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THE SYNTHESIS OF SUBSTITUTED SUCCINIC ACIDS

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A very convenient method for the synthesis of substituted succinic acids is through hydrolysis of the hydrogen cyanide addition products of alkylidenemalonates (1) or alkylidenecyanoacetates (2). Recently Smith and Horwitz (3) introduced a very useful modification of the Lapworth-McRae procedure in which formation of the alkylidenecyanoacetate and addition of potassium cyanide are allowed to proceed simultaneously so that the equilibrium condition in the formation of the alkylidenecyanoacetate is pushed in the desired direction through combination of the alkylidenecyanoacetate with potassium cyanide. They studied their process by employing several aliphatic and aromatic aldehydes and ketones. Except in the case of aromatic aldehydes and ketones satisfactory results were generally obtained.

TABLE I

Substituted Succinic Acids

Compound	Procedure adopted	Yield, %	M.P.,[a] °C.	Analysis			
				Found		Calc'd	
				C	H	C	H
Methylsuccinic acid	A	32	114[b]				
n-Propylsuccinic acid (5)	A	56	98–99[c]	52.6	7.7	52.5	7.5
Phenylsuccinic acid (6)	A	91	167[d]				
p-Methoxyphenylsuccinic acid (7)	B	88	203[e]	58.5	5.7	58.9	5.4
3-4-Dimethoxyphenylsuccinic acid (8)	B	50	126[f]	56.3	6.0	56.7	5.5
m-Methoxyphenylsuccinic acid (9)	B	32	177[g]	59.2	5.6	58.9	5.4

[a] All melting points are uncorrected. [b] Compared with authentic sample. In one experiment the intermediate ethyl α,β-dicyanobutyrate was isolated in 33% yield. [c] After one crystallization from petroleum ether. [d] After one crystallization from water. [e] After one crystallization from water. The melting point appears to depend on the rate of heating. [f] After one crystallization from water. The m.p. was 174° on drying. Analysis was performed on the dried sample. [g] After one crystallization from water.

We felt the need for the supply of α-substituted succinic acids and decided to try the Smith-Horwitz procedure (described here as procedure *A*) employing several aldehydes. Our results are shown in the accompanying table. An important modification introduced by us is that unlike Smith and Horwitz we did not isolate the intermediate cyanoesters, but the crude reaction products were directly hydrolyzed with hydrochloric acid to the appropriate succinic acids. The crude acids thus obtained had m.p.'s only 2–3 degrees lower than those given in literature. After one crystallization correct m.p.'s were obtained in each case. Smith and Horwitz reported poor results with benzaldehyde which gave an excellent over-all yield in our hands. Other aromatic aldehydes like anisaldehyde, *m*-methoxybenzaldehyde, and veratraldehyde gave unsatisfactory results according to the above procedure. In the case of these aldehydes we adopted a slightly modified procedure. The arylidenecyanoacetates were first prepared by the procedure of Cope (4). Potassium cyanide then was added to the crude product and the resulting product was hydrolyzed directly. This procedure has been named procedure *B* in the table. The low yield in the case of veratraldehyde is perhaps due to the pronounced insoluble character of the arylidenecyanoacetate which necessitated employment of dioxane as solvent during potassium cyanide addition while that in the case of *m*-methoxybenzaldehyde is attributed to unsatisfactory hydrolysis.

EXPERIMENTAL

Procedure A. A mixture of aldehyde (0.1 mole), pyridine (0.1 mole), ethyl cyanoacetate (0.1 mole), and glacial acetic acid (6.4 ml.) was heated under reflux over a water-bath for 1½ hours. Ethanol (10 ml.) then was added followed by finely powdered potassium cyanide (0.15 mole) in one lot to the hot solution. A vigorous reaction set in and after refluxing for one hour the mixture became a slurry. It was cooled and decomposed with hydrochloric acid (1:3, 100 ml.). The separated oil was thoroughly extracted with ether. Ether then was removed and the residual oil was refluxed with conc'd hydrochloric acid (50–60 ml.) for eight hours. In the case of benzaldehyde, phenylsuccinic acid directly separated from the hydrolysate whereas in the case of acetaldehyde and *n*-butyraldehyde the hydrolysate was evaporated to dryness on a water-bath and the succinic acids were extracted from the dried mass with ether.

Procedure B. A mixture of aldehyde (0.1 mole), ethyl cyanoacetate (0.1 mole), acetamide (2 g.), and glacial acetic acid (30 ml.) was refluxed for two hours. During refluxing acetic acid (25 ml.) was slowly removed by distillation keeping the temperature of the distilling vapor at 110°. The residue then was treated with ethanol (32 ml.; in case of veratraldehyde 290 ml. of dioxane was used to keep the arylidenecyanoacetate in solution) and warmed on the water-bath. Potassium cyanide (0.15 mole) was added in one lot after which a vigorous reaction set in. After refluxing for one hour the mixture was cooled and the resulting slurry was acidified with hydrochloric acid (1:3); an oil separated which was taken up in benzene. After removal of benzene the residual oil was hydrolyzed with conc'd hydrochloric acid (50–60 ml.) for eight hours. The separated solid acids were purified by treatment with sodium carbonate.

SUMMARY

A modified Smith-Horwitz procedure for the synthesis of α-substituted succinic acids has been studied by employing several aliphatic and aromatic aldehydes. The yields are generally satisfactory.

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