate to give the expected product [*m*-ClC$_6$H$_4$N=CHCH(COCH$_3$)$_2$]. The reaction of ethyl acetonedicarboxylate led to a compound having the composition of the pyridone II; the same product was obtained by way of the isolated di-(ethoxymethylene) derivative of the ester.



II

The structure II is assigned to the product on the basis of the synthesis by Errera[4] of the analogous pyridone from the di-(ethoxymethylene) derivative of the ester and ammonia.

The active methylene component of lowest reactivity tested was ethyl phenylacetate. It was not possible to isolate ethyl α-phenyl-β-(*m*-chloroanilino)-acrylate, but treatment of the reaction mixture under the usual conditions for the cyclization did result in the formation of a small

(1) The work reported 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.

(1a) For the preceding paper in this series, see Price, Leonard and Herbrandson, THIS JOURNAL, **68**, 1251 (1946).

(2) Claisen, *Ann.*, **287**, 366 (1895).

(3) Dains, *Ber.*, **35**, 2507 (1902).

(4) Errera, *ibid.*, **31**, 1690 (1898).

TABLE I

	Compound	Yield, %	Melting point,[a] °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	Ethyl α-cyano-β-(*p*-methoxyanilino)-acrylate	85	105–107	63.40	63.55	5.73	5.93
2	Ethyl α-cyano-β-(*m*-trifluoromethylanilino)-acrylate	79.5	144–146	54.93	55.64	3.90	4.19
3	Ethyl α-cyano-β-(N-methylanilino)-acrylate	53.5	100–102	67.81	67.89	6.13	6.31
4	α-Carbethoxy-β-(N-chloroanilino)-*m*-chloroacrylanilide	77	113	56.98	56.71	4.24	4.51
5	Ethyl α-carbanilido-β-(*m*-chloroanilino)-acrylate	27.2	93–95	62.70	62.59	4.97	5.01
6	Ethyl α-phenyl-β-(*m*-chloroanilino)-acrylate	(Not isolated)		...	...	..	..
7	Ethyl α-acetyl-β-(*m*-chloroanilino)-acrylate	79	87–89	58.32	58.28	5.27	5.31
8	3-(*m*-Chloroanilinomethylene)-acetylacetone	46.5	92–94	60.63	60.46	5.09	5.08
9	Ethyl α-cyano-β-(*m*-chloroanilino)-acrylate	94	126–128	Reference [1a]			
10	N-*m*-Chlorophenyl-3,5-dicarbethoxy-4-pyridone[b]	17.3	198–199	57.87	58.06	4.65	4.68

[a] All melting points are uncorrected. [b] Nitrogen analysis: calcd., N, 4.01; found, N, 4.27.

TABLE II

	Compound	Yield, %	Melting point, °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	3-Cyano-4-hydroxy-7-trifluoromethylquinoline	50.5	325–330	55.47	55.48	2.12	2.11
2	3-*m*-Chlorocarbanilido-4-hydroxy-7-chloroquinoline	50	320–322	Reference [1a]			
3	3-Phenyl-4-hydroxy-7-chloroquinoline	1	355–360	70.45	70.51	3.94	4.13
4	3-Acetyl-4-hydroxy-7-chloroquinoline	90.5	315	59.62	59.46	3.64	3.59
5	3-Cyano-4-hydroxy-7-chloroquinoline	90.2	365–370	Reference [1a]			

amount of a substance having the composition of 3-phenyl-4-hydroxy-7-chloroquinoline.

Only one secondary amine was tested in the synthesis: N-methylaniline reacted smoothly with ethyl orthoformate and cyanoacetic ester to give ethyl α-cyano-β-(N-methylanilino)-acrylate (53.5% yield). This reaction was of especial interest because the amine cannot form an amidine and hence the formation of the substituted acrylate could not have occurred by way of scheme A. The occurrence of the reaction suggested the trial of a monosubstituted malonic ester, such as ethyl benzylmalonate, which could not react according to scheme B. The substituted malonic ester did react with ethyl orthoformate and *m*-chloroaniline to give, in very low yield (*ca.* 4%), a solid having the composition of III.

$$C_6H_5CH_2CH(CO_2C_2H_5)_2 + HC(OC_2H_5)_3 +$$

$$m\text{-}ClC_6H_4NH_2 \longrightarrow m\text{-}ClC_6H_4N{=}CH{-}\underset{\displaystyle CONHC_6H_4Cl\text{-}m}{\overset{\displaystyle CH_2C_6H_5}{\overset{|}{\underset{|}{C}}}}{-}CO_2C_2H_5$$

III

It is altogether possible that neither of the schemes A and B correctly represents the reactions involved in the direct synthesis of the substituted acrylates. Precursors of the amidine and of the ethoxymethylene compound [such as $ArNHCH(OC_2H_5)_2$ and $(C_2H_5O)_2CHCH(CN)CO_2C_2H_5$] may be the reactive intermediates.

The products of the last two experiments were of possible interest in connection with the cyclization of the anilinoacrylates to hydroxyquinolines. The reaction may be written with either of the tautomeric forms (vinylamine or anil) of a compound such as I. The product, mentioned above, from methylaniline can exist only as the vinylamine and that III from the benzylmalonate only as the anil. It was expected that only one of the two substances could be converted to a quinoline derivative. Actually, neither underwent cyclization under the usual conditions. Such a cyclization would have formed a product containing a pyridone system which could not aromatize; it seems likely that an important driving force of the cyclization is the formation of the aromatic system.

Experimental

1. Direct Preparation of α-Substituted β-Anilinoacrylates.—Equimolar quantities of ethyl orthoformate, the active methylene component and the aromatic amine were mixed in a flask fitted for distillation. The mixture was heated in an oil-bath at a temperature of 160–165° and held at this point until the calculated volume of alcohol had distilled. The time of the reaction varied from twenty minutes to several hours depending upon the activity of the methylene group of the active methylene reagent. The details of the individual reactions appear in Table I.

2. Thermal Cyclization of Acrylates to 4-Hydroxyquinolines.—All cyclizations were run in diphenyl ether; the variations in the individual reactions were in dilution in the boiling solvent and in the time of reflux. Individual experimental conditions are shown in Table II. The general procedure was as follows.

The required amount of diphenyl ether was placed in a flask fitted with a short air-cooled reflux condenser and heated to boiling. Heating was discontinued and the acrylate was slowly added (portionwise, if solid) to the hot solvent. When the addition was complete, heating was resumed and the solution was refluxed for a period of one-half to four hours. The mixture was allowed to cool and was diluted with twice its volume of petroleum ether. The substituted 4-hydroxyquinoline was removed by filtration, washed twice with petroleum ether, twice with ethyl ether, and dried. The yields varied widely according to the nature of the acrylate (see Table II).

Summary

In a three-component mixture, an active methylene reagent, an aromatic amine and ethyl

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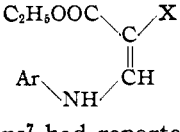
Synthesis of 4-Hydroxyquinolines. IV. A Modified Preparation through *bis*-(*m*-Chlorophenyl)-formamidine[1]

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.

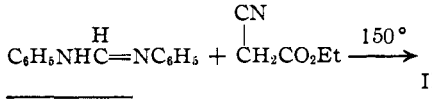
In the second paper[5] a procedure was outlined for the preparation of the α-carbanilido (II) analog of I and in the third[6] for the simple, direct preparation of II and the α-cyano- (III) analogs of I. For each of these, it was possible to eliminate the preparation of ethoxymethylenemalonic ester. 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.

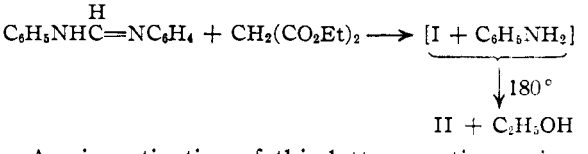


I, X = $COOC_2H_5$
II, X = CONHAr
III, X = CN

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



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



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.