The Decarboxylation of α-Cyano- and α-Carboxycinnamic Acids

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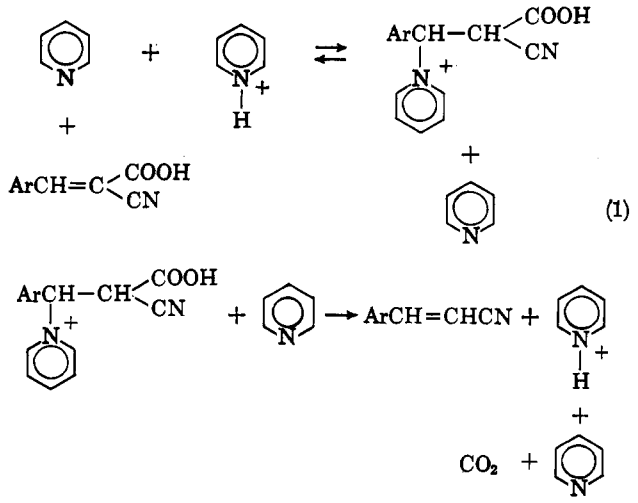
The steric course of the decarboxylation of benzylidenecyanoacetic and cinnamylidenemalonic acids depends on the solvent used and on other reaction conditions. Different mechanisms for the decarboxylations in pyridine and quinoline solutions are discussed.

Recently,[2] we have prepared a series of α-cyanocinnamic acids by condensation of acetals of aromatic aldehydes with cyanoacetic acid, and thought it of interest to study the stereochemistry of their decarboxylation in view of the fact that Liebermann[3] isolated *trans–cis*-styrylacrylic acid from the product of decarboxylation of cinnamylidenemalonic acid in quinoline, whereas Doebner[4] obtained the *trans* isomer by decarboxylation of this acid in pyridine.

The decarboxylation of α-cyanocinnamic acid in pyridine has already been studied by Corey.[5] The reaction was found to depend on the concentration of the unsaturated acid and the pyridinium ion, and an addition–elimination mechanism (1) was proposed.[5]

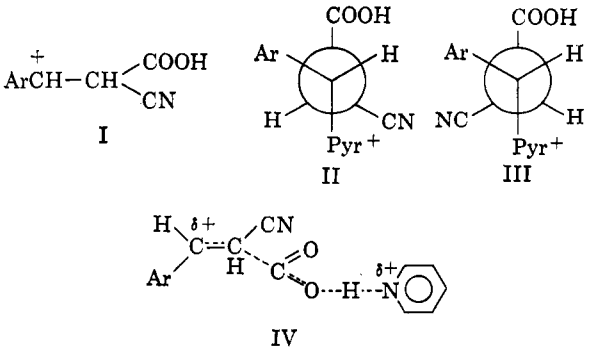


(1)

The two processes were assumed to proceed in *trans* fashion and should have given one cinnamonitrile. The product of the decarboxylation, however, contained the equilibrium mixture of 35% *cis*- and 65% *trans*-cinnamonitrile, and equilibration of the nitrile formed under the reaction conditions was assumed.[5]

Our experiments confirmed the results of Corey as to the composition of the product of decarboxylation of α-cyanocinnamic acid in pyridine. However, the decarboxylation of this acid in quinoline has given, in different experiments, between 50 and 98% of the *cis* isomer, as determined by optical refraction measurements.[6]

Harfenist and Phillips[7] have reported that the copper-catalyzed decarboxylation of *o*-chlorocyanocinnamic acid yielded a product containing 52% of *cis*-*o*-chlorocinnamonitrile. We have found 65% of *cis*-cinnamonitrile in the cuprous chloride-catalyzed decarboxylation of α-cyanocinnamic acid and 46 to 60% of this isomer in the noncatalyzed, solventless decarboxylation of the same acid, depending on the conditions of the reaction. The high proportion of the less stable cinnamonitrile observed in the decarboxylation in quinoline at 130–150° makes improbable the assumption that the primary product has equilibrated when the decarboxylation was carried out in pyridine at 110°. Indeed, when cinnamonitrile with a high *cis* content was subjected to conditions of decarboxylation in pyridine in the absence or in the presence of α-cyanocinnamic acid, isomerization took place only to a small extent. This shows that the product of decarboxylation is kinetically controlled, and the identity of its composition with that of the equilibrium mixture of the isomers is probably connected with the similarity between the transition state in pyridine and the product of reaction. The addition of a proton to the double bond, therefore, takes place before the decarboxylation step, as assumed by Corey,[5] but either the addition of the proton is not *trans* and simultaneous with the addition of pyridine to the other end of the double bond, or the elimination of CO_2 and pyridinium ion in the decarboxylation step is not concerted. It seems more probable that the first step is not concerted and a carbonium ion (I) solvated by pyridine molecules is obtained, which collapses to a mixture of isomers II and III, where II predominates because it would be more stable. An even more probable hypothesis would be that I undergoes direct decarboxylation as in IV and that the breaking of the bond between the carboxyl and carbon is advanced in the transition state, so that the composition of the product will be similar to the equilibrium mixture of the stereoisomers. In both mechanisms, the positive charge formed in the molecule by addition of a proton or of a pyridinium ion favors the decarboxylation because of its electron-attracting character.



IV

The results of decarboxylation in quinoline show that in this solvent a mechanism different from that in pyridine is operative. Since more of the less stable isomer is obtained, it has to be assumed that the addition of

(1) Taken in part from the M.S. thesis of A. Y. M., The Hebrew University, 1960. A preliminary communication was published: *Bull. Res. Council Israel, Sect. A*, **9**, 62 (1960).

(2) J. Klein and A. Y. Meyer, *J. Org. Chem.*, **29**, 1035 (1964).

(3) C. Liebermann, *Ber.*, **28**, 1438 (1895).

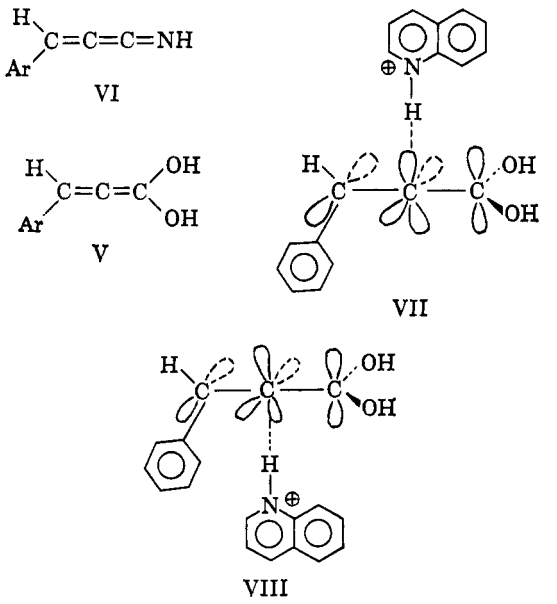
(4) O. Doebner, *ibid.*, **35**, 2129 (1902).

(5) E. J. Corey and G. Fraenkel, *J. Am. Chem. Soc.*, **75**, 1168 (1953).

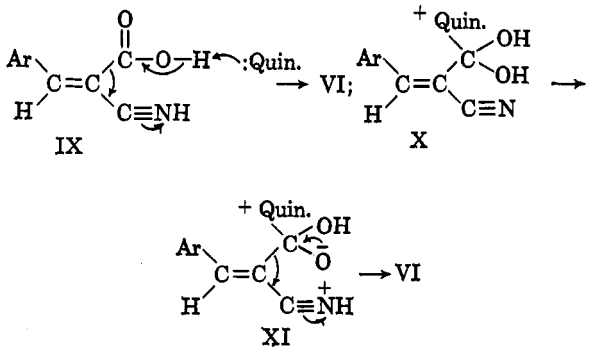
(6) G. B. Kistiakowsky and W. R. Smith, *ibid.*, **58**, 2438 (1936).

(7) M. Harfenist and A. P. Phillips, *ibid.*, **80**, 6261 (1958).

hydrogen takes place in a fast reaction and is not subject to thermodynamic control. Such addition is known in the case of ketonization of various enols and also during the decarboxylation of 1,1-cyclohexanedicarboxylic acid. This last reaction proceeds also through the intermediary of an enol[8] which is then protonated from the sterically more accessible side of the cyclohexane system. Decarboxylation of an unsaturated dicarboxylic acid[9] without previous addition of a proton or of a quinolinium ion to the double bond will give an enol or enolate which has the character of an allene with two cumulative bonds, V, or an enol-like intermediate VI in the case of α-cyano acids. The protonation of this enol will be easier from the side remote from the aryl substituent, since the proton-bearing acid has to approach the molecule in the same plane in which the aryl is located, as in VII, which gives the *cis* product, or, as in VIII, which yields the *trans* isomer. The approach of the acid depicted in VII is more favorable than that in VIII, and the *cis* product will be formed predominantly.



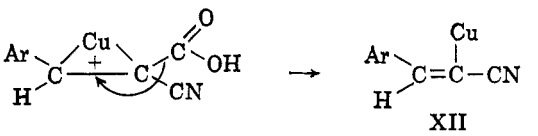
The reason for the difference in the mechanism of decarboxylation in quinoline and in pyridine is not entirely clear. One reason could be the greater bulk of quinoline which would not favor the addition to the double bond or the stabilization of the tertiary carbonium ion by solvation. It could be that 1,4-addition of quinoline takes place,[11] but more probably the quinolinium ion protonates the second carboxyl or cyano group instead of the double bond, and decarboxylation of this ion gives the enol as in IX. Another possibility is that a preliminary 1,2-addition of quinolinium ion or quinoline to the carboxyl takes place followed by intramolecular proton transfer and finally by decarboxylation; *i.e.*, X → XI. Although decarboxylation in quinoline occurs at a higher temperature than in pyridine, it proceeds, nevertheless, at a much lower temperature than solvent-



less decarboxylation. This indicates participation of quinoline in the reaction.

The erratic results of the decarboxylation in quinoline (50 to 98% *cis* isomer in the product) could be traced to the source of the quinoline. In the synthetic quinoline the reaction is slowest and the *cis* isomer content in the product highest (98%); with pure commercial quinoline from coal tar the rate is higher and the amount of *cis* isomer lower. It seems, therefore, that coal tar quinoline contains a catalyst, which permits the reaction to proceed partly *via* a double bond addition mechanism. Corey[5] has already found a large acceleration of the decarboxylation in pyridine by addition of a sulfur compound.

The results of the cuprous chloride-catalyzed decarboxylation can be correlated with those in quinoline. Cuprous ions are known to coordinate with double bonds,[12] and the positive center formed by this coor-



dination lowers the activation energy of decarboxylation and yields a cuprous enolate XII which is protonated to give predominantly the *cis* product.[13]

(8) H. E. Zimmerman and T. Cutshall, *J. Am. Chem. Soc.*, **80**, 2893 (1958).

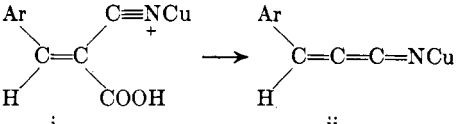
(9) This discussion is pertinent only in the case of conjugated acids, where isomerization by migration of the double bond is impossible. The acids which can isomerize to β,γ-unsaturated compounds have been shown by Corey[10] to decarboxylate through the intermediary of the latter.

(10) E. J. Corey, *J. Am. Chem. Soc.*, **74**, 5897, 4952 (1952); **75**, 1163 (1953).

(11) We are grateful to Professor E. J. Corey for this suggestion.

(12) G. N. Schrauzer, *Ber.*, **95**, 260 (1962).

(13) The copper in the enolate also may be located on the nitrogen, and the reaction proceeds perhaps *via* a nitrogen-complexed compound i → ii. A different form of coordination with chelate formation (iii) is also possible.



The reaction then proceeds iii → iv. This form of chelate corresponds to a cyclic proton transfer in the noncatalyzed decarboxylation (v). Similar chelates would be formed less readily in α-cyano acids but are possible.

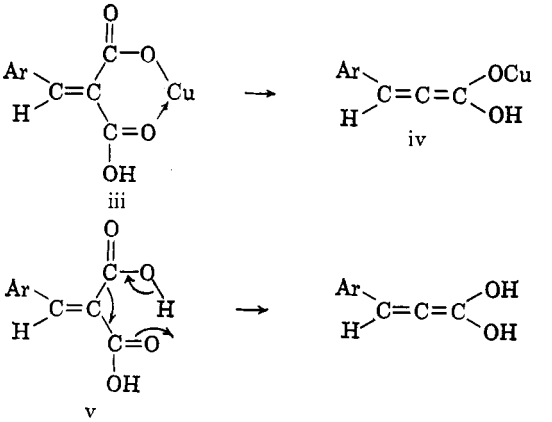


TABLE I

DECARBOXYLATION OF α-CYANOCINNAMIC ACID[a]

Starting acid, g.	Solvent, ml.	Temp., °C.	Time, hr.	Yield,[b] %	n_D[b]	% *cis*[c]	% acid[c]
8	Pyridine, 50	110°	8.5	72	1.5965	35	..
10	Quinoline,[d] 20	140°	5	40	1.5946	45	25
8	Quinoline,[e] 20	155°	2	13	1.5852	96	75
10	Quinoline,[f] 100	140°	5	45	1.5939	50	22
10	Collidine, 50	150°	4	35	1.5964	36	..
10	Collidine, 50	150°	1	28	1.5930	56	17

[a] All the experiments were performed at least twice. The numbers are average values. [b] Cinnamonitrile. [c] Recovered starting materials. [d] B. D. H. reagent. [e] Eastman Kodak synthetic. [f] Practical grade.

Noncatalyzed decarboxylation requires higher temperatures than the copper-catalyzed reaction or the reaction in quinoline. In spite of the high amount of *trans* isomer in the product, we favor the enol mechanism in this case. The different composition of the reaction product in different runs may well indicate that two reactions take place in these difficultly controllable conditions, one of decarboxylation, another of isomerization. The direct product of noncatalyzed decarboxylation probably contains more of the *trans* isomer than the copper-catalyzed product, since the stereospecificity of the reaction will be lower at higher temperatures. The formation of a highly reactive allenic enol in the solventless catalyzed decarboxylation is reflected in the formation of tars during this reaction. The amount of tar formed is higher in the noncatalyzed reaction.

We have also reinvestigated quantitatively the decarboxylation of cinnamylidenemalonic acid in pyridine[4] and quinoline.[3] The ratio of the stereoisomers formed was determined by infrared analysis. The product obtained in pyridine contained 80 ± 5% of the *trans* isomer, that in quinoline 80 ± 5% of the *cis* isomer. The analysis of the ultraviolet spectra of the products gave somewhat different figures: 93% *cis* form in the quinoline and 22% in the pyridine product.

We have also carried out the decarboxylation of α-cyanocinnamic and cinnamylidenemalonic acids in 2,4,6-collidine to see if in this hindered pyridine derivative the results of decarboxylation are similar to those in quinoline. In fact, cinnamylidenemalonic acid yielded a product containing 90% of the *cis* isomer, and α-cyanocinnamic acid gave a *cis* isomer content of 56%.

These results seem to support the view that steric hindrance plays an important role in the geometrical course of the decarboxylation reaction.

Experimental

α-Cyanocinnamic acid was prepared from benzaldehyde diethyl acetal[2] or by the following method. A solution of 105 g. of cyanoacetic acid in 150 ml. of water was neutralized by 30% aqueous sodium hydroxide, and 106 g. of freshly distilled benzaldehyde dissolved in 250 ml. of ethanol was added.

The solution was acidified after 24 hr., and 162 g. (93%) of the acid, m.p. 185°, was collected.

Cinnamylidenemalonic Acid.—A 56-g. portion of piperidine was added to a cooled solution of 70 g. of malonic acid and 88 g. of freshly distilled cinnamaldehyde in 350 ml. of ethanol. The solution was kept for 24 hr. at room temperature and acidified, and 133 g. (91%) of the acid, m.p. 212°, was collected.[3]

***trans–trans*-Styrylacrylic Acid.**—A 30-g. sample of benzylidenemalonic acid and 100 ml. of pyridine were heated at 110° for 6 hr. The solution was cooled and poured onto ice and concentrated hydrochloric acid. The precipitate which formed was collected, washed with dilute hydrochloric acid, and dissolved in 10% aqueous sodium carbonate. The solution obtained was neutralized slowly with hydrochloric acid but not acidified completely. This procedure precipitates the monocarboxylic acid, but leaves the residual dicarboxylic acid in solution. The precipitate was collected, washed with water, and crystallized from ethanol. Thus 7 g. of the *trans* acid, m.p. 164–166°,[4] was obtained.

***trans–cis*-Styrylacrylic Acid.**—A 10-g. sample of benzylidenemalonic acid and 80 ml. of redistilled quinoline were heated for 1.5 hr. at 140°, then for 15 min. at 160°. The cooled solution was poured onto ice and concentrated hydrochloric acid, and the precipitate which formed was collected. There was obtained 8.5 g. of a product, m.p. 128–133°. Crystallization from benzene gave 5.5 g. of the acid melting at 141–142°.[3]

Decarboxylation of α-Cyanocinnamic Acid in Solution.—The acid was dissolved in five times its weight of an aromatic base and heated (duration of heating and temperature of bath are recorded in Table I). The solution was then cooled, poured onto ice and hydrochloric acid, and the product was extracted with benzene. The benzene solution was washed twice with dilute hydrochloric acid, then with 10% aqueous sodium carbonate, and finally with water. The benzene solution was distilled and the isomer composition of the obtained nitrile determined by its refractive index.[5] The alkaline solution was acidified and the recovered acid collected.

Isomerization of Cinnamonitrile. A.—A 10-g. sample of cinnamonitrile, containing 27% of the *trans* isomer, was heated for 8.5 hr. at reflux with 150 ml. of pyridine and 5.5 g. of *p*-nitrobenzoic acid. The solution was worked up as above, and 9 g. (90%) of the nitrile was isolated by distillation at 135° (20 mm.), $n^{22}D$ 1.5931 (47% *trans*).

B.—A 2.9-g. sample of cinnamonitrile containing 25% of the *trans* isomer and 3.9 g. of α-cyanocinnamic acid was heated for 8.5 hr. at reflux in 50 ml. of pyridine. After the usual work-up, there was isolated 3.5 g. of the nitrile (60%), $n^{23}D$ 1.5939, containing 50% of the *trans* isomer. Assuming the usual yield of 72% in the decarboxylation and proportional losses during the isolation of the product in the original nitrile and in the one formed by decarboxylation, an isomerization from 25 to 40% *trans* content can be found.

Decarboxylation of cinnamylidenemalonic acid was carried out similarly to that of α-cyanocinnamic acid. The results are summarized in Table II.

TABLE II

DECARBOXYLATION OF CINNAMYLIDENEMALONIC ACID[a]

Solvent[b]	Time, hr.	Temp., °C.	Yield,[c] %	% *cis*
Pyridine	10.5	110	94	20
Quinoline	1.5	140	75	90
Collidine	1.5	150	81	90

[a] Two grams of the acid was decarboxylated in each run. [b] Amount, 10 ml. [c] Styrylacrylic acid.

Solventless Decarboxylation of α-Cyanocinnamic Acid.—A Claisen flask containing 20 g. of the acid was immersed in an oil bath at 180°. The temperature of the bath was raised slowly.

A slow evolution of gas started at 205° (internal temperature). The melt was heated for 30 min. at 210–220°, at which temperature the decarboxylation proceeded fast. Distillation gave then 3.8 g. (26%) of the nitrile, boiling at 135° (25 mm.), $n^{23}D$ 1.5955 (60% of *trans*).

The decarboxylation of the acid was repeated in the presence of 0.2 g. of cuprous chloride. The decarboxylation started at 190° (internal temperature) and was finished after 10 min. at 210°. Distillation then gave 10.3 g. (69%) of the nitrile boiling at 135° (20 mm), $n^{23}D$ 1.5919 (35% *trans*-nitrile).

The Rates of Acid Hydrolysis of the Phenyl β-D-Glucopyranosiduronic Acids and Phenyl β-D-Glucopyranosides of Phenol, *p*-Cresol, and *p*-Chlorophenol

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The effects of the electron affinity of the aglycon group on the rates of acid hydrolysis of phenyl β-D-glucopyranosiduronic acids and phenyl β-D-glucopyranosides were studied. The aglycon groups were *p*-cresyl, phenyl, and *p*-chlorophenyl, and the rates were determined at 50–60° in 2.00–20.0 wt. % sulfuric acid. Linear correlations between the logarithms of the first-order rate constants and the Hammett acidity function were found for both series. The large positive entropies of activation were essentially the same for both series (+10 cal. per °K. per mole) so that the greater free energies of activation of the phenyl β-D-glucopyranosiduronic acids (2.0 kcal. per mole greater) were due to greater enthalpies of activation. The Hammett ρ-values for the phenyl β-D-glucopyranosides and β-D-glucopyranosiduronic acids were −0.48 ± 0.04 and −0.09 ± 0.05, respectively. These results are most consistent with the interpretation that the two series hydrolyzed *via* the rapid protonation of the glycosidic oxygen followed by slow heterolysis of the glycosyl oxygen bond. The stabilizing effect of the C-5 carboxyl group compared to the hydroxymethyl group was due to a greater inductive effect of the latter. The nature of the inductive effect is discussed.

Of recent interest has been the stabilizing effect produced when a C-5 hydroxymethyl group of a glycopyranoside is replaced by a carboxyl group (carboxyl stabilizing effect).[2-8] While the carboxyl stabilizing effect seems well-established, the nature of the effect is not well-understood. Two explanations have been offered. The first of these is the inductive effect hypothesis which proposes that the hydrolysis takes place *via* a cyclic mechanism [A-1 (A) mechanism], and that the carboxyl stabilizing effect is due to the greater inductive effect of the carboxyl group.[3-9] The proposed cyclic mechanism of acid-catalyzed glycoside hydrolysis[10-12] is shown in Fig. 1.

More recently, a second explanation has been offered based on work on the acid hydrolysis of methyl uronosides.[2,7] It was suggested that replacement of the C-5 hydroxymethyl group with a carboxyl group causes an undefined change in the reaction mechanism.

For the most part, kinetic studies of the carboxyl stabilizing effect have been confined to the effect of temperature on the acid hydrolysis rates of the uronosides and their corresponding C-5 hydroxymethyl glycosides at a given acid concentration.[2,6,7] In some cases, these rates were determined only at a single temperature and acid concentration.[3,8] A better understanding of the carboxyl stabilizing effect would be gained through an investigation of the effect of the electron affinity of the aglycon group as well as the effects of temperature and acid concentration. The β-D-glucopyranosiduronic acids (β-D-glucuronides) and β-D-glucopyranosides (β-D-glucosides) of phenol, *p*-chlorophenol, and *p*-cresol were chosen for this purpose.

Results

Figure 2 shows plots of the first-order rate constants of phenyl β-D-glucuronide *vs.* the hydronium ion concentration. The hydronium ion concentrations were calculated from the ionization of aqueous sulfuric

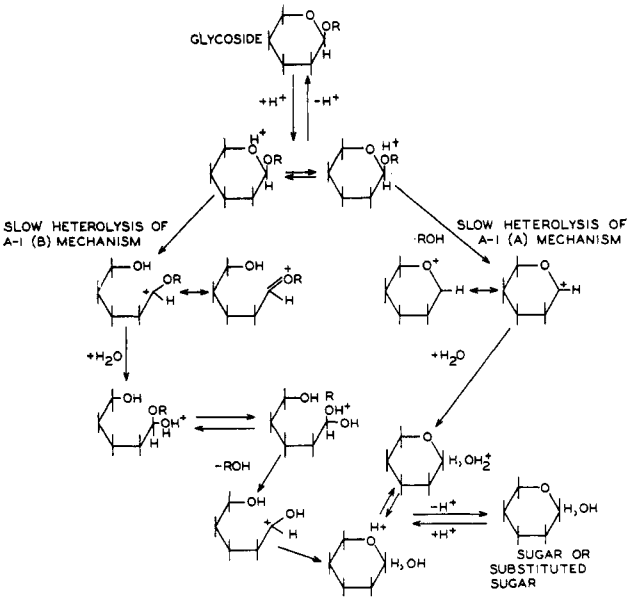

Fig. 1.—Proposed mechanisms of acid-catalyzed glycoside hydrolysis.

(1) A portion of a thesis submitted in partial fulfillment of the requirements of The Institute of Paper Chemistry for the degree of Doctor of Philosophy from Lawrence College, Appleton, Wis., June, 1963.

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