Specific Synthesis and Selective Alkylation and Condensation of Monoesters of Substituted Succinic Acids

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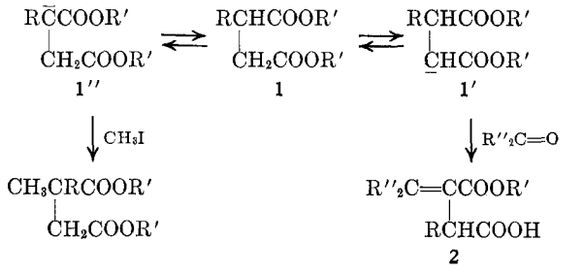
Monoesters of unsymmetrical alkylsuccinic acids are converted by 2 equiv of amide ion in liquid ammonia to dianions in which the proton α to the ester moiety has been ionized. The dianion reacts with alkyl halides to yield an alkylated product and with carbonyl compounds to yield a condensation product. The use of this dianion thus affords a single product of predictable structure, while alkylation of the diester or the imide yields a mixture of both possible products. The substituted monoesters are prepared by attaching an acetic acid residue to an ester chain, by attaching an acetate ester moiety to an acid chain, by hydrogenation of monoesters of itaconic acids, or by alkylation of ethyl hydrogen succinate.

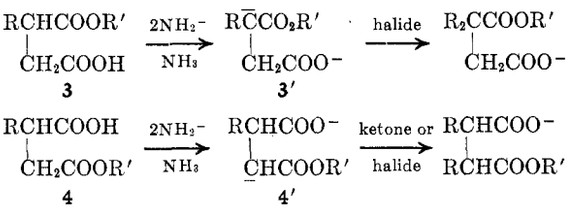
Although carbanions derived from esters of succinic acid and from succinimide have been useful synthetic intermediates in condensation and alkylation reactions,[2,3] there has been little investigation into the use of derivatives of substituted succinic acids in such reactions. Esters of alkylsuccinic acids (**1**, R = CH_3, $C_6H_5CH_2$, etc.) undergo the Stobbe reaction to give alkylidene products (**2**). This suggests ionization at the unsubstituted carbon (to give **1′**);[4,5] however, the Stobbe reaction involves several equilibria which are shifted toward product by formation of a carboxylate salt (of **2**),[2] and the equilibrium can only be so shifted for products of ion **1′** and not **1″**. Esters of phenylsuccinic acid preferentially form ion **1″** (R = C_6H_5), as is demonstrated by alkylation (an irreversible reaction) of diethyl phenylsuccinate exclusively on the substituted carbon, but the product of the Stobbe reaction is derived from ion **1′** (R = C_6H_5)[6] (see Scheme I).

SCHEME I



The acidity of a proton α to a carboxyl function can be profoundly affected by the nature of the carboxyl derivative. Thus while ethyl 3-bromopropionate is dehydrohalogenated by potassium diphenylmethide, in the 3-bromopropionate ion the acidity of the α proton has been decreased by the negative charge of the carboxylate moiety, and reaction with potassium diphenylmethide proceeds by displacement of the bromide ion to give a salt of 4,4-diphenylbutyric acid.[7] It thus seemed reasonable that a monoester of an alkylsuccinic acid would form that dianion with a negative charge α to the ester portion regardless of the position of the substituent, and thus alkylation or condensation reactions would take place exclusively at that same position (Scheme II).

SCHEME II



Alkylation and Condensation of Anions.—The dianion obtained from methyl hydrogen succinate and 2 molar equiv of lithium amide was alkylated with methyl iodide to form 2-methylsuccinic acid 1-methyl ester. As is usually the case with esters not activated by aromatic substituents, better yields were obtained by use of lithium amide in excess of the stoichiometric 2 molar equiv.[8] The structure of the alkylated esters was demonstrated by decarboxylation of the free carboxyl group by means of the Cristol modification of the Hunsdiecker reaction.[9] Thus 2-methylsuccinic acid 1-methyl ester (**3**, R = R′ = CH_3) gave methyl 2-methyl-3-bromopropionate, while 2-methylsuccinic acid 4-methyl ester (**4**, R = R′ = CH_3) afforded methyl 3-bromobutyrate. The linear and branched isomeric esters are readily distinguished by nmr. The isomeric monoesters (**3** and **4**) cannot be distinguished by nmr, since the chemical shifts of the protons are almost the same whether α to an ester or to a free carboxyl group. Thus methyl hydrogen succinate shows a singlet for the four methylene protons. However, a second useful technique for assigning structures to alkylated monoesters was provided by a comparison of the nmr spectra of the ester–acid and its potassium salt (the monomethyl esters were used to avoid overlapping of ethyl–CH_3 and alkyl resonances). Thus when potassium carbonate is added to the solution of methyl hydrogen succinate, the singlet is replaced by a complex A_2B_2 pattern. In all cases studied protons α or β (and even γ) to the carboxyl group are shifted upfield in the salt, but the shift is larger the closer the proton is to the carboxyl function. The spectra of the monoesters and their salts are summarized in Table I. Both isomers of the half-esters of 2-methylsuccinic acid, 2-isopropylsuccinic acid, and 2-phenylsuccinic acid (**3** and **4**, R =

(1) NDEA Fellow, 1969–1970.
(2) For a review of the Stobbe condensation, see W. H. Johnson and G. H. Daub, *Org. React.*, **6**, 1 (1951).
(3) D. R. Bryant and C. R. Hauser, *J. Amer. Chem. Soc.*, **83**, 3468 (1961).
(4) H. Stobbe and F. Gollucke, *Ber.*, **39**, 1066 (1906).
(5) A. Weizmann, *J. Org. Chem.*, **8**, 285 (1943).
(6) A. M. Islam and M. T. Zemaity, *J. Amer. Chem. Soc.*, **80**, 5806 (1958).
(7) W. G. Kofron and N. I. Gottfried, *J. Org. Chem.*, **31**, 3426 (1966).
(8) C. R. Hauser, and W. J. Chambers, *ibid.*, **21**, 1524 (1956); (b) W. R. Dunnavant and C. R. Hauser, *ibid.*, **25**, 503 (1963).
(9) S. J. Cristol and W. C. Firth, *ibid.*, **26**, 280 (1961).

TABLE I

NMR SHIFTS FOR PROTONS IN ACIDS[a]

Compd	Registry no.	Proton	$\Delta_{acid-salt}$, cps (upfield)	τ_{acid}
B A CH_3CH_2COOH	79-09-4	A	14	7.59
		B	4.5	8.90
C B A $CH_3CH_2CH_2COOH$	107-92-6	A	13	7.65
		B	5	8.35
		C	4	9.04
CH_3 A B CHCOOH CH_3	79-31-2	A	21	7.38
		B	7	8.80
A CH_2COOH CH_2COOCH_3	26248-95-3	A	9	7.30[b]
		B	5	
		C	2	6.27
B C A CH_2COOH $CH_3CHCOOCH_3$	32980-25-9	A		7.31[c]
		B	9[c]	
		C	0	8.775
C B D B A $CH_3CHCOOH$ CH_2COOCH_3	23268-03-3	D	1	6.29
		A	6	7.13
		B	4	8.78
		C	4	7.38
C D A CH_2COOH $(CH_3)_2CCOOCH_3$	32980-26-0	D	0	6.28
		A	11	7.32
		C	2	8.74
		D	0	6.26
C D				

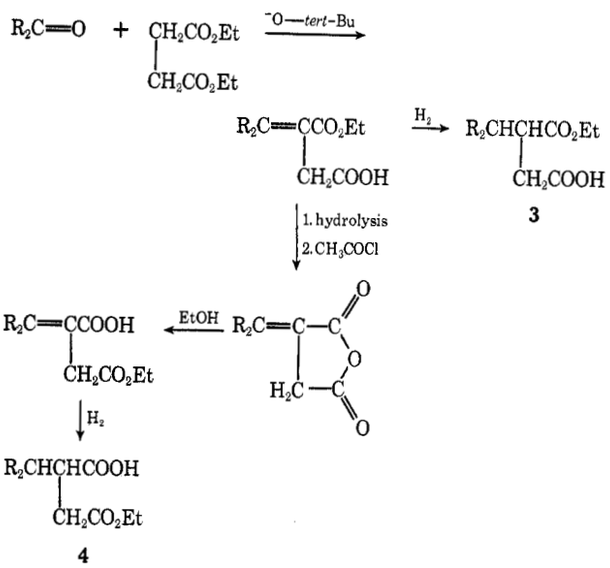
[a] Spectra were run in D_2O containing sodium dimethylsilapentanesulfonate as standard (τ 10.000) (Silanor D_2O) or in D_2O containing sodium trimethylsilylpropionate-*2,2,3,3-d*$_4$ (Silanor D_2O–TSP). The salt was prepared by addition of potassium carbonate to the sample in the nmr tube, and the spectrum was run again. Shifts were determined by measuring the midpoint of the integration trace, since multiplets were not symmetrical. [b] A singlet for both methylenes is observed in the acid. [c] Methylene and methine protons could not be completely separated, and the value is for the midpoint of the integration trace and is thus a weighted average. Both methylene and methine signals are complex multiplets.

CH_3, *i*-C_3H_7 or C_6H_5; R′ = CH_3 or C_2H_5) were studied, and in all cases, even 2-phenylsuccinic acid 4-ethyl ester, alkylation took place exclusively on the carbon atom adjacent to the ester function. In contrast, the anion obtained from diethyl 2-methylsuccinate gave on methylation a mixture of alkylated esters including the diesters of 2-methylsuccinic (starting material), 2,2-dimethylsuccinic, and 2,3-dimethylsuccinic acids. Similarly, methylation of the dianion obtained from 2-methylsuccinimide gave a mixture of 2,2- and 2,3-dimethylsuccinimide.

Condensation of the monoester dianions with ketones or benzaldehyde similarly took place at the carbon α to the ester group, but only when this methylene was not substituted (*i.e.*, **4**). Condensation products were not obtained from the isomers (**3**). During the reaction or the work-up the intermediate hydroxy acid salts cyclized to lactones. The reactions of ketones with 2-methylsuccinate and 2-phenylsuccinate diesters have already been shown to take place at the unsubstituted carbon. The alkylation and condensation reactions are summarized in Table II, p 558.

Specific Synthesis of Monoesters.—Monoesters are readily obtained by the reaction of cyclic anhydrides with 1 molar equiv of an alcohol; however, unsymmetrical (*e.g.*, monosubstituted) anhydrides might give either or both of the isomeric monoesters (**3** or **4**). Methylsuccinic anhydride, on treatment with ethanol, produced a mixture of isomers which could not be separated by distillation or gas chromatography.[10] The Stobbe condensation produces specifically a monoester, and hydrogenation of this compound affords the pure saturated monoester **3**. Also, alkylation of the dianion of monoethyl succinate affords pure **3**. The isomeric unsaturated monoester can be obtained from the itaconic anhydride,[11] and hydrogenation affords the pure saturated monoester **4** (see Scheme III).

SCHEME III



Alkylation of a carbanion with sodium chloroacetate has previously been useful to introduce a carboxymethyl group.[7] This method was applied to the synthesis of 2-phenylsuccinic acid 1-ethyl ester (**3**, R = C_6H_5; R′ = C_2H_5), by alkylation of the lithium or potassium salt of ethyl phenylacetate. Attempts to prepare analogous esters (*e.g.*, **3**, R = CH_3) were unsuccessful. Similarly, alkylation of a carboxylic acid, *via* its dianion, with ethyl bromoacetate would afford the isomeric monoester **4**. This method was successful with the dilithium derivative of phenylacetic acid but not with the dipotassium salt.

As can be seen from Table II, trialkylsuccinic acids can also readily be prepared by further alkylation of

(10) The literature on this reaction is quite confusing. The original report claimed that the product with methanol was 2-methylsuccinic acid 4-methyl ester (**4**, R = R′ = CH_3); see W. A. Bone, J. J. Sudborough, and C. H. G. Sprankling, *J. Chem. Soc.*, **85**, 534 (1904). The Beilstein listing [H **2**, 639] cites this reference for the isomer (**3**). Subsequently this reaction was used to prepare the isomer (**3**), but large amounts of **4** were also found; see J. E. H. Hancock and R. P. Linstead, *ibid.*, 3490 (1953). Authentic 2-methylsuccinic acid 4-methyl ester (**4**) was prepared by reduction of the corresponding itaconic half ester, prepared from the reaction of itaconic anhydride with 1 molar equiv of methanol.[11]

(11) B. R. Baker, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **17**, 116 (1952). We have reexamined these reactions and agree with the latter two reports.

dialkyl compounds. In the cases where 2,3-dialkylsuccinic acids are formed, stereoisomers may be produced. Generally mixtures of threo and erythro (or *dl* and *meso*) compounds were formed and were converted to the diesters for analysis by gas chromatography.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus, using a calibrated thermometer. Infrared spectra were obtained on Nujol mulls for solids and capillary films for liquids. Nmr spectra were determined on a Varian A-60 spectrometer in D_2O containing DSS or TSP, unless otherwise specified. Microanalyses were performed by Goodyear Research Laboratories and/or Galbraith Laboratories. Gas chromatograms were obtained on an F & M Model 500 chromatograph, using a 12-ft 10% SE-30 or a 20-ft 12.5% Ucon 50 column.

Alkylation of Diethyl Succinate.—An ethereal solution of 8.7 g (0.05 mol) of diethyl succinate was added to a stirred suspension of 0.05 mol of lithium amide in 200 ml of liquid ammonia, prepared from 0.35 g (0.05 g-atom) of lithium. The mixture was stirred for 1 hr and 7.1 g (0.05 mol) of methyl iodide in a little ether was added. The mixture was stirred for 1 hr and the ammonia was evaporated. The residue was stirred with ether and ice-cold dilute hydrochloric acid, and the ethereal solution was separated, dried, and evaporated to give 6.7 g of an oil, shown by gas chromatography to be 99% diethyl succinate and 1% diethyl methylsuccinate. From the aqueous layer was obtained a mixture of succinic acid and monoethyl succinate.

The experiment was repeated using 2 molar equiv of lithium amide. Gas chromatography indicated the product (4.0 g) to contain 25% diethyl succinate, 29% diethyl methylsuccinate, 5% diethyl 2,3-dimethyl succinate, 1% diethyl 2,2-dimethylsuccinate, and several unidentified compounds.

2-Isopropylsuccinic Acid 1-Ethyl Ester.—A solution of 1.86 g (0.01 mol) of 2-isopropylidenesuccinic acid 1-ethyl ester[12] in 50 ml of methanol was hydrogenated at atmospheric pressure using 50 mg of 10% Pd/C. The solution was filtered and evaporated, and the residue was distilled at 0.1 mm to give 1.7 g (90%) of 2-isopropylsuccinic acid 1-ethyl ester, bp 102–104°; saponification with aqueous base followed by acidification gave the diacid, mp 115–116° (lit.[12] mp 115–115.5°).

Alkylation of Monoesters.—A typical procedure is given in detail. Table II indicates mole ratio of amide employed and yield obtained.

2-Isopropyl-2-methylsuccinic Acid 1-Ethyl Ester.—An ethereal solution of 2.5 g (0.013 mol) of 2-isopropylsuccinic acid 1-ethyl ester was added to 0.052 mol of lithium amide in 200 ml of liquid ammonia, and the mixture stirred for 1 hr. An ethereal solution of 1.9 g (0.013 mol) of methyl iodide was added, and the mixture was stirred for 1 hr. Ammonium chloride was added and the ammonia was evaporated. The residue was stirred with ice and dilute hydrochloric acid and ether, and the ethereal solution was dried and evaporated. The resulting oil was chromatographed over neutral alumina to give 1.1 g (43%) of 2-isopropyl-2-methylsuccinic acid 1-ethyl ester. The monoester was saponified with aqueous base to the diacid: mp and mmp 136–138°; nmr (DMSO-d_6) τ 9.16 (d, 6), 8.9 (s, 3), 7.6–8.6 (m, 3).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.26; H, 8.12.

2-Isopropylsuccinic Acid 4-Ethyl Ester.—A solution of 7.5 g (0.054 mol) of isopropylidenesuccinic anhydride[13] in 100 g of ethanol and 100 g of chloroform was refluxed for 4 hr. The solvent was evaporated and the resulting solid recrystallized from benzene–hexane to give 7.6 g (76%) of 2-isopropylidenesuccinic acid 4-ethyl ester, white needles, mp 112–114°.

Anal. Calcd for $C_9H_{14}O_4$: C, 58.06; H, 7.58. Found: C, 58.31; H, 7.33.

A solution of 1.5 g (0.008 mol) of the monoester in 50 ml of ethanol was hydrogenated for 12 hr at atmospheric pressure with 50 mg of 10% Pd/C. The solution was filtered and evaporated and the residue distilled at 0.1 mm to give 1.3 g (87%) of 2-isopropylsuccinic acid 4-ethyl ester, bp 103–105°.

Anal. Calcd for $C_9H_{16}O_4$: C, 57.44; H, 8.57. Found: C, 57.68; H, 8.49.

Saponification in aqueous base and acidification gave 2-isopropylsuccinic acid, mp and mmp 115–116°.

2-Isopropyl-3-methylsuccinic Acid.—An ethereal solution of 3.7 g (0.02 mol) of 2-isopropylsuccinic acid 4-ethyl ester was added to 0.06 mol of lithium amide in 200 ml of liquid ammonia, and the mixture was stirred for 1 hr. An ethereal solution of 5.7 g (0.04 mol) of methyl iodide was added, and the mixture was stirred for 1 hr. Ammonium chloride was added, the ammonia was evaporated, and the residue was stirred with ice and dilute hydrochloric acid and ether. The ethereal solution was dried and evaporated and the oil was chromatographed over alumina to give 2.1 g (51%) of 2-isopropyl-3-methylsuccinic acid 4-ethyl ester. Saponification afforded 2-methyl-3-isopropylsuccinic acid in 90% yield: mp 171–173° (lit.[13] 174–175°); nmr (DMSO-d_6) τ 9.06 (d, 6), 8.90 (d, 3), 7.18–8.34 (m, 3), −1.56 (s, 2).

Alkylation of 2-Methylsuccinimide.—Finely powdered 2-methylsuccinimide (5.0 g, 0.044 mol) was added to 0.088 mol of lithium amide in 250 ml of liquid ammonia. After 1 hr an ethereal solution of 7.2 g (0.044 mol) of methyl iodide was added. After 1 hr excess ammonium chloride was added and the ammonia was evaporated. The residue was stirred with ice and dilute hydrochloric acid and ether, and the ethereal solution was dried and evaporated to give 3.8 g of an oil, shown by gas chromatography to contain 2,2- and 2,3-dimethylsuccinimide (10 and 31% yields) as well as starting material and lower boiling compounds.

Condensation of Carbonyl Compounds with Monoesters.—A typical procedure is given in detail; minor variations are noted in Table II. An ethereal solution of 7.3 g (0.05 mol) of monoethyl succinate was added to a suspension of 0.15 mol of lithium amide in 200 ml of liquid ammonia, and the mixture was stirred for 1 hr. An ethereal solution of 5.6 g (0.05 mol) of cycloheptanone was added, the mixture was stirred vigorously for 3 min, and an excess of ammonium chloride was added at once. The ammonia was evaporated and the residue stirred with ice and dilute hydrochloric acid and ether. The ethereal solution was dried and concentrated to give an oil with ir bands at 1785 and 1745 cm^{-1}. Chromatography on neutral alumina gave 5.2 g (43%) of the pure paraconic ester, homogeneous by tlc.

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.28; H, 8.55.

2-Phenylsuccinic Acid 1-Ethyl Ester.—To a stirred solution of 0.1 mol of ethyl potassiophenylacetate in 250 ml of liquid ammonia, prepared from 16.4 g (0.1 mol) of ethyl phenylacetate and 0.1 mol of potassium amide, ws added 11.6 g (0.1 mol) of sodium chloroacetate, and the resulting colorless mixture was stirred while the ammonia evaporated. The residue was stirred with water and ether, and the ethereal solution was separated, dried, and evaporated to give 2.1 g (14%) of ethyl phenylacetate. The aqueous layer was acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was separated, dried, and evaporated to give 16 g (72%) of crude monoester. Recrystallization from aqueous ethanol afforded 15.5 g (70%) of white crystals: mp 87–89°; homogeneous by tlc; ir 1720, 1745 cm^{-1}; nmr (CCl_4) τ 8.84 (t, 3), 7.16 (m, 2), 6.0 (m, 3, OCH_2 + ArCH).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.95; H, 6.45.

Hydrolysis afforded 2-phenylsuccinic acid, mp 166–168°, in 89% yield.

The experiment was repeated with ethyl sodiophenylacetate, and the yield of recrystallized monoester was 71%.

2-Phenylsuccinic Acid 4-Ethyl Ester.—To a solution of 0.1 mol of lithium lithiophenylacetate[14] in 250 ml of liquid ammonia was added an ethereal solution of 16.6 g (0.1 mol) of ethyl bromoacetate. The ammonia was evaporated and the residue was stirred with water and ether. Evaporation of the ether gave only a trace of ethyl bromoacetate. The aqueous layer was acidified with 10% hydrochloric acid and extracted with ether. Evaporation of the ether gave 13.8 g of residue. Recrystallization from hexane afforded 11.9 g (53%) of the monoester: mp 90–92°; ir 1720 and 1745 cm^{-1}; nmr (CCl_4) τ 8.82 (t, 3), 8.2 (m, 2), 5.96 (m, 3, OCH_2 + ArCH), −0.74 (s, 1).

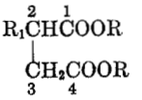
(12) C. G. Overberger and C. W. Roberts, *J. Amer. Chem. Soc.*, **71**, 3618 (1949).

(13) W. H. Bentley, W. H. Perkin, and J. F. Thorpe, *J. Chem. Soc.*, 270 (1896).

(14) P. J. Hamrick and C. R. Hauser, *J. Amer. Chem. Soc.*, **82**, 1957 (1960).

TABLE II

ALKYLATION AND CONDENSATION OF SUBSTITUTED SUCCINIC ACID DERIVATIVES



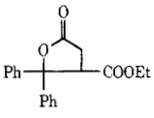
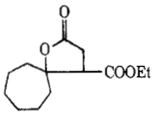
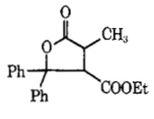
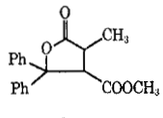
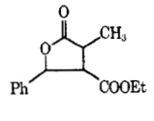
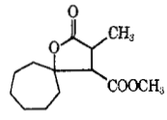
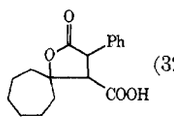
R_1	1 Function	4 Function	Amide (mol)	Reagent	Product (%)	Registry no.	Mp or bp (mm) °C	Diacid, mp (lit. mp)
H	COOEt	COOH	$LiNH_2$ (3)	CH_3I	2-CH_3 (35–46)	32980-27-1	88–89 (0.05)	108–110 (110)[a]
H	COOEt	COOH	$LiNH_2$ (4)[b]	CH_3I	2,2-$(CH_3)_2$ (21)	32980-28-2		135–137 (136–137)[a]
H	$COOCH_3$	COOH	$LiNH_2$ (3)	CH_3I	2-CH_3 (31)		92–94 (0.1)	109–110 (110)
H	COOEt	COOH	$LiNH_2$ (3)	$C_6H_5CH_2Cl$	2-$C_6H_5CH_2$ (40)	32980-29-3		162–163 (162)[c]
H	COOEt	COOH	$LiNH_2$ (3)	$(C_6H_5)_2CO$	 (41)	14596-64-6	149–150	169–170 (168–169)[d]
H	COOEt	COOH	$LiNH_2$ (3)	Cycloheptanone	 (43)	33021-07-7		187–188 (184–186)[e]
CH_3	COOEt	COOH	$LiNH_2$ (4)	CH_3I	2,2-$(CH_3)_2$ (40)			136–138 (136–137)
CH_3	$COOCH_3$	COOH	$LiNH_2$ (4)	CH_3I	2,2-$(CH_3)_2$ (31)	32980-26-0	98–99 (0.1)	135–137 (136–137)
CH_3	COOEt	COOH	$LiNH_2$ (4)	$C_6H_5CH_2Cl$	2-CH_3, 2-$C_6H_5CH_2$ (23)	32980-32-8		117–119[f]
CH_3	COOEt	COOH	$LiNH_2$ (4)	$(CH_3)_2CHI$	2-CH_3, 2-$(CH_3)_2CH$ (10)	32971-20-3		136–138[g]
CH_3	COOH	$COOCH_3$	$LiNH_2$ (3)	CH_3I	2,3-$(CH_3)_2$ (80)[h]	608-40-2	97–98 (0.07)	196–198 (198), *meso*
						608-39-9		121–123 (123), *dl*
CH_3	COOH	$COOCH_3$	$LiNH_2$ (3)	$C_6H_5CH_2Cl$	2-CH_3, 3-$C_6H_5CH_2$ (64)	32980-34-0	93–95	138–140 (138)[i]
CH_3	COOH	COOEt	$LiNH_2$ (3)	$(C_6H_5)_2CO$	 (30)	33021-08-8	144–146	*j*
CH_3	COOH	$COOCH_3$	$LiNH_2$ (3)	$(C_6H_5)_2CO$	 (46)	33021-09-9	153–154	*k*
CH_3	COOH	COOEt	$LiNH_2$ (3)	C_6H_5CHCO	 (21)	33021-10-2	135–140 (0.1)	*l*
CH_3	COOH	$COOCH_3$	$LiNH_2$ (3)	Cycloheptanone	 (49)	33980-35-1		*m*
$(CH_3)_2CH$	COOEt	COOH	$LiNH_2$ (4)	CH_3I	2-CH_3, 2-$(CH_3)_2CH$ (43)	32971-20-3		136–138
$(CH_3)_2CH$	COOH	COOEt	$LiNH_2$ (3)	CH_3I	2-$(CH_3)_2CH$, 3-CH_3 (51)	32980-36-2		171–173 (174–175)[n]
CH_3	COOEt	COOEt	$LiNH_2$ (1)	CH_3I	2-CH_3 (80)[o] 2,3-$(CH_3)_2$ (3)[o]	4676-51-1		
CH_3	COOEt	COOEt	$LiNH_2$ (2)	CH_3I	2-CH_3 (70)[o] 2,2-$(CH_3)_2$ (3)[o] 2,3-$(CH_3)_2$ (10)[o]			
C_6H_5	COOEt	COOEt	$LiNH_2$ (1)	CH_3I	2-CH_3, 2-C_6H_5 (55)	32980-38-4	110–112 (0.2)	161–163 (163–164)[p]
C_6H_5	COOEt	COOH	$LiNH_2$ (2)	CH_3I	2-CH_3, 2-C_6H_5 (86)	33021-11-3	89–91	161–163 (163–164)
C_6H_5	COOH	COOEt	$LiNH_2$ (2)	CH_3I	2-C_6H_5, 3-CH_3 (91)	32980-39-5		177–179 (170–171)[q] 190–192 (192–193)[q]

TABLE II (*Continued*)

R_1	1 Function	4 Function	Amide (mol)	Reagent	Product (%)	Registry no.	Mp or bp (mm), °C	Diacid, mp (lit. mp)
C_6H_5	COOEt	COOEt	$LiNH_2$ (1)	C_6H_5CHO	2-C_6H_5, 3-benzylidene (20)	32980-40-8		187–188[r]
C_6H_5	COOH	COOEt	$LiNH_2$ (2)	$(C_6H_5)_2CO$	2-C_6H_5, 3-benzhydrylidene (45)	32980-41-9		203–205[s]
C_6H_5	COOH	COOEt	$LiNH_2$ (2)	Cycloheptanone	 (32–49)	32980-42-0		*t*
C_6H_5	COOEt	COOH	$LiNH_2$ (2)	$C_6H_5CH_2Cl$	2-C_6H_5, 2-$C_6H_5CH_2$ (74)	32980-43-1	110–112	190–192 (194)[u]
C_6H_5	COOH	COOEt	$LiNH_2$ (2)	$C_6H_5CH_2Cl$	2-C_6H_5, 3-$C_6H_5CH_2$ (64)	32980-44-2	126–130	183–185 (185)[v]
C_6H_5	COOEt	COOH	$LiNH_2$ (2)	C_4H_9Br	2-C_4H_9, 2-C_6H_5 (86)	32980-45-3	150–155 (0.01)	148–150 (152)[w]
C_6H_5	COOH	COOEt	$LiNH_2$ (2)	C_4H_9Br	2-C_6H_5, 3-C_4H_9 (58)	32980-46-4	165–170 (0.06)	183–185[x]

[a] L. Higginbotham and A. Lapworth, *J. Chem. Soc.*, 49 (1922). [b] The reaction mixture was neutralized with excess NH_4Cl 3 min after the benzophenone had been added. When the mixture was neutralized after 1 hr, starting material was recovered. Compare ref 8b. [c] J. A. McRae and L. Marion, *Can. J. Res., Sect. B*, **15**, 480 (1937). [d] H. Stobbe, *Justus Liebigs Ann. Chem.*, **308**, 89 (1899). [e] Lactone acid; J. W. Cook, R. Philip, and A. R. Sommerville, *J. Chem. Soc.*, 164 (1948). [f] Registry no. 32980-47-5. *Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.31. Found: C, 64.98; H, 6.45. [g] Registry no. 5703-04-8. *Anal.* Calcd for $C_8H_{14}O_4$: C, 55.17; H, 8.05. Found: C, 55.26; H, 8.16. [h] Gas chromatography showed 90% *meso* and 10% *dl* after conversion to the diester; W. A. Bone and W. H. Perkin, *J. Chem. Soc.*, 253 (1896). [i] Gas chromatography of the diesters showed only a trace of the higher boiling isomer; C. A. Bischoff and A. von Kuhlberg, *Ber.*, **23**, 1942 (1890). [j] *Anal.* Calcd for $C_{20}H_{20}O_4$: C, 74.07; H, 6.17. Found: C, 73.88; H, 6.14. [k] *Anal.* Calcd for $C_{19}H_{18}O_4$: C, 73.55; H, 5.81. Found: C, 73.80; H, 5.69. [l] *Anal.* Calcd for $C_{14}H_{16}O_4$: C, 67.74; H, 6.45. Found: C, 67.82; H, 6.51. [m] *Anal.* Calcd for $C_{13}H_{20}O_4$: C, 65.00; H, 8.33. Found: C, 65.18; H, 8.47. [n] A trace of the ester corresponding to the acid of mp 125–126° was detected by gas chromatography after esterification; W. H. Bentley, W. H. Perkin, and J. F. Thorpe, *J. Chem. Soc.*, 270 (1896). [o] Yields were determined by gas chromatography. [p] H. LeMoal, A. Foucaud, R. Carrie, J. Hamelin, and C. Sevellec, *Bull. Soc. Chim. Fr.*, **5**, 913 (1964). [q] N. Zelinsky and L. Buchstab, *Ber.*, **24**, 1876 (1891). [r] Registry no. 32980-49-7. *Anal.* Calcd for $C_{17}H_{14}O_4$: C, 72.34; H, 4.96. Found: C, 72.18; H, 4.76. [s] Registry no. 32980-50-0. *Anal.* Calcd for $C_{23}H_{18}O_4$: C, 77.09; H, 5.02. Found: C, 77.37; H, 5.22. [t] *Anal.* Calcd for $C_{17}H_{20}O_4$: C, 70.83; H, 6.94. Found: C, 70.90; H, 6.85. [u] Anhydride, formed by distillation of monoester; F. Salmon-Legagneur and H. LeMoal, *C. R. Acad. Sci.*, **229**, 126 (1949). [v] Only a trace of higher isomer by vpc of diesters; J. Jarrouse, *ibid.*, **204**, 132 (1937). [w] G. Poulain, *Bull. Soc. Chim. Fr.*, **5**, 913 (1964). [x] Only isomer by vpc of diesters. Registry no. 32980-51-1. *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.20; H, 7.20. Found: C, 67.50; H, 7.16.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.83; H, 6.54.

Registry No.—2-Isopropylidenesuccinic acid 4-ethyl ester, 32980-52-2; 2-isopropylsuccinic acid 4-ethyl ester, 32980-53-3; 2-phenylsuccinic acid 1-ethyl ester, 32971-21-4; 2-phenylsuccinic acid, 635-51-8; 2-phenylsuccinic acid 4-ethyl ester, 32980-55-5;

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