An Improved Synthesis of Ethyl (α-Carbethoxy-β-m-chloranilino)acrylate

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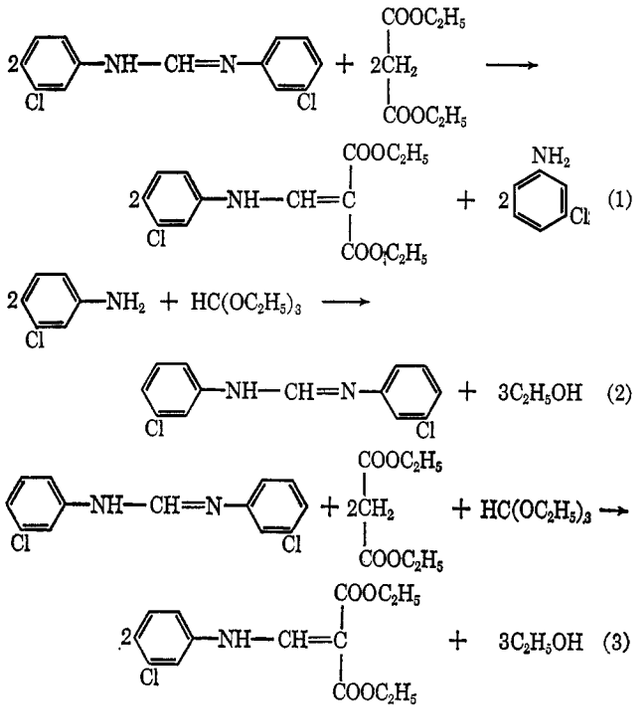
Several syntheses have been reported for the preparation of β-substituted acrylic esters. Though they proceed by different routes, a common feature is that all of them involve the use of three substances, an amine, ethyl orthoformate, and an active methylene compound. The syntheses are normally carried out in several steps, and they are mostly variations concerning the order of allowing the three components to react.

The semianilide of ethyl (α-carbethoxy-β-m-chloroanilino)acrylate was prepared first by Dains[1] by reaction of bis(m-chlorophenyl)formamidine with diethyl malonate. The reaction was modified by Price, *et al.*,[2] so that the desired acrylate itself could be isolated, however, in rather low yields (40%). The "direct synthesis" of Snyder and Jones[3] using m-chloroaniline, ethyl orthoformate, and diethyl malonate would bear resemblance to the present process; however, owing to simultaneous aminolysis, it gives again only the semianilide of the desired compound.

The method developed in this laboratory is based on the work of the former authors; however, it yields pure ethyl (α-carbethoxy-β-m-chloroanilino)acrylate without by-products. This is achieved by the proper selection of the conditions of the reaction of bis(m-chlorophenyl)-formamidine with diethyl malonate, in the presence of ethyl orthoformate acting as an amine acceptor.

The reaction steps taking place in the three-component mixture may be visualized as shown in eq 1 and 2, or as the over-all reaction (eq 3).



The possibility of regeneration of bis(m-chlorophenyl)formamidine allows two techniques to be considered: the first is a stepwise, and the second a direct reaction. In the stepwise variant, reactions 1 and 2 proceed simultaneously; thus, the reaction of 2 moles of the bis(m-chlorophenyl)formamidine with 2 moles of diethyl malonate and 1 mole of ethyl orthoformate gives rise to 2 moles of the acrylic ester, 1 mole of formamidine being regenerated at the same time (half-conversion).

The over-all reaction scheme (eq 3) represents the direct variant of the process. Here the m-chloroaniline produced in the reaction reacts with ethyl orthoformate to give bis(m-chlorophenyl)formamidine which immediately reacts with the malonate; this process is then carried on until all malonate and bis(m-chlorophenyl)formamidine are entirely used up (total conversion).

In order to achieve such an over-all reaction, the partial processes must be coordinated; otherwise side reactions leading to by-products (such as the semianilide of the acrylate and of diethyl malonate) become predominating.

The prerequisite of realizing such a concerted reaction sequence is the knowledge of the course of the principal reaction taking place between bis(m-chlorophenyl)formamidine and malonate, and of the reaction rates of m-chloroaniline with the three esters present in the mixture. It has been found that m-chloroaniline reacts most rapidly with ethyl orthoformate, the reaction with ethyl malonate is less rapid, and the final product, the acrylate, is the slowest to react.

In view of these facts, a process has been evolved which is characterized by adding the malonate and ethyl orthoformate to formamidine in such a way that ensures constant excess of the ethyl orthoformate and does not allow the concentration of malonate to exceed a certain limit. Under such conditions the m-chloroaniline produced will react exclusively with ethyl orthoformate, formation of the semianilide of malonate is avoided, and the reaction selectively affords the required acrylic ester.

The simplest way to ensure constant excess of ethyl orthoformate consists in adding the entire required quantity to the formamidine at the start of the reaction, while half of the diethyl malonate is added later.

It should be noted that the initial great excess of ethyl orthoformate does not alter the course of the desired reaction, since in the absence of an acid catalyst and at the relatively low temperature employed, m-chloroaniline and ethyl orthoformate do not combine to give ethoxymethylene-m-chloroaniline as described by Glickman.[4]

The explanation of the reaction mechanism proposed by Snyder, *et al.*[3] assuming precursors, such as the compounds prepared by Glickman, as intermediates is

(1) F. B. Dains, *Ber.*, **35**, 2506 (1902).
(2) C. C. Price and R. N. Roberts, *J. Am. Chem. Soc.*, **68**, 1255 (1946).
(3) H. R. Snyder and R. E. Jones, *ibid.*, **68**, 1253 (1946).
(4) S. A. Glickman, U. S. Patent 2,684,976, assignor to General Aniline and Film Corp., New York, N. Y. (July 27, 1954).

not applicable in this case, since neither ethoxymethylene malonate nor ethoxymethylene aniline was detectable in the reaction mixture.

Experimental Section

Bis(*m*-chlorophenyl)formamidine used in these investigations was prepared by the known reaction of *m*-chloroaniline and ethyl orthoformate. *m*-Chloroaniline (51.0 g) and ethyl orthoformate (29.6 g) were refluxed for 2 hr in a reaction vessel provided with a short column filled with Raschig rings to allow the alcohol formed to distil slowly. After the termination of the reaction the column was removed, the vessel was put under vacuum and the remaining base was used in the next step without any further treatment.

Method A. "Total-Conversion" Method. Ethyl (α-Carbethoxy-β-*m*-chloroanilino)acrylate.—The above reaction product, or crystalline bis(*m*-chlorophenyl)formamidine base (53 g, 0.2 mole), ethyl orthoformate (35.6 g, 0.2 mole +20% excess), and diethyl malonate (32 g, 0.2 mole) were stirred for 20 hr at 126°. The evolved alcohol was continuously removed by distillation.

To the half-converted reaction mixture a further portion (32 g, 0.2 mole) of diethyl malonate was added, and stirring was continued for 48 hr at 126°. From the product the small quantities of unchanged malonate, ethyl orthoformate, and alcohol were removed by distillation under vacuum.

The viscous residue was dissolved in benzene (120 ml) and shaken with 10% hydrochloric acid (120 ml) to remove traces of basic impurities. The benzene layer containing the acrylic ester was washed with water, filtered, and dried over sodium sulphate, and the solvent was evaporated under vacuum.

The distillation residue (112.5 g, 94%) a light colored substance, crystallized within a short time.

This crude product containing about 96% of acrylic ester may be used without further purification in the cyclization step of the 4-hydroxy-7-chloroquinoline synthesis. Recrystallization from petroleum ether (bp 40–60°) gave the pure acrylic ester (mp 57–58°) in 90% yield.

Method B. "Half-Conversion" Method.—Bis(*m*-chlorophenyl)formamidine (53 g, 0.2 mole), ethyl orthoformate (17 g, 0.1 mole +15% excess), and diethyl malonate (32 g, 0.2 mole) were stirred for 20 hr at 126°. The mixture was dissolved in benzene (400 ml) and diluted with 10% hydrochloric acid (300 ml) to precipitate the formed bis(*m*-chlorophenyl)formamidine hydrochloride. This was filtered off, washed with benzene, and dried (30 g). The benzene filtrate was washed with three 80-ml portions of water and dried over sodium sulfate; then the solvent was evaporated under reduced pressure. The residual oil was dissolved in petroleum ether (47 ml) and allowed to stand overnight. The substance which separated was recovered by filtration and dried to give 45.2 g of product, 76%, mp 56–57°.

Synthesis of Podophyllotoxin[1,2]

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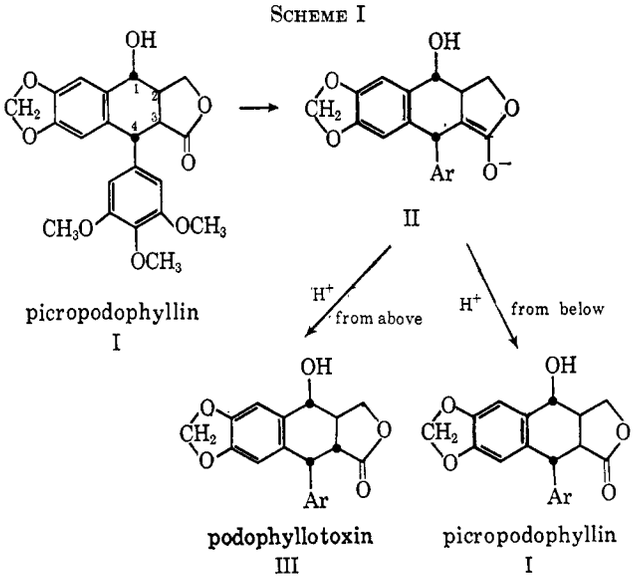
Picropodophyllin and podophyllotoxin can be converted to their O-tetrahydropyranyl derivatives. Treatment with aqueous acid regenerates the starting materials. The podophyllotoxin derivative epimerizes with mild base to the picropodophyllin derivative. The action of triphenylmethylsodium on either tetrahydropyranyl derivative produces the enolate common to both. Irreversible protonation of the enolate followed by removal of the protective group gives a 45:55 (approximate) mixture of podophyllotoxin and picropodophyllin. An interpretation of the results based on a model for the transition states is proposed. Since picropodophyllin has been synthesized, its conversion to podophyllotoxin completes a total synthesis of podophyllotoxin.

Podophyllotoxin (III) and other related lignan lactones from *Podophyllum* species have received considerable attention as cancer chemotherapeutic agents.[3,4] Although a number of podophyllotoxin derivatives have been synthesized,[4-7] podophyllotoxin itself has not. In this connection, since picropodophyllin (I), an epimer, has been synthesized,[8] its conversion to podophyllotoxin (III) would constitute the last step in a total synthesis of podophyllotoxin. The present paper is concerned with this conversion[9] (see Scheme I).

Podophyllotoxin (III) epimerizes readily under base catalysis to picropodophyllin (I).[10] The reverse reaction has also been demonstrated,[11] so that picropodophyllin can, in fact, be converted to podophyllotoxin by equilibration. The proportion of podophyllotoxin in the equilibrium mixture (*ca.* 3%) is too small, however, for this to be regarded as a practical—much less, an attractive—means of arriving at podophyllotoxin.

SCHEME I



(1) (a) This is paper XVII in the series entitled Compounds Related to Podophyllotoxin. (b) The preceding paper is by W. J. Gensler and C. D. Gatsonis, *J. Org. Chem.*, **31**, 3224 (1966).

(2) This investigation was supported by Public Health Service Research Grant No. CA-02891 from the National Cancer Institute.

(3) See, *inter alia*, J. L. Hartwell and M. Shear, *Cancer Res.*, **7**, 716 (1947); M. Belkin, *J. Pharmacol. Exptl. Therap.*, **93**, 18 (1948); M. G. Kelley and J. L. Hartwell, *J. Natl. Cancer Inst.*, **14**, 967 (1954).

(4) H. Emmenegger, H. Stähelin, J. Rutschmann, J. Renz, and A. von Wartburg, *Arzneimittel-Forsch.*, **11**, 327, 459 (1961).

(5) *Cf.* J. L. Hartwell and A. W. Schrecker, *Progr. Chem. Org. Nat. Prod.*, **15**, 83 (1958).

(6) J. Renz, M. Kuhn, and A. von Wartburg, *Ann.*, **681**, 207 (1965).

(7) J. Rutschmannn and J. Renz, *Helv. Chim. Acta*, **42**, 890 (1959).

(8) W. J. Gensler, C. M. Samour, S. Y. Wang, and F. Johnson, *J. Am. Chem. Soc.*, **82**, 1714 (1960).

(9) A brief note appeared earlier: W. J. Gensler and C. D. Gatsonis, *ibid.*, **84**, 1748 (1962).

(10) W. Borsche and J. Niemann, *Ann.*, **494**, 126 (1932); E. Späth, F. Wessely, and L. Kornfeld, *Ber.*, **65**, 1536 (1932); A. Robertson and R. B. Waters, *J. Chem. Soc.*, 83 (1933).

(11) Paper XVI.[1b]