

1 : 2-Dicarboxylic Acids. Part II.* The Diastereoisomeric $\alpha\alpha'$ -Dimethylsuccinic Acids and their Derivatives. Effect of Conformation on Stability.

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The relative stabilities of the two diastereoisomeric $\alpha\alpha'$ -dimethylsuccinic acids and of their open-chain and heterocyclic derivatives are reviewed. The results are the exact opposite of those encountered among the corresponding hexahydrophthalic acids and their derivatives. This difference is explained in terms of conformations.

The preparative methods for the $\alpha\alpha'$ -dimethylsuccinic acids and their derivatives are compared and the literature is corrected in certain respects. The two diastereoisomeric nitriles have been made.

WE were first led to study the $\alpha\alpha'$ -dimethylsuccinic acids from interest in the synthesis of dimethylsuccinimidine and octamethyltetrazaporphin. This required, in particular, a reinvestigation of the nitrogenous derivatives such as the imides. However, a wider interest was involved. The acids constitute a classical example of stereoisomerism involving two adjacent asymmetric carbon atoms; after the tartaric acids, they are perhaps the best investigated system of the kind. Inversions between the two stereoisomeric series (*DL* † and *meso*) can be studied at various points and thus a direct indication can be obtained of the relative stabilities of the various forms. We find that the results are capable of an orderly explanation on the basis of conformations.

It is generally accepted that the most stable conformation of the ethane molecule is staggered; similarly the preferred arrangement of *n*-butane, with the lowest potential energy, is one in which the four carbon atoms lie in a planar zig-zag. If hydrogen atoms in the 2- and the 3-position in butane are substituted, structural factors are introduced which affect the stability of the simple zig-zag type with results that can be studied chemically. As will appear in the sequel, the $\alpha\alpha'$ -dimethylsuccinic acids are very convenient compounds for this purpose.

The Diastereoisomeric $\alpha\alpha'$ -Dimethylsuccinic Acids.—We first examined the preparation of ten key crystalline compounds: the parent acids, and the amides, nitriles, anhydrides, and imides of the two series. Our data on the acids, anhydrides, and the *DL*-imides agreed substantially with those in the literature, but in earlier work on the two amides and the *meso*-imide the pure isomerides were not obtained owing to the ease of inversion. The two dinitriles (2 : 3-dicyanobutanes) are new (see Table 1).

The methods for the preparation of the acids are described in a later section. They yielded mixtures of isomerides, generally in about equal amounts. The *meso*-acid, m. p. 209°, was easily separated by crystallisation. On esterification with methanol and mineral acid in boiling benzene it gave a pure *meso*-ester. (The configuration of this and of the other derivatives described later was determined by hydrolysis with boiling hydrochloric acid for two hours. Separate experiments showed that the *meso*-acid was completely unaffected by this treatment and the *DL*-acid almost so. The *DL*-acid was gradually isomerised by long treatment under these conditions so that *prolonged* acid hydrolysis of *DL*-derivatives does not give reliable evidence of configuration, particularly as the less soluble *meso*-acid tends to crystallise first from hydrolysates.) The *meso*-ester failed to give a diamide with aqueous or methanolic ammonia at room temperature or with methanolic ammonia at 90°. At 165° with aqueous-methanolic ammonia, however, it slowly yielded the pure *meso*-diamide, m. p. 301—303°. This diamide could not be obtained from the *DL*-imide on treatment with ammonia under a variety of conditions. Dehydration of the *meso*-amide with carbonyl chloride in pyridine gave the *meso*-dinitrile, m. p. 45—46°. Hydrolysis of both amide and nitrile gave pure *meso*-acid. We found

* Part I, *J.*, 1953, 3490.

† For use of *DL*, see *J.*, 1950, 3333, 3701, and *J.*, 1951, 3516.

the *meso*-anhydride very difficult to obtain pure. Previous workers had obtained it by the action of acetyl chloride on the *meso*-acid (Hückel and Müller, *Ber.*, 1931, **64**, 1983; Berner and Leonardsen, *Tidsskr. Kjemi*, 1943, **3**, 64). In our hands this gave essentially the *DL*-isomeride, m. p. 88—89°. However, the action of thionyl chloride on the sodium salt of the *meso*-acid yielded the *meso*-anhydride, m. p. 39—40°. Dimethylmaleic anhydride resisted catalytic hydrogenation; like other similar maleic anhydrides it appears to be a powerful poison for the usual catalysts. *meso*-1 : 2-Dimethylsuccinimide could not be prepared by conventional routes from dimethylsuccinic derivatives as these gave mixtures containing largely the *DL*-isomeride. The *meso*-imide was, however, readily obtained by catalytic hydrogenation of dimethylmaleinimide. The product melted at 45—47° and yielded the *meso*-acid on hydrolysis. The m. p. of the imide was depressed on admixture with the *DL*-isomeride. Crystallisation or sublimation led to very considerable inversion. Earlier workers have reported *meso*-imides with higher melting points (Bischoff and Voit, *Ber.*, 1889, **22**, 389; 1890, **23**, 623, m. p. 78°; Hückel and Müller, *loc. cit.*, m. p. 66—72°). We have obtained samples of imide melting in about this range, but these all contained considerable amounts of the *DL*-form. From a mixed melting point curve we estimate the Bischoff and the Hückel product to have contained about 87% and 76% respectively of the *DL*-isomeride.

The easy catalytic hydrogenation of the dimethylmaleinimide in comparison with the obstinate resistance of the corresponding anhydride is very striking. These and similar hydrogenations are being investigated further. For the present it need only be observed that the reaction of the imide provides another example of the formation of a hydride in its unstable form by one-sided addition of hydrogen (see Linstead, Doering, *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 1985).

For the preparation of stereochemically homogeneous derivatives of the other diastereoisomeric series it was unnecessary to start with the pure *DL*-acid. The usual synthetic mixture of *DL*- and *meso*-acids was converted into the ammonium salts, dry distillation of which gave pure *DL*-imide, m. p. 107—109° (cf. Zelinsky and Krapivin, *Ber.*, 1889, **22**, 646; McRae, Weston, and Hubbs, *Canad. J. Res.*, 1937, **15**, 436). Short acid-hydrolysis of this gave nearly pure *DL*-acid, which could easily be purified by crystallisation. This process provides a reliable method for the preparation of this isomeride. Treatment of the *DL*-imide with concentrated aqueous ammonia at room temperature or with methanolic ammonia at 90° readily gave the homogeneous *DL*-diamide, m. p. 221—223°. When this compound was heated with aqueous ammonia or glacial acetic acid, as in crystallisation procedures, the melting point was raised but the product was less pure for, on hydrolysis, it gave appreciable amounts of *meso*-acid. Dehydration of the *DL*-amide by carbonyl chloride in pyridine gave in excellent yield *DL*- $\alpha\alpha'$ -dimethylsuccinonitrile (2 : 3-dicyanobutane), m. p. 57—59°, which gave the *DL*-acid on hydrolysis.

Esterification of the original mixture of *meso*- and *DL*-acids gave a mixture of methyl esters which on treatment with aqueous ammonia gave, slowly and in poor yield, a mixture of diamides. The melting point of this varied in different preparations from 235° to 250°, and it was presumable mainly the *DL*-isomeride. Morrell (*J.*, 1914, **105**, 2698) reports the preparation, in poor yield, of diamides from the *meso*- and *DL*-esters and aqueous ammonia, the melting points being given as 244° “*cis*” (*meso*), and 238° “*trans*” (*DL*). McRae, Weston, and Hubbs (*loc. cit.*) obtained a diamide, m. p. 244° after crystallisation, both from the *DL*-imide and from an ester of unstated configuration. No hydrolyses are reported by these workers and there is little doubt that these various products were mixtures, containing mainly the *DL*-form.

The melting points of the various members of the two stereoisomeric series are summarised in Table I.

At this stage reference should be made to the nomenclature of the acids. Some confusion exists in the literature owing to the superficial resemblance between the stable, high-melting, dimethylsuccinic acid (the *meso*-acid) and fumaric acid. This has led to the former being called “fumaroid” (see Beilstein’s “Handbuch”) and “*trans*” (see Heilbron’s “Dictionary”), the labile acid of m. p. 127° (the *DL*-acid) being called

"maleinoid" or "cis." If, however, one considers the geometry of the heterocyclic derivatives of the *DL*-acid, then the two methyl groups are on opposite sides of the hetero-ring. This would entitle them to be called *trans*- although on the old nomenclature they belong to the "cis" or "maleinoid" series. Clearly the use of the terms *cis*, *trans*, maleinoid, and fumaroid is most undesirable and only the terms "*meso*" and *DL*- should be applied to these and similar compounds. The configurations have, of course, been established with certainty; they rest on the classical resolution of the *DL*-acid by Werner. An example of the confusion which may result from the use of other terms is

TABLE 1. *Melting points of $\alpha\alpha'$ -dimethylsuccinic acids and their derivatives.*

	<i>meso</i> -Series		<i>DL</i> -Series	
	Present work	Lit.	Present work	Lit.
Acid	209°	209° ¹	127°	129° ¹
Diamide	301—303	244 ²	221—223	238 ²
Dinitrile	45—46	—	57—59	—
Anhydride	39—40	42—43 ^{1, 3, 4}	89	87, ⁴ 88—89 ⁵
Imide	45—47	78, ⁴ 66—72 ⁶	107—109	109—110 ⁷

¹ Bone and Perkin, *J.*, 1896, **69**, 253. ² Morrell, *loc. cit.* ³ Higson and Thorpe, *J.*, 1906, **89**, 1455. ⁴ Bischoff and Voit, *loc. cit.* ⁵ Fieser and Daudt, *J. Amer. Chem. Soc.*, 1941, **63**, 782. There is an accidental error in this paper, which refers to the high-melting acid as *DL*, the low melting as *meso*. The configurations given to the anhydrides are, however, correct. ⁶ Hüchel and Müller, *loc. cit.* ⁷ Zelinsky and Krapivin, *loc. cit.*

to be seen in the paper of Kühn and Ebel (*Ber.*, 1925, **58**, 2091) where some of Auwers's early data (*Annalen*, 1899, **309**, 316) are reinterpreted. The two series are wrongly named: for example, Auwers's "*mal*-imide" (formed from both stereoisomeric amic acids by the action of acetyl chloride) becomes "*ms*-imide" in Kühn's paper. It is, in fact, the *DL*-imide (cf. Hüchel and Müller, *Ber.*, 1931, **64**, 1981, footnote). The same criticism cannot be applied to the naming of the hexahydrophthalic acid series. Here the term *trans* is reasonable for the *DL*-acid as it denotes that the two functional groups are on opposite sides of the ring. It is true, however, that now that the ring is known to be multiplanar, these two "sides" no longer retain all their old precision.

Inversion of the 1:2-Dimethylsuccinic Acids and their Derivatives.—Key results are given in Table 2. Precise measurements of the various changes have not been made and it is not known whether the inversions are reversible. If so the equilibria must lie on the side indicated in the Table, which summarises broadly the direction of the changes. The corresponding data for the related cyclic acids, the hexahydrophthalic (see Ficken, France, and Linstead, following paper), have been added to Table 2 for comparison. Nitriles are omitted as no clear-cut inversion of them has been observed.

TABLE 2. *Inversion of dimethylsuccinic and hexahydrophthalic acids and their derivatives.*

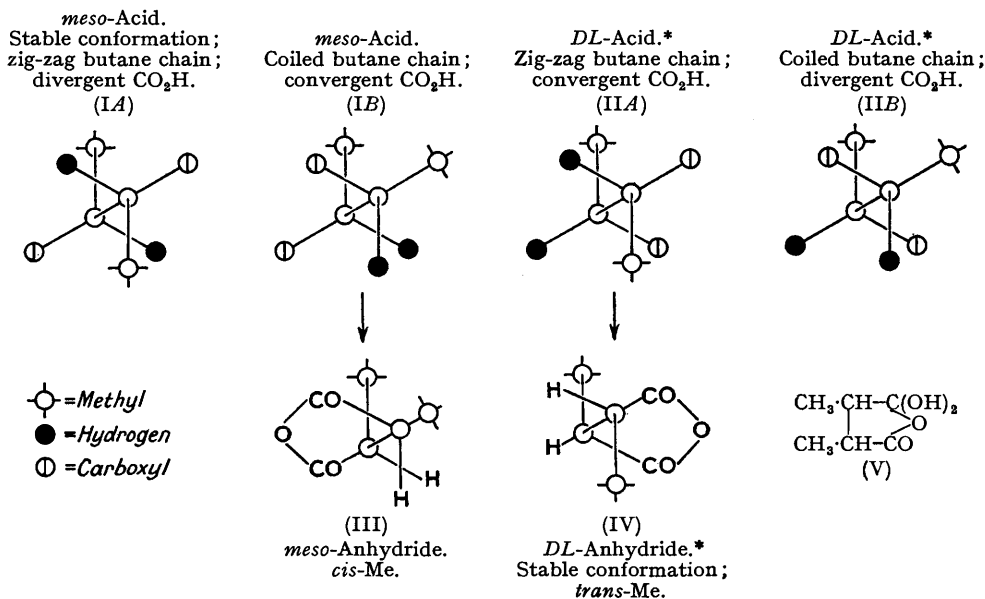
	$\alpha\alpha'$ -Dimethylsuccinic	Hexahydrophthalic
Acid	<i>DL</i> \longrightarrow <i>meso</i>	<i>meso</i> \longrightarrow <i>DL</i> (<i>cis</i> \longrightarrow <i>trans</i>)
Diamide	<i>DL</i> \longrightarrow <i>meso</i>	<i>meso</i> \longrightarrow <i>DL</i>
Anhydride	<i>meso</i> \longrightarrow <i>DL</i>	<i>DL</i> \longrightarrow <i>meso</i> (<i>trans</i> \longrightarrow <i>cis</i>)
Imide	<i>meso</i> \longrightarrow <i>DL</i>	<i>DL</i> \longrightarrow <i>meso</i> *

* Attempts to make the *DL*-hexahydrophthalimide have so far only given the stable *meso*-isomeride (Ficken, France, and Linstead, *loc. cit.*).

Discussion.—A striking contrast between the aliphatic and the alicyclic compounds is at once apparent from Table 2. In the dimethylsuccinic series, the open-chain compounds are stable in the *meso*-form and their heterocyclic derivatives in the *DL*-forms, whereas in the hexahydrophthalic series the reverse is true. These facts can be accounted for as follows:

(1) The dimethylsuccinic acids would, in the absence of effects associated with the carboxyl groups, tend to take up a staggered conformation with a planar zig-zag arrangement of the butane chain. If a model of this is set up for the *meso*-acid, it will be seen (IA) that the carboxyl groups are at maximum divergence. If, on the other hand, the

carbon atoms of the *DL*-isomeride are arranged in a planar zig-zag conformation, the carboxyl groups come together (IIA). Unless special factors operate, it is to be expected that the most favoured conformation will be that with the bulky groups as far apart as possible. The main special factors for the free acids might be attractive forces between the carboxyl groups. If these groups tend to come together by hydrogen bonding or, in the extreme case, by the formation of a dihydroxy-ring compound of the Anschütz type (V), then we could expect a departure from the requirements of the simple conformational argument. It is obvious, however, from empirical considerations that this is not true: if the favoured conformations of the acids were those with convergent carboxyl groups, the relative stabilities of the acids would be the same as those of their anhydrides. The reverse is true. It is concluded therefore that the acid which, in its most favoured conformation, can have a zig-zag butane chain and a divergent arrangement of carboxyls will be more stable than its isomeride. This is the *meso*-acid (IA) and in our view this is the explanation for its superior stability over the *DL*-isomeride, which must fluctuate between relatively unfavourable arrangements such as (IIA and B). Conformation (IA)



* These diagrams correspond to only one enantiomorph, but this does not affect the argument.

represents, of course, only the most favoured, not the unique, arrangement for the *meso*-acid. The same basic arguments can be applied to the open-chain derivatives of the acids.

(2) The heterocyclic derivatives are different. In these the conformation of the acid with convergent carboxyl groups has in effect been stabilised (IB → III, IIA → IV). When this is done in the *meso*-series, the methyl groups are brought into a coiled, *cis*-arrangement; whereas the anhydride of the *DL*-acid is formed with the methyl groups divergent and *trans* with respect to the hetero-ring. This explains the relative stability of the *DL*-anhydride and the imide.

(3) In the hexahydrophthalic series, these simple effects are complicated by the restraint placed upon the molecule by the substitution of the ring for the two methyl groups. Although some flexibility remains, the carbon substituents are no longer free to take up any position at will. The deciding factors are those which operate generally for 1 : 2-disubstituted derivatives of *cyclohexane*. In the *DL*-series the two functional groups can both take up equatorial positions, but in the *meso*-series one is axial and the other equatorial. The former is accordingly the preferred arrangement.

(4) The data for the heterocyclic derivatives of the hexahydrophthalic acids are the least easy to interpret. The system is similar to that of the indan-1-ones in which the *cis*- is known to be more stable than the *trans*-form. Some factor is operating which makes the best arrangement for the *cis*-isomerides more stable than the best for the *trans*-isomerides. It is not known whether this favoured conformation contains a chair *cyclohexane* ring fused to a somewhat puckered hetero-ring (perhaps with hydrogen bonding between carbonyl-oxygen and nuclear hydrogen atoms) or a boat *cyclohexane* ring fused to a planar hetero-ring.

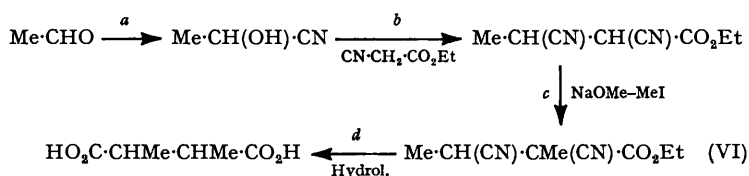
The treatment of the dimethylsuccinic acids given above (paras. 1 and 2) can clearly be applied to other aliphatic systems, although in many cases the results will be less clear-cut. Somewhat analogous arguments have been advanced to explain the effect of stereochemical factors on the ease of formation of cyclic acetals of polyhydric alcohols (Barker, Bourne, and Whiffen, *J.*, 1952, 3865).

On this basis both in the alicyclic and the dimethylsuccinic series the stable acids and amides have statistically the widest spread of the functional groups. The comparative steric freedom of the carboxyl and the carboxyamido-groups should permit a greater measure of intermolecular association through hydrogen bonding. In agreement with this, the stable acids and amides have higher melting points than their diastereoisomerides, whereas a similar effect is not shown by the corresponding nitriles in which hydrogen bonding is not possible.

A Note on the Preparative Methods for Dimethylsuccinic Acids.—On pp. 3722—3733 we described the preparation of pure diastereoisomeric materials from the mixture of acids normally obtained. We now add a note on the various methods for the synthesis of this mixture. Three broad routes are open: (1) The condensation of α -bromopropionic ester with ethyl sodiomalonate, followed by methylation and hydrolysis. There are numerous variants, of which the most interesting is the process investigated by Zelinsky (*Ber.*, 1888, 21, 3160) and by Bone and Perkin (*J.*, 1896, 69, 63 etc.), according to which the action of cyanide on α -bromopropionic ester gives some dimethylcyanosuccinic ester direct. Our work on the Zelinsky–Bone–Perkin process and on other variants of the bromo-ester–sodio-ester reaction leads us to conclude that they are less attractive than the Higson–Thorpe procedure (see below) for routine preparative work.

As the molecule of dimethylsuccinic acid is made up of two similar parts, it is easy to formulate synthetic schemes, depending on the twinning of two free radicals (cf. Fichter and Heer, *Helv. Chim. Acta*, 1936, 19, 149): $2\text{Me}\cdot\dot{\text{C}}\text{HX} \longrightarrow \text{Me}\cdot\text{CHX}\cdot\text{CHX}\cdot\text{Me}$. Exploratory investigation of a number of such processes has yielded nothing of preparative value.

Our preferred process is as illustrated. Acetaldehyde cyanohydrin was prepared in excellent and reproducible yield by the use of piperidine as catalyst. Stages (b) and (c),



which could be carried out in one series of operations, followed Higson and Thorpe (*loc. cit.*). The overall yield of $\alpha\beta$ -dicyano- α -methylbutyric ester (VI) was 75%. Complete hydrolysis then gave a mixture of the stereoisomeric $\alpha\alpha'$ -dimethylsuccinic acids in nearly theoretical yield and approximately equal proportions.

In view of our requirement for dimethylsuccinonitrile, the partial hydrolysis of the dicyano-ester (VI) was also examined. Treatment of this material with cold methanolic potassium hydroxide deposited some insoluble potassium salt but the bulk of the product remained in solution. After removal of the insoluble salt, attempts were made to isolate the dicyanomethylbutyric acid corresponding to (VI), but these failed owing to the onset of decarboxylation. This was accordingly completed by vacuum-distillation. The viscous

distillate deposited some solid *DL*- $\alpha\alpha'$ -dimethylsuccinonitrile, identified by hydrolysis to the *DL*-acid and by comparison with that already described. The uncrystallisable residue from the solid dinitrile was a mixture of *meso*- and *DL*-isomers. If the potassium salt was not removed before this process was carried out, the dinitrile obtained was contaminated with *DL*-imide and some $\alpha\alpha'$ -dimethylsuccinamic acid (mainly *meso*). The potassium salt on acidification yielded $\alpha\beta$ -dicyano- α -methylbutyric acid hydrate, the acid corresponding to the ester (VI). The acid, on hydrolysis, gave a mixture of dimethylsuccinic acids, mainly *meso*. Decarboxylation by heat afforded a mixture of $\alpha\alpha'$ -dimethylsuccinonitriles, the *meso*-form again predominating. The synthesis thus provides both $\alpha\alpha'$ -dimethylsuccinonitriles, although only the *DL*-form was obtained pure, but is far inferior to that involving dehydration of the diamides by carbonyl chloride.

EXPERIMENTAL

Acetaldehyde Cyanohydrin.—Acetaldehyde (50 g.) was added dropwise to liquid hydrogen cyanide (49 c.c.) and piperidine (2.5 c.c.). The mixture was left at about 10° overnight. Concentrated sulphuric acid (2.5 c.c.) was then added and the mixture distilled, giving acetaldehyde cyanohydrin (68 g., 85%), b. p. 102°/30 mm. We are indebted to Imperial Chemical Industries Limited, Dyestuffs Division, for communication of this considerable improvement on literature methods.

Partial Hydrolysis of Ethyl $\alpha\beta$ -Dicyano- α -methylbutyrate (VI).—(a) *$\alpha\alpha'$ -Dimethylsuccinonitrile*. The ester (40 g.), prepared from acetaldehyde cyanohydrin and ethyl cyanoacetate, followed by methylation (Higson and Thorpe, *loc. cit.*), was added to potassium hydroxide (14 g.) in methanol (40 c.c.), and the solution left at room temperature for 48 hr. The crystalline solid A was separated. Most of the methanol was evaporated under reduced pressure, the residue dissolved in water (40 c.c.), and the solution extracted with ether overnight. Hydrolysis, with concentrated hydrochloric acid, of the oil extracted by the ether gave *meso*- $\alpha\alpha'$ -dimethylsuccinic acid (1.5 g.), m. p. 195—197°. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether overnight. The viscous oil obtained after concentration of the ether extract was distilled (b. p. 95—110°/1 mm.), decarboxylation occurring. The distillate (5.1 g.) was dissolved in light petroleum (b. p. 60—80°) and ethanol, and the solution frozen in liquid nitrogen. As the mixture warmed, the solid was filtered off, the process being repeated until no more solid, m. p. 41—43°, was obtained. The solid was recrystallised from light petroleum-ethanol or from water, giving colourless prisms of *DL*- $\alpha\alpha'$ -dimethylsuccinonitrile (1.4 g., 6%), m. p. 56—58° (Found: C, 66.8; H, 6.9; N, 25.7. $C_6H_8N_2$ requires C, 66.6; H, 7.5; N, 25.9%). *DL*-Dimethylsuccinonitrile (102 mg.) was refluxed for 2 hr. with concentrated hydrochloric acid (3 c.c.). *DL*- $\alpha\alpha'$ -Dimethylsuccinic acid (98 mg., 71%), m. p. 125—127°, separated.

The uncrystallisable residue contained *meso*-material, and hydrolysis of 1 g. with concentrated hydrochloric acid gave 520 mg. of *meso*- $\alpha\alpha'$ -dimethylsuccinic acid and 340 mg. of the *DL*-acid.

(b) *$\alpha\beta$ -Dicyano- α -methylbutyric acid*. The yield of the potassium salt A was greater in small-scale experiments, less heat being generated to cause decarboxylation. Ethyl $\alpha\beta$ -dicyano- α -methylbutyrate (136.5 g.) was divided into 14 batches, each of which was treated with potassium hydroxide (3.5 g.) in methanol (35 c.c.). After 3 hr. at room temperature the solutions were cooled in ice for 30 min. and the precipitates collected. The dried potassium salt was dissolved in the minimum amount of water, and the solution filtered through kieselguhr and acidified with hydrochloric acid. The solid was collected, dried (18.2 g., 14%), and crystallised from ethanol-ether, giving *$\alpha\beta$ -dicyano- α -methylbutyric acid monohydrate*, m. p. 175—177° (with evolution of carbon dioxide) (Found: C, 49.2; H, 6.1; N, 16.4. $C_7H_{10}O_3N_2$ requires C, 49.4; H, 5.9; N, 16.5%). The acid (500 mg.) was hydrolysed with concentrated hydrochloric acid (5 c.c.), giving *meso*- (380 mg.; m. p. 193°) and *DL*-dimethylsuccinic acid (130 mg.; m. p. 104—109°) (see below).

(c) *Decarboxylation of $\alpha\beta$ -dicyano- α -methylbutyric acid*. The acid (1.0 g.) was heated at 170° under reduced pressure for 20 min. Vigorous evolution of carbon dioxide occurred and a colourless substance sublimed (m. p. 40—42°; 231 mg., 36%). The substance was resublimed at atmospheric pressure and twice crystallised from water, giving a mixture of *meso*- and *DL*- $\alpha\alpha'$ -dimethylsuccinonitrile, m. p. 41—43° (Found: C, 66.5; H, 7.6; N, 25.5. Calc. for

$C_6H_8N_2$: C, 66.6; H, 7.5; N, 25.9%). Hydrolysis of the nitrile (100 mg.) with concentrated hydrochloric acid (2 c.c.) gave *meso*- $\alpha\alpha'$ -dimethylsuccinic acid (82 mg., 61%), m. p. 189—193°.

(d) $\alpha\alpha'$ -Dimethylsuccinamic acids. If the potassium salt A was not removed from the reaction mixture before acidification of the hydrolysate, the *DL*- $\alpha\alpha'$ -dimethylsuccinonitrile was contaminated with *DL*- $\alpha\alpha'$ -dimethylsuccinimide, m. p. 104—106°, and with $\alpha\alpha'$ -dimethylsuccinamic acids; the acids were separated from the imide by means of sodium carbonate solution, reprecipitated with hydrochloric acid, and crystallised from ethanol; they had m. p. 153—158° (Found: C, 49.3; H, 7.6; N, 10.4. Calc. for $C_6H_{11}O_3N$: C, 49.6; H, 7.6; N, 9.7%). Hüchel and Müller (*Ber.*, 1931, **64**, 1989) give m. p. 165—167° for *meso*- $\alpha\alpha'$ -dimethylsuccinamic acid, and m. p. 148—149° for the *DL*-acid. $\alpha\alpha'$ -Dimethylsuccinamic acid (170 mg.) on hydrolysis with concentrated hydrochloric acid (3 c.c.) gave *meso*- $\alpha\alpha'$ -dimethylsuccinic acid (80 mg., 47%).

$\alpha\alpha'$ -Dimethylsuccinamic acid (107 mg.) was warmed on the steam-bath with acetyl chloride (8 drops) for 4 hr. A little water was added and the solution extracted with ether. The oily residue, after evaporation of the ether, was sublimed, giving *DL*- $\alpha\alpha'$ -dimethylsuccinimide, m. p. and mixed m. p. 103—105°.

Complete Hydrolysis of Ethyl $\alpha\beta$ -Dicyano- α -methylbutyrate.—The ester (50 g.) was refluxed with concentrated hydrochloric acid (300 c.c.) for 24 hr. On cooling, *meso*- $\alpha\alpha'$ -dimethylsuccinic acid (15 g., 38%), m. p. 198—202°, crystallised. Recrystallisation several times from water and from concentrated hydrochloric acid gave pure *meso*-acid, m. p. 209°. Continuous ether-extraction of the filtrate overnight gave the remainder of the $\alpha\alpha'$ -dimethylsuccinic acid (*DL* and some *meso*) (19.5 g., 48%).

Separation of meso- and DL- $\alpha\alpha'$ -Dimethylsuccinic Acids.—Mixed $\alpha\alpha'$ -dimethylsuccinonitriles (1.0 g.) and concentrated hydrochloric acid (5 c.c.) were refluxed for 2 hr., then cooled; *meso*- $\alpha\alpha'$ -dimethylsuccinic acid (520 mg.), m. p. 193—195°, separated. The filtrate was extracted with ether overnight and the ether removed. The residue was cooled in ice and treated with 2—3 drops of cold water, and the remaining solid (47 mg.), m. p. 130—135° (a mixture of *meso* and *DL*), was filtered off. The water was removed from the filtrate in a vacuum-desiccator, and the gummy residue recrystallised from concentrated hydrochloric acid, giving *DL*- $\alpha\alpha'$ -dimethylsuccinic acid (340 mg.), m. p. 123—127°.

Isomerisation of DL- $\alpha\alpha'$ -Dimethylsuccinic Acid.—*DL*- $\alpha\alpha'$ -Dimethylsuccinic acid (100 mg.) was refluxed with concentrated hydrochloric acid for 40 hr. The hydrochloric acid was removed and the residue crystallised from water, to give *meso*- $\alpha\alpha'$ -dimethylsuccinic acid (5 mg.; 5% conversion), m. p. 191—193°.

DL- $\alpha\alpha'$ -Dimethylsuccinimide.—Mixed *meso*- and *DL*- $\alpha\alpha'$ -dimethylsuccinic acids (30 g.) were dissolved in aqueous ammonia (*d* 0.880; 45 c.c.), and the mixture distilled. The fraction of b. p. <110° was rejected, most of the imide distilling at 240—260°. The oily distillate was crystallised twice from water, giving colourless prisms of *DL*- $\alpha\alpha'$ -dimethylsuccinimide (17.5 g., 71%), m. p. 107—109° (Found: N, 10.8. Calc. for $C_6H_9O_2N$: N, 11.0%). The imide (50 mg.) was refluxed with concentrated hydrochloric acid (2 c.c.) for 2 hr., *DL*- $\alpha\alpha'$ -dimethylsuccinic acid (45 mg., 78%), m. p. 125—127°, separating on cooling.

DL- $\alpha\alpha'$ -Dimethylsuccinamide.—(a) *DL*- $\alpha\alpha'$ -Dimethylsuccinimide (2.0 g.) was dissolved in aqueous ammonia (*d* 0.880; 8 c.c.), and the solution kept at room temperature for 48 hr. *DL*- $\alpha\alpha'$ -Dimethylsuccinamide was filtered off and washed well with cold water and with methanol to remove traces of unchanged imide. The yield of amide was 1.44 g. (64%) and the m. p. 221—223° (Found: C, 50.0; H, 8.5; N, 20.0. Calc. for $C_6H_{12}O_2N_2$: C, 50.0; H, 8.4; N, 19.4%) (Morrell, *J.*, 1914, **105**, 2698, gives m. p. 238°). Attempts to recrystallise the diamide from water, glacial acetic acid, or dilute acetic acid invariably led to partial isomerisation to the *meso*-amide.

(b) *DL*- $\alpha\alpha'$ -Dimethylsuccinimide (1.0 g.) was heated with methanolic ammonia (5 c.c.) (prepared from 5 c.c. of methanol and 5 c.c. of liquid ammonia) in a sealed tube at 90° for 8 hr. After evaporation of the ammonia, *DL*- $\alpha\alpha'$ -dimethylsuccinamide (0.81 g., 72%), m. p. 221—223°, was collected.

DL- $\alpha\alpha'$ -Dimethylsuccinamide (198 mg.) was refluxed with concentrated hydrochloric acid (4 c.c.) for 2 hr. *DL*- $\alpha\alpha'$ -Dimethylsuccinic acid (120 mg., 60%), m. p. 125—127°, separated on cooling. The *DL*-amide (112 mg.) was heated at 220° until evolution of ammonia ceased. The residue was sublimed under reduced pressure, yielding *DL*- $\alpha\alpha'$ -dimethylsuccinimide (69 mg., 70%), m. p. 104—106°.

DL- $\alpha\alpha'$ -Dimethylsuccinonitrile.—*DL*-Dimethylsuccinamide (50.5 g.) was suspended in dry pyridine (610 c.c.), and carbonyl chloride (about 87 g.; dried by passage through concentrated

sulphuric acid) was bubbled into the rapidly stirred solution. The temperature was kept at 60—70° by control of the rate of gas-flow. The solution was allowed to cool for 3 hr., poured on ice, and made acid to Congo-red with concentrated hydrochloric acid. The dark red solution was continuously extracted with ether for several days, and the ether extracts were evaporated. *DL*- $\alpha\alpha'$ -Dimethylsuccinonitrile (28.1 g., 75%), m. p. 48—51°, was obtained by crystallisation of the residue from water (charcoal). Further crystallisation from ethanol-light petroleum (b. p. 60—80°) raised the m. p. to 57—59°. The mixed m. p. with *DL*- $\alpha\alpha'$ -dimethylsuccinonitrile, obtained by hydrolysis of ethyl $\alpha\beta$ -dicyano- α -methylbutyrate, was undepressed (Found: C, 66.3; H, 7.6. Calc. for $C_6H_8N_2$: C, 66.6; H, 7.5%).

A small amount of uncrystallisable oil (2.1 g.) gave *meso*- $\alpha\alpha'$ -dimethylsuccinic acid (0.6 g.), m. p. 191—195°, on hydrolysis with concentrated hydrochloric acid.

DL- $\alpha\alpha'$ -Dimethylsuccinonitrile (110 mg.; prepared from diamide) on hydrolysis with concentrated hydrochloric acid (1.5 c.c.) gave *DL*- $\alpha\alpha'$ -dimethylsuccinic acid (103 mg., 70%), m. p. 126—127°. The *DL*-nitrile was not isomerised when refluxed with phosphorus oxychloride in pyridine.

Dimethyl meso- $\alpha\alpha'$ -*Dimethylsuccinate*.—*meso*- $\alpha\alpha'$ -Dimethylsuccinic acid (13 g.), m. p. 193—196°, methanol (25 c.c.), benzene (50 c.c.), and concentrated sulphuric acid (5 c.c.) were refluxed for 7 hr. and then cooled. The benzene layer was shaken with sodium carbonate solution and water, and dried (Na_2SO_4). Evaporation of the benzene and distillation of the residue gave dimethyl *meso*- $\alpha\alpha'$ -dimethylsuccinate (12 g., 80%), b. p. 110—112°/35 mm. Hydrolysis of the *meso*-ester (1.2 g.) with concentrated hydrochloric acid gave *meso*-acid (0.8 g., 80%), m. p. 204—206°.

meso- $\alpha\alpha'$ -*Dimethylsuccinamide*.—Methanol was added to a mixture of dimethyl *meso*- $\alpha\alpha'$ -dimethylsuccinate (31.5 g.) and aqueous ammonia (d 0.880; 90 c.c.) until the mixture became homogeneous. The solution was heated at 165° for 5 days. After evaporation of some of the ammonia and methanol, a solid, m. p. 290—293°, separated. Recrystallisation from glacial acetic acid gave colourless prisms of *meso*- $\alpha\alpha'$ -dimethylsuccinamide (5.4 g., 21%), m. p. 300—302° (Found: C, 49.7; H, 8.4; N, 19.0. Calc. for $C_6H_{12}O_2N_2$: C, 50.0; H, 8.4; N, 19.4%) (Morrell, *loc. cit.*, gives m. p. 244°).

meso- $\alpha\alpha'$ -Dimethylsuccinamide (104 mg.) was hydrolysed with concentrated hydrochloric acid (2 c.c.), giving *meso*- $\alpha\alpha'$ -dimethylsuccinic acid, m. p. 201—204°.

meso- $\alpha\alpha'$ -*Dimethylsuccinonitrile*.—*meso*- $\alpha\alpha'$ -Dimethylsuccinamide (5.4 g.) was suspended in pyridine and treated with carbonyl chloride (about 9 g.) as for the *DL*-amide. Continuous ether-extraction of the resulting solution for 48 hr. gave a viscous oil which partly crystallised during 3 weeks. The solid was separated from the oil and crystallised twice (charcoal) from water, to give colourless needles of *meso*- $\alpha\alpha'$ -*dimethylsuccinonitrile* (0.51 g., 13%), m. p. 45—46°, and mixed m. p. 43—44° with *DL*- $\alpha\alpha'$ -dimethylsuccinonitrile (m. p. 57—59°) (Found: C, 66.4; H, 7.4; N, 26.1. $C_6H_8N_2$ requires C, 66.6; H, 7.5; N, 25.9%).

meso- $\alpha\alpha'$ -Dimethylsuccinonitrile (50 mg.) gave on hydrolysis with concentrated hydrochloric acid (2 c.c.), *meso*- $\alpha\alpha'$ -dimethylsuccinic acid (52 mg., 77%), m. p. 201—204°.

meso- $\alpha\alpha'$ -*Dimethylsuccinic Anhydride* (with P. WALKER).—Sodium *meso*- $\alpha\alpha'$ -dimethylsuccinate (2.7 g.) was suspended in dry ether (40 c.c.), and thionyl chloride (1.5 c.c.) added dropwise with shaking. The mixture was kept overnight in a desiccator, and the sodium chloride removed by centrifugation. The resulting solution gave *meso*- $\alpha\alpha'$ -dimethylsuccinic anhydride (1.35 g., 74%), m. p. 39—40°, on evaporation. Attempted recrystallisation of the anhydride from benzene gave anhydride containing *meso*-acid. An ethereal solution of anhydride slowly deposited *meso*-acid.

meso- $\alpha\alpha'$ -Dimethylsuccinic anhydride (0.1 g.) was hydrolysed with concentrated hydrochloric acid (0.2 c.c.), giving *meso*- $\alpha\alpha'$ -dimethylsuccinic acid, m. p. 198—199°.

meso- $\alpha\alpha'$ -*Dimethylsuccinimide*.—Dimethylmaleinimide (459 mg.) in ethanol (10 c.c.) was shaken under hydrogen with Adams platinum oxide catalyst (23 mg.) for 30 min. during which 1 mol. of hydrogen was taken up. The catalyst was removed and the filtrate evaporated to dryness at room temperature. The remaining oil slowly crystallised, giving *meso*- $\alpha\alpha'$ -dimethylsuccinimide (426 mg., 92%), m. p. 45—47° (Found: C, 56.5; H, 7.2; N, 11.6. Calc. for $C_6H_8O_2N$: C, 56.7; H, 7.1; N, 11.0%).

Hydrolysis of the *meso*-imide (117 mg.) with concentrated hydrochloric acid (1 c.c.) gave *meso*- $\alpha\alpha'$ -dimethylsuccinic acid (98 mg., 75%), m. p. 202—205°.

Mixtures of the two dimethylsuccinimides melted at the following temperatures:

<i>meso</i> (%)	0	10	20	30	40	50	60	70	80	90	100
M. p.	107°	84°	79°	60°	52°	45°	39°	34°	32°	37°	45°

Sublimation of the *meso*-imide gave a mixture, m. p. 78—84°, which was hydrolysed to a mixture of $\alpha\alpha'$ -dimethylsuccinic acids (mainly *DL*), m. p. 107—121°. The sublimed imide was estimated from the mixed m. p. curve to contain 87% of the *DL*-isomer.

Analyses in this and the following paper were carried out in the Microanalytical Laboratory (Mr. F. H. Oliver) of this Department.

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