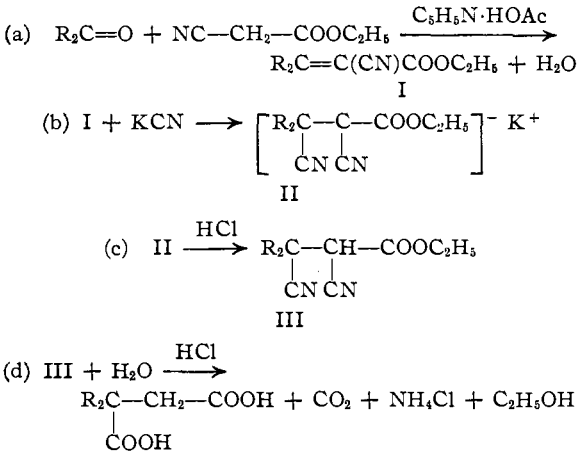
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

# A Synthesis for Unsymmetrically Substituted Succinic Acids[1]

BY PETER A. S. SMITH AND JEROME P. HORWITZ[2]

A convenient and somewhat general procedure which we have developed for the synthesis of succinic acids of the type $HOOC-CR_2-CH_2-COOH$ is described here as applied to seven examples. The procedure, which consists of two laboratory steps, takes place according to the equations



Reaction (b) is combined with reaction (a), which is only partially complete at equilibrium, in order to draw reaction (a) more completely in the desired direction. This same effect was accomplished by Cope and Alexander,[3] who added hydrogen instead of potassium cyanide to the unsaturated ester (I). Reaction (a) may also be driven to completion by removal of the water by distillation.[4]

It is in the actual laboratory procedure that the method reported here represents an improvement over a stoichiometrically similar method described by Lapworth and McRae.[5]

Their procedure involves isolation of the alkylidene cyanoacetic ester before treatment with potassium cyanide. This gives from cyclohexanone and cyanoacetic ester, for example, a 53% yield of cyclohexylidenecyanoacetic ester; by the procedure reported in this paper, the corresponding hydrogen cyanide addition product is obtained in 75% yield from the same starting materials. The Lapworth and McRae procedure gives superior results, however, with aromatic aldehydes.

Our attention was directed toward this method when a need arose for a supply of $\alpha,\alpha$-dimethylsuccinic acid. The preparation of this acid according to Higson and Thorpe[6] by the condensation of acetone cyanohydrin with sodiocyanoacetic ester, followed by hydrolysis and decarboxylation of the $\alpha,\alpha$-dimethyl-$\beta$-carboethoxysuccinonitrile so produced, was found to be manipulatively inconvenient and sensitive to variations in conditions which are difficult to control. By the method described here we were able consistently to obtain $\alpha,\alpha$-dimethylsuccinic acid in two convenient steps in over-all yields above 50%. Because of this success, we were led to extend the method to the synthesis of some additional succinic acids. The satisfactory results with unhindered aliphatic ketones and aldehydes show that this procedure is of synthetic value for the preparation of alkyl- and $\alpha,\alpha$-dialkylsuccinic acids. The poor results with benzaldehyde and acetophenone, and the complete lack of reaction of diisopropyl ketone, are indicative of the probable limitations of the method.

## Experimental

The condensation of the aldehydes and ketones with cyanoacetic ester and the hydrolysis and decarboxylation of the resulting dicyano ester was essentially the same in all the cases here reported. For this reason only the operations leading to $\alpha,\alpha$-dimethylsuccinic acid are described in detail; the results of the other preparations are given in the accompanying table. Analyses of new compounds are given in footnotes to the table.

**Ethyl $\alpha,\beta$-Dicyano-$\beta$-methylbutyrate.**—A mixture of 58 g. (1 mole) of dry acetone, 113 g. (1 mole) of ethyl cyanoacetate, 79 g. (1 mole) of pyridine and 63 g. (1 mole) of glacial acetic acid was refluxed for one hour. Absolute ethyl alcohol (100 ml.) was then added, and as soon as active boiling subsided, 65 g. (1 mole) of potassium cyanide was added through the neck of the flask. The condenser was immediately replaced, and the refluxing which occurred because of the ensuing vigorous spontaneous reaction was continued by the application of heat when necessary for a total of one hour. It is important that the cyanide addition be made before the mixture has cooled appreciably below the temperature of active refluxing, for the reaction with the potassium cyanide cannot otherwise be made complete, and low yields and an impure product result.

The slurry which formed on cooling was then treated with 400 ml. of 1:3 hydrochloric acid, and swirled and gently warmed until all solid disappeared. The aqueous layer, after separation of the oil, was extracted with two 100-ml. portions of ether, and the combined organic layers were neutralized with sodium bicarbonate, dried over sodium sulfate, and distilled; yield 126 g. (70%), b. p. 136–141° (9 mm.).

**$\alpha,\alpha$-Dimethylsuccinic Acid.**—A mixture of 126 g. of ethyl $\alpha,\beta$-dicyano-$\beta$-methylbutyrate and 600 ml. of concentrated hydrochloric acid was refluxed for five hours, after which 150 ml. more acid was added and the refluxing was continued three hours. Distillation to dryness under aspirator vacuum left a cake of $\alpha,\alpha$-dimethylsuccinic acid and ammonium chloride, from which the acid was extracted with several 100-ml. portions of boiling ether

(1) Taken from part of the doctoral thesis of Jerome P. Horwitz, (1949).

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(3) A. C. Cope and E. R. Alexander, THIS JOURNAL, **66**, 886 (1944).

(4) A. C. Cope, C. M. Hoffman, C. Wyckoff and E. Hardenbergh, *ibid.*, **63**, 3452 (1941); A. C. Cope, *ibid.*, **59**, 2326 (1937).

(5) Lapworth and McRae, *J. Chem. Soc.*, **121**, 2741 (1922).

(6) A. Higson and J. F. Thorpe, *ibid.*, **89**, 1455 (1906).

TABLE I

α,β-DICYANO-ESTERS AND SUCCINIC ACIDS

| Carbonyl compound | Yield, % | Dicyano-ester B. p., °C. | Mm. | Succinic acid | Yield, % | M. p., °C. |
|---|---|---|---|---|---|---|
| Acetone | 70 | 136–141 | 9 | α,α-Dimethylsuccinic acid | 76 | 138–139 |
| Methyl ethyl ketone | 49 | 145–146 | 10 | α-Methyl-α-ethylsuccinic acid[a] | 73 | 101–102 |
| Cyclohexanone | 75 | 177–179 | 10 | 1-Carboxycyclohexylacetic acid[b] | 75 | 131–132 |
| Propionaldehyde | 53 | 158–160 | 12 | Ethylsuccinic acid[c] | 60 | 98–100 |
| Isobutyraldehyde | 67 | 151–155 | 10 | Isopropylsuccinic acid[d] | 78 | 115–116 |
| Acetophenone | 17 | 140–145 | 0.1 | α-Phenyl-α-methylsuccinic acid[e] | 60 | 157–158 |
| Benzaldehyde | [f] | 145–158 | 0.1 | Phenylsuccinic[f] acid and α-cyanocinnamic acid | 12 | |

[a] Higson and Thorpe[6] report ethyl α,β-dicyano-β-methylvalerate, b. p. 162° (20 mm.), and α-ethyl-α-methylsuccinic acid, m. p. 102–103°. [b] Dickens, Horton and Thorpe, *J. Chem. Soc.*, 125 (1934), report ethyl 1-cyanocyclohexylcyanoacetate, b. p. 210–212° (22 mm.), and (1-carboxycyclohexyl)-acetic acid, m. p. 132°. [c] Ethyl α,β-dicyanovalerate: *Anal.* Calcd. for $C_9H_{12}O_2N_2$: N, 15.56. Found: N, 15.62.[7] [d] Ethyl α,β-dicyano-γ-methylvalerate: *Anal.* Calcd. for $C_{10}H_{14}O_2N_2$: N, 14.43. Found: N, 14.41.[7] Von Braun and Reinhardt, *Ber.*, **62**, 2585 (1929), report isopropylsuccinic acid, m. p. 116°. [e] α-Phenyl-α-methylsuccinic acid: *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.77; neut. equiv., 104. Found: C, 63.32; H, 5.82[8]; neut. equiv., 107. [f] The mixture of esters was hydrolyzed without separation to give phenylsuccinic acid and α-cyanocinnamic acid, which were separated by means of the solubility of the former in hot water, in 12% over-all yield each.

The product was obtained in a very pure state by evaporation to a volume of about 125 ml., heating to boiling with 1 l. of benzene, and allowing to stand until crystallization was complete (about one day); yield 77 g. (76%), m. p. 138–139° (lit. 139°[6]). The acid can also be recovered from the hydrolysis mixture more simply, but in lower yield (*ca.* 60%), by allowing crystallization to take place instead of distilling the mixture to dryness, and extracting the filtered solids with ether as described.

The hydrolyses of the other dicyano-esters reported in the table were essentially the same, except that 1-carboxycyclohexylacetic acid had to be precipitated from benzene solution by the addition of petroleum ether (60–75°), and α-phenyl-α-methylsuccinic acid was freed from ammonium chloride by crystallization from hot water.

(7) Analysis by Micro-Tech Laboratories, Skokie, Illinois.

## Summary

A convenient synthesis for certain succinic acids is described which employs the condensation of aldehydes or ketones with cyanoacetic ester and potassium cyanide.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

# Synthetic Analogs of Oxytocic Drugs. II. β-Hydroxyphenethyl-β-alanine Esters[1]

BY RICHARD BALTZLY AND ARTHUR P. PHILLIPS

Oxytocic activity having been found in a family of phenethyl-β-alanine esters[2] the effect of introducing an hydroxyl group in the side-chain was studied. Data on the compounds prepared for this purpose and on new intermediates are presented in Table I.

Although the available methods of assay render any precise conclusions on the influence of the hydroxyl group questionable, its presence appears advantageous. While compounds IV and V were not clearly more active than the comparable substances without the hydroxyl group, compounds I–III are also of the same order of activity, whereas in the phenethyl series[2] maximum activity was observed only with two alkoxyl substituents on the aromatic ring.

The preferred method of synthesis was by the addition of the appropriate phenylalkanolamine to methyl acrylate

$$RCHOHCH_2NHMe + CH_2{=}CHCOOMe \longrightarrow RCHOHCH_2N(Me)CH_2CH_2COOMe$$

Under the conditions described in the experimental section this reaction appears to be quantitative. Compound I was prepared from *d,l*-ephedrine and ethyl-β-bromopropionate. Compound V was obtained from IV by ester exchange.[2]

The secondary amines required from compounds II–IV are known.[3,4] The intermediate for compound VI, N-methyl-β-hydroxy-β-(3,4-dimethoxyphenyl)-ethylamine (XI)[5] is less easily prepared than might be supposed. When the corresponding benzylmethylaminoketone hydrochloride (VIII) was hydrogenated with Adams catalyst in the expectation of obtaining XI, cleavage of the dimethoxyphenacyl group appeared to compete with debenzylation. A considerable quantity of neutral material less volatile than toluene was present in the reaction mixture and XI was iso-

(1) The work here reported is part of a joint program carried out in collaboration with a pharmacological group in these laboratories.

(2) Baltzly, Dvorkovitz and Phillips, THIS JOURNAL, **71**, 1162 (1949).

(3) Baltzly and Buck, *ibid.*, **62**, 164 (1940).

(4) Ardis, Baltzly and Schoen, *ibid.*, **68**, 591 (1946).

(5) Mannich, *Arch.*, **248**, 127 (1910), prepared the base but could not obtain crystalline salts.