BONE AND SPRANKLING: RESEARCHES ON THE

the Alkyl-substituted Succinic LV.—Researches on Acids. Part II. s-Dipropyl, s-Diisopropyl, and aa,-Propylisopropyl-succinic Acids.

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OF the acids which form the subject of this communication, only s-diisopropylsuccinic has been previously investigated, and our knowledge of it even has not only been incomplete, but in certain respects very unsatisfactory.

In 1889, Hell and Mayer (Ber., 1889, 22, 48) obtained two crystalline dibasic acids of the formula $C_{10}H_{18}O_4$, melting at 168-169° and 199-200° respectively, by hydrolysing the oil obtained by the action of molecular silver upon ethyl a-bromoisovalerate at a temperature of Both acids were sparingly soluble in cold water, and formed 150°. characteristic insoluble calcium, barium, and strontium salts; they could be separated by distillation with steam, for the acid of lower melting point formed a volatile anhydride, whereas the other was nonvolatile, and moreover, did not give an anhydride when heated to a temperature of 210°. Hell and Mayer suggested that the acids might be the two stereoisomeric s-diisopropylsuccinic acids, formed from ethyl a-bromoisovalerate, as follows:

$$2(CH_3)_2CH \cdot CHBr \cdot CO_2Et + 2Ag = (CH_3)_2CH \cdot CH - CH \cdot CH(CH_3)_2 + 2AgBr.$$
$$CO_2Et \quad CO_2Et$$

Considering, however, that the action of molecular silver upon such a-bromo-esters was known to be a somewhat complex one (compare V. Meyer and Auwers, Ber., 1889, 22, 3005; 1890, 23, 295), and does not merely consist in the elimination of bromine and the coupling up of two residues, as indicated by the foregoing equation, they admitted the possibility of structural difference between the two acids, and even suggested that, whereas one of them was probably a s-diisopropylsuccinic acid, the other might be aaa_1a_1 -tetramethyladipic acid.

In 1896, Auwers re-investigated the products of the same reaction (Annalen, 1896, 292, 162), but was quite unable to isolate more than one acid of the formula $C_{10}H_{18}O_4$. It melted at 178-182°, a temperature, it will be observed, intermediate between the melting points of the two acids obtained by Hell and Mayer ; it was sparingly soluble in water, yielded a very stable and volatile liquid anhydride, and an anilic acid melting at 179-180°. He had no hesitation in pronouncing it to be a s-diisopropylsuccinic acid. As s-diisopropylsuccinic acid contains two asymmetric carbon atoms, and should, therefore, like other

symmetrically di-substituted succinic acids, exist in two inactive forms, Auwers tried to effect the conversion of his acid into a stereoisomeric form, by heating it in sealed tubes with water or hydrochloric acid at 180-200°, but was quite unsuccessful. On the results of these two or three isolated negative experiments, he felt justified in concluding that "die symmetrische Diisopropylbernsteinsäure besteht im Gegensatze zu andern symmetrisch disubstituirten Bernsteinsäuren nur in einer Modification" (the italics are his), and further that the acid possesses such peculiar properties, "dass die Existenz einer zweiten Modification dieser Säure als sehr unwahrscheinlich gelten muss. Jedenfalls müsste dieses hypothetische Isomere weit labiler sein, als alle bekannten stereoisomeren Dicarbonsäuren" (ibid., 164 and 166). We shall have no difficulty in showing that his conclusions were illfounded.

Auwers' acid possessed one remarkable property for an acid of the succinic series, namely, a high dissociation constant. Whereas this value for succinic acid itself is 0.0068, whilst those for its mono-alkyl derivatives vary between 0.0075 and 0.0088, and those for other s-dialkylsuccinic acids never exceed 0.0250, Auwers found that the value for his acid varied from 0.2047 to 0.3586, according to the concentration of the solution, thus:

		I.	II	
v.	μ_{v} .	100k.	μ_v .	100k.
256	$211 \cdot 2$	0.3586		
512	$247 \cdot 0$	0.3302	248.7	0.3407
1024	$275 \cdot 2$	0.2815	278.9	0.3004
2048	291.9	0.2047	$301 \cdot 1$	0.2584
		0.2938		0.2998

It is difficult to reconcile these results with the supposition that the acid under examination was a homogeneous substance, for, of course, the constant of a pure acid is independent of the dilution. Auwers did, indeed, for this very reason, suspect "dass die sorgfältig gereinigte Säure doch ein Gemisch von zwei Stereoisomeren sei, die durch fractionirte Krystallisation nicht zu trennen seien," but a further study of the acid convinced him that there was no ground for any such suspicion.

Some months ago (Trans., 1899, **75**, 839), we described a new method for preparing alkyl-substituted succinic acids in quantity from ethyl cyanoacetate; we determined to synthesise s-diisopropylsuccinic acid by means of it, in order to obtain further evidence as to its stereochemical character. We were also led to prepare and examine the hitherto unknown s-dipropyl- and αa_1 -propylisopropyl-succinic acids.

Ethyl propylcyanosuccinate and isopropylcyanosuccinate were prepared by the interaction of ethyl sodiocyanacetate and ethyl a-bromovalerate or a-bromoisovalerate respectively; the resulting oils were then propylated or isopropylated, as the case might be, in the usual manner. The propylated or isopropylated products were hydrolysed in two stages, namely, first by treatment with alcoholic potash, and then by heating the resulting mixture of acids with 50 per cent. sulphuric acid, in order to complete the hydrolysis of the cyano-group, and to ensure the total elimination of carbon dioxide from the resulting tricarboxylic acid.* The acid liquid was at once subjected to distillation with steam, when, in every case, a volatile anhydride passed over, leaving a non-volatile acid behind. Thus, in all three cases, we were able to obtain two different acids, which subsequent investigation proved to be stereoisomeric, being respectively the cis- and transmodifications.

The six acids are all sparingly soluble in water, and yield characteristic, sparingly soluble calcium salts. The trans-acids are either quite insoluble, or only sparingly soluble, in benzene, whereas the cisisomerides are all readily soluble in this solvent. All the acids yield their own liquid anhydrides on being heated with acetyl chloride, the cis., however, much more readily than the trans. These anhydrides are very stable substances, and are not decomposed to any appreciable extent by being boiled with water. They readily dissolve, however, in warm dilute sodium hydroxide, in each case forming the sodium salt of the acid from which the anhydride was originally derived. Each anhydride, with aniline, yields a characteristic anilic acid, and, except in the case of cis-aa, propylisopropylsuccinic, these anilic acids are all solids.

When a mixture of cis- and trans-acids is dissolved in 50 per cent. sulphuric acid, and the solution subjected to distillation with steam, the cis-isomeride is converted into its anhydride, which is volatile, whereas the trans-acid remains behind unchanged. In this way, a quantitative separation of the two isomerides may be effected.

We have also shown that a cis- or trans-acid may be partly converted into the opposite isomeride by heating it with hydrochloric acid in sealed tubes at temperatures varying from 180° to 230°, and that, provided the time of heating be in either case sufficiently prolonged, the final state of equilibrium between the two isomerides is the same. The trans-acids or anhydrides are gradually but completely converted into the *cis*-anhydrides by boiling them with acetic anhydride. The mutual convertibilities of the stereoisomerides are shown in the following diagram :

* The reasons for conducting the hydrolysis in two stages will be fully discussed later.



The melting points of the several acids and their anilic acids may be tabulated as follows:

	Trans.		Cis.	
	Acid.	Anilic acid.	Acid.	Anilic acid.
s-Dipropylsuccinic s-Diisopropylsuccinic aa ₁ -Propylisopropylsuccinic	$182 - 183^{\circ} \\ 226^{\circ} \\ 192 - 194^{\circ}$	$184 - 185^{\circ} \\ 201 - 202^{\circ} \\ 147 - 149^{\circ}$	$121^{\circ} \\ 171^{\circ} \\ 151 - 152^{\circ}$	101—102° 184—185° liquid

We have also investigated the dissociation constants of each of the three pairs of acids. In the case of the s-dipropyl and aa_1 -propyliso-propyl acids, the expected values were obtained, those of the *cis*-acids being approximately double those of the corresponding *trans*-isomerides. The presence of two isopropyl groups in the 'succinic' molecule, however, has an extraordinary influence upon the conductivity of the acids, the value for the *cis*-s-diisopropyl acid being much higher than has hitherto been observed in the case of any other member of the succinic series, and over twenty times as great as that of the *trans*-isomeride. These results are discussed at the end of this paper.

EXPERIMENTAL.

A. Preparation of Ethyl β -Propylcyanosuccinate and β -Isopropylcyanosuccinate.

The details of the operations involved in the preparation of ethyl β -propylcyanosuccinate and β -isopropylsuccinate by the interaction of ethyl sodiocyanoacetate and ethyl *a*-bromovalerate, or *a*-bromoisovalerate respectively, are practically identical with those described in our previous paper in the case of ethyl $\beta\beta$ -dimethylcyanosuccinate (Trans., 1899, 75, 854). The yields of refractionated oils obtained VOL. LXXVII. Z Z

	B. p. 19—21 mm.	d 0°/4°.	μ _{Να} .
Ethyl β -propylcyanosuccinate	171°	1.0638	1·4395
Ethyl β -isopropylcyanosuccinate	165—167°	1.0620	1·4413

amounted to between 44 and 50 per cent. of those theoretically possible. The properties of the esters may be tabulated as follows:

The oils were analysed with the following results:

Ethyl β -Propylcyanosuccinate :

0.1965 gave 0.4300 CO₂ and 0.1360 H_2O . C = 59.68; H = 7.78. 0.2237 , 11.2 c.c. nitrogen at 6° and 773 mm. N = 6.15.

Ethyl β -Isopropylcyanosuccinate:

0.2270 gave 0.4951 CO₂ and 0.1618 H₂O. C = 59.62; H = 7.92. 0.2548 ,, 13.2 c.c. nitrogen at 5° and 762 mm. N = 6.24. $C_{10}H_{10}O_4N$ requires C = 59.75; H = 7.88; N = 5.80 per cent.

In order to be quite sure that the oils just described had the constitutions assigned to them, we hydrolysed small portions of each with concentrated hydrochloric acid, and then isolated the resulting dicarboxylic acid by means of its sparingly soluble calcium salt. In each case, almost theoretical yields of one, and one only, of two acids were obtained, the melting points $(91-92^{\circ} \text{ and } 114^{\circ} \text{ respectively})$ and dissociation constants (0.00886 and 0.00760 respectively) of which showed that they were undoubtedly propyl- and isopropyl-succinic acids respectively.* Analyses of the acids, I, m. p. $91-92^{\circ}$; II, m. p. 114° , were made.

I. 0.1324 gave 0.2556 CO₂ and 0.0918 H₂O. C=52.50; H=7.50. II. 0.1363 ,, 0.2622 CO₂ ,, 0.0943 H₂O. C=52.45; H=7.68. $C_7H_{12}O_4$ requires C=52.50; H=7.50 per cent.

The anilic acids of these propyl- and isopropyl-succinic acids, which so far as we know have not yet been described, melt at 148° and 139° respectively.

B. Propylation (Isopropylation) of Ethyl β-Propylcyanosuccinate and β-Isopropylcyanosuccinate.

These operations were effected by heating molecular proportions of the sodium derivative of the cyano-compound and the alkyl iodide in alcoholic solution on the water-bath until the liquid became neutral.

^{*} Propylsuccinic acid, m. p. 91° (Waltz, Annalen, 1882, 214, 59), K=0.00886 (Walden). Isopropylsuccinic acid, m. p. 113° (Hlasiwetz and Grabouski, Annalen, 1867, 144, 207), K=0.0075 (Walden).

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The time required varied from 36 to 48 hours. The liquid was then in each case poured into water and the oils extracted with ether and isolated in the usual manner. Each product was then carefully fractionated and refractionated under reduced pressure, the fractions of lower boiling point, which consisted of a mixture of unchanged cyano-compound and alkyl iodide, were again treated with sodium (in alcohol) and an additional quantity of the iodide. Calculated from the theoretical, the yields of refractionated propylated (isopropylated) products were as follows:

Ethyl $\alpha\beta$ -dipropylcyanosuccinate (from ethyl β -propylcyanosuccinate and propyl iodide) 78 per cent.

Ethyl $\alpha\beta$ -diisopropylcyanosuccinate (from ethyl β -isopropylcyanosuccinate and isopropyl iodide) 70 ,

Ethyl α -propyl- β -isopropylcyanosuccinate (from ethyl β -isopropylcyanosuccinate and propyl iodide) 81.5 ,,

These substances are colourless oils, and the following table shows their properties :

	B. p. 19—21 mm.	$d \ 0^{\circ}/4^{\circ}$.	μ_{Na} .
Ethyl αβ-dipropylcyanosuccinate Ethyl αβ-diisopropylcyanosuccinate Ethyl α-propyl-β-isopropylcyanosuccinate	$176-178^{\circ} \\ 173-175^{\circ} \\ 175-177^{\circ}$	$1.0247 \\ 1.0575 \\ 1.0325$	1·4440 1·4492 1·4452

On analysing them, the following numbers were obtained :

Ethyl $\alpha\beta$ -Dipropylcyanosuccinate.

0.1996 gave 0.4640 CO₂ and 0.1601 H₂O. C = 63.39; H = 8.91. 0.1943 , 8.4 c.c. nitrogen at 8° and 772 mm. N = 5.3.

Ethyl $\alpha\beta$ -Diisopropylcyanosuccinate.

Ethyl a-Propyl-β-isopropylcyanosuccinate. 0·1720 gave 0·3980 CO₂ and 0·1385 H₂O. C=63·4; H=8·95. 0·1766 ,, 5 c.c. nitrogen at 10° and 761 mm. N=5·10. C₁₅H₂₅O₄N requires C=63·6; H=8·89; N=4·94 per cent.

C. Hydrolysis of the Oils.

We experienced some difficulty in devising a good method for hydrolysing the oils we have described in the preceding section. In our earlier experiments, which were all carried out with ethyl $\alpha\beta$ -diisopropylcyanosuccinate, we tried the effect of boiling the oil with

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concentrated hydrochloric acid, a process which we had shown to be admirably adapted to the hydrolysis of the ethyl esters of methylsubstituted cyanosuccinates (Trans., 1899, 75, 855). We found, however, that the diisopropyl compound strongly resisted the hydrolytic action of the acid, and that after 120 hours continuous heating nearly one-third of the oil remained undecomposed. No better result was obtained by heating the oil with the acid, under pressure, at 150° for 2 days. An examination of the acid liquor remaining after the removal of any unchanged oil, showed that, besides cis- and trans-s-diisopropylsuccinic acids, it contained a fair quantity of an acid of the formula $C_{7}H_{10}O_{41}$ which melted at 114°, and subsequently proved to be monoisopropylsuccinic acid. Since analyses of the original oil left no doubt in our minds that it was a pure specimen of ethyl aß-diisopropylcyanosuccinate, and since the same oil, when hydrolysed by the following method, yielded no acid other than the two s-diisopropylsuccinic acids, we can only account for the presence of mono-isopropylsuccinic acid among the hydrolytic products when hydrochloric acid was employed, on the supposition that a portion of the oil had lost an isopropyl group during the process.

Experiments with hydrochloric acid having proved unsuccessful, we next proceeded to try several other energetic hydrolytic agents, but found that no one of them singly sufficed to effect the purpose in view; we finally adopted the plan of hydrolysing the oils in two stages, namely, first with alcoholic potash, and then with 50 per cent. sulphuric acid. The process was conducted somewhat as follows.

Twenty grams of the oil were boiled with an alcoholic solution of 16 grams of potassium hydroxide in a reflux apparatus for 36 hours. The oil quickly disappeared, and in a short time a quantity of potassium The liquid was subsequently evaporated to dryness on salt separated. the water-bath in order to expel alcohol, and the residue dissolved in water. The solution was added to a large excess of hydrochloric acid, the whole at once extracted with ether, and the ethereal solution dried over anhydrous sodium sulphate. On distilling off the ether, about 13 grams of an oily acid remained. In the case of the dipropylcyano-compound, this oil soon solidified, and the dipropylcyanosuccinic acid was obtained without difficulty in a pure condition.* In the other two cases, the oils showed no signs of crystallisation, even on prolonged standing in a vacuum over sulphuric acid, and we therefore made no attempt to isolate the cyano-acids. As little, if any, evolu-

* a β -Dipropylcyanosuccinic Acid.—A white solid which after recrystallisation from benzene melted at 192°. On analysis :

0.1973 gave 0.4233 CO₂ and 0.1381 H₂O. C=58.5. H=7.78.

0.3070 ,, 16.4 c.c. nitrogen at 15° and 762 mm. N=6.26.

 $C_{11}H_{17}O_4N$ requires C=58.15; H=7.5; N=6.16 per cent.

tion of ammonia was observed during the process just described, and as the resulting oils contained much nitrogen, the cyano-group must have been practically unacted on by the alcoholic potash.

The oil, or solid cyano-acid, was then dissolved in an excess of 50 per cent. sulphuric acid, and the solution boiled in a reflux apparatus on the sand-bath for 6 hours. During the process, the liquid darkened in colour, and oily particles of the anhydride of the *cis*-succinic acid separated, forming a layer on the surface, and finally, on cooling, crystals were deposited.

C. Separation of the cis- and trans-Acids by Distillation with Steam.

The acid liquid just described was at once subjected to distillation with steam, when the oily anhydride of the *cis*-succinic acid was passed over, leaving the *trans*-acid behind. The separation was complete in the cases of *s*-dipropylsuccinic and aa_1 -propylisopropylsuccinic acids, but in the case of *s*-diisopropylsuccinic acid we were never able to distil over the whole of the *cis*- acid as anhydride, and it was necessary to treat the residual *trans*-acid with warm benzene in order to remove last traces of the *cis*-isomeride.

(a) Distillates.—These were always turbid with oily particles, and had a strong acid reaction; the oil at once dissolved when the liquid was made alkaline with ammonia. The solution of the ammonium salt was in each case concentrated to a small bulk on the water-bath, strong ammonia being added at intervals in order to counteract any tendency to dissociation. The whole was then added to an excess of strong hydrochloric acid, and the liquid thoroughly extracted with ether. The whole of the *cis*-acid could in this way be obtained in a pure condition.

(b) Residual Liquors.—These were thoroughly extracted with ether, whereby the non-volatile *trans*-acids were isolated; these were always obtained in a pure state after one or two recrystallisations from hot benzene, in which the *cis*-acids are very soluble.

E. General Properties of the Acids.

Anhydrides, anilic acids, and characteristic sparingly soluble calcium salts of the s-dipropyl-, s-diisopropyl-, and aa_1 -propylisopropylsuccinic acids were obtained by methods similar to those explained in our earlier paper (*loc. cit.*, 859). The following general statements may be made with regard to the properties of the acids.

Solubility.—The acids are all sparingly soluble in water, but readily dissolve in alcohol, acetone, and ethyl acetate. The cis-acids readily

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dissolve in warm benzene, whereas the trans-isomerides are either quite insoluble or only very sparingly soluble in that solvent. In the case of the diisopropyl acids, a complete separation of the isomerides can be effected by treatment with warm benzene. No general statement can be made with regard to solubility in chloroform.

Salts.-Those of the heavy metals and alkaline earths are sparingly soluble; others are soluble.

Anhydrides.—Each acid dissolves in acetyl chloride, forming its own anhydride; the trans-acids require a much longer treatment, however, The anhydrides are all remarkably stable than the *cis*-isomerides. substances, and can be boiled for a long time with water without undergoing any appreciable change; with aniline, they at once yield characteristic anilic acids. The trans-anhydrides are quantitatively converted into cis-isomerides on being heated for several hours with acetic anhydride at 170° in sealed tubes.

F. s-Diisopropylsuccinic Acids.

trans-s-Diisopropylsuccinic acid is quite insoluble in hot benzene and melts at 226-228°. On analysis:

0.1057 gave 0.2295 CO₂ and 0.0839 H_2O . C = 59.22; H = 8.91. $C_{10}H_{18}O_4$ requires C = 59.40; H = 8.91 per cent.

Silver Salt.

0.2736, on ignition, gave 0.1412 Ag. Ag = 51.61.

 $C_{10}H_{16}O_4Ag_2$ requires Ag = 51.92 per cent.

Calcium Salt, C₁₀H₁₆O₄Ca,H₂O.-A specimen, dried over sulphuric acid in a vacuum, on analysis, gave the following results :

0.4248 lost 0.0551 H_oO at 150°. $H_0O = 12.98$. 0.3697 anhydrous salt gave 0.0870 CaO. CaO = 23.53. Calculated, $H_{0}O = 13.05$; CaO (in anhydrous salt) = 23.33 per cent.

Anhydride.—The acid was very slowly acted on by boiling acetyl chloride, upwards of 3 hours being required for its complete solution. The resulting anhydride is a colourless liquid, which, under 752 mm. pressure, distilled over at 263-265°; no signs of crystallisation were evident, even after the substance had stood for many days at 0° over sulphuric acid. On analysis :

The liquid was not appreciably changed by the prolonged action of boiling water, but it instantly dissolved in a warm 50 per cent. solution of sodium hydroxide. On acidifying the solution, a white, crystalline acid was precipitated which melted between 210° and 215° ; on treating this with hot benzene, a very small quantity of the *cis*-acid (m. p. 170°) was extracted, and the insoluble residue now melted at 226° .

It is evident, therefore, that the *trans*-acid, with acetyl chloride, yielded *its own* anhydride, a small portion of which, most probably on distillation, had been converted into the *cis*-modification.

Anilic acid, made from a portion of anhydride which had not been distilled, and recrystallised from hot benzene, melted at 201-202°. On analysis, it yielded the following results:

0.1719 gave 0.4333 CO₂ and 0.1372 H₂O. C = 69.62; H = 8.87. 0.2536 ,, 11.33 c.c. nitrogen at 18° and 762 mm. N = 5.16. $C_{16}H_{23}O_{3}N$ requires C = 69.31; H = 8.66; N = 5.05 per cent.

Cis-s-Diisopropylsuccinic acid, recrystallised from hot benzene, melted at $168-170^{\circ}$, but after being transformed into the anhydride and reconverted into acid, melted very sharply at 171° . On analysis:

0.1520 gave 0.3316 CO₂ and 0.1250 H₂O. C=59.50; H=9.14. C₁₀H₁₈O₄ requires C=59.40; H=8.91 per cent.

Silver Salt :

0.1160, on ignition, gave 0.0602 Ag. Ag = 51.89.

 $C_{10}H_{16}O_4Ag_2$ requires Ag = 51.92 per cent.

Calcium Salt, $C_{10}H_{15}O_4Ca, 4H_2O$.—A specimen dried over sulphuric acid in a vacuum was analysed :

0.3937 lost 0.0927 H_2O at 150°. $H_2O = 23.54$. 0.3010 anhydrous salt gave 0.0698 CaO. CaO = 23.19. Calculated, $H_2O = 23.08$, CaO (in anhydrous salt) = 23.33 per cent.

It may be here noted that the calcium salt of the acid melting at $168-169^{\circ}$, described by Hell and Mayer (*loc. cit.*), had the composition $C_{10}H_{16}O_4Ca, 4H_2O$, a circumstance which indicates that their acid was identical with our *cis*-acid.

Anhydride.—The acid dissolved very readily in cold acetyl chloride with evolution of hydrogen chloride. The anhydride distilled over between 250° and 260° under 752 mm. pressure as a colourless liquid which did not solidify even after long standing in a vacuum over sulphuric acid. On analysis :

0.1200 gave 0.2862 CO₂ and 0.0980 H_2O . C = 65.16; H = 8.80. C₁₀ $H_{16}O_3$ requires C = 65.21; H = 8.69 per cent.

Like the anhydride of the *trans*-acid, this liquid was remarkably stable, and was not decomposed by boiling water. It dissolved in warm 50 per cent. sodium hydroxide solution, and on acidifying with hydrochloric acid the original acid (m. p. 171°) was precipitated.

Anilic acid, prepared from the anhydride and recrystallised from hot benzene, melted at 184-185°. On analysis:

0.1521 gave 0.3853 CO₂ and 0.1218 H₂O. C = 69.09; H = 8.90. 0.3039 , 13.6 c.c. nitrogen at 17° and 760 mm. N = 5.21. $C_{16}H_{22}O_3N$ requires C = 69.13; H = 8.66; N = 5.05 per cent.

Mutual Conversion of the cis- and trans-Acids.—(1) Action of Hydrochloric Acid.—We have already stated in the introductory portion of this paper that Auwers was unable to effect the slightest change in his acid by heating it in sealed tubes with hydrochloric acid to $180-200^{\circ}$. We had a similar experience in the case of the cis-acid, but on repeating the experiment at a temperature of $220-230^{\circ}$ a small but quite appreciable quantity of it was converted into the trans-modification. On subjecting the trans-acid to the same treatment, by far the greater part was converted into the cis-form. The state of equilibrium between the two isomerides finally attained in each of the two experiments was as nearly as possible the same.

(2) Action of Acetic Anhydride.—On boiling the trans-acid or its anhydride with acetic anhydride, it was gradually converted into the *cis*-anhydride. The conversion was complete in a few hours when the experiment was carried out at 170° in sealed tubes.

G. s-Dipropylsuccinic Acids.

trans-s-*Dipropylsuccinic acid* is slightly soluble in benzene, and completely so in chloroform. It is best recrystallised from a mixture of benzene and light petroleum, and when pure melts at 182-183°. On analysis:

0.1628 gave 0.3537 CO₂ and 0.1320 H₂O. C=59.27; H=9.01. C₁₀H₁₈O₄ requires C=59.40; H=8.91 per cent.

Silver Salt.

0.2212, on ignition, gave 0.1146 Ag. Ag = 51.84. $C_{10}H_{16}O_4Ag_9$ requires Ag = 51.92 per cent.

Calcium Salt, $C_{10}H_{16}O_4Ca, 2H_2O$.—Specimen dried in a vacuum over sulphuric acid. On analysis :

0.1922 lost 0.0259 H₂O at 150° . H₂O = 13.50.

0.1998 of anhydrous salt gave 0.0462 CaO. CaO = 23.13.

Calculated : $H_2O = 13.06$; CaO (in anhydrous salt) = 23.33 per cent.

Anhydride.—The acid dissolved more readily than the trans-disopropyl acid in boiling acetyl chloride, only 45 minutes being required for complete solution. The anhydride is a colourless liquid, which distilled over at $269-274^{\circ}$ under 768 mm. pressure. On analysis :

0.1721 gave 0.4101 CO₂ and 0.1349 H₂O. C = 65.00 ; H = 8.71. C₁₀H₁₆O₃ requires C = 65.21 ; H = 8.69 per cent.

A portion of the liquid was dissolved in a hot 50 per cent. solution of sodium hydroxide, and on acidifying the solution with hydrochloric acid, an acid melting at $160-170^{\circ}$ separated, from which a small quantity of the *cis*-acid (m. p. $115-117^{\circ}$) could be extracted with benzene.

It is evident therefore that, as in the case of the s-diisopropyl acids, some of the *trans*-anhydride was, on distillation, converted into the *cis*-modification, for the undistilled anhydride yielded only the sodium salt of the *trans*-acid on being dissolved in sodium hydroxide.

Anilic acid, prepared from undistilled anhydride and recrystallised from benzene, melted at $184-185^{\circ}$. On analysis:

0.1121 gave 0.2831 CO_2 and 0.0902 H_2O . C = 68.90; H = 8.94.

0.2444 , 10.9 c.c. nitrogen at 18° and 764 mm. N = 5.20.

 $\mathrm{C_{16}H_{23}O_{3}N}$ requires $\mathrm{C}=69{\cdot}31$; $\mathrm{H}=8{\cdot}66$; $\mathrm{N}=5{\cdot}05$ per cent.

cis-s-Dipropylsuccinic acid, when recrystallised from benzene, melted at 115—117°, but on being transformed into anhydride and then reconverted into acid, melted at 119—121°. On analysis :

0.1698 gave 0.3690 CO_2 and 0.1347 H_2O . C = 59.26; H = 8.99. $C_{10}H_{18}O_4$ requires C = 59.40; H = 8.91 per cent.

Silver Salt.

0.2364, on ignition, gave 0.1224 Ag. Ag = 51.79.

 $C_{10}H_{16}O_4Ag_2$ requires Ag = 51.92 per cent.

Calcium Salt, $C_{10}H_{16}O_4Ca, H_2O$.—Specimen dried in a vacuum over sulphuric acid. On analysis :

0.3127 lost 0.0225 H_2O at 150°, $H_2O = 7.20$.

0.4390 anhydrous salt gave 0.1021 CaO. CaO = 23.26.

Calculated: $H_2O = 6.96$; CaO (in anhydrous salt) = 23.33 per cent.

Anhydride.—The acid dissolved very rapidly in cold acetyl chloride. The resulting anhydride was a colourless liquid which distilled at $266-270^{\circ}$ under 768 mm. pressure. On analysis :

The liquid was dissolved in a hot 50 per cent. solution of sodium hydroxide; on acidifying the solution with hydrochloric acid, the original *cis*-acid, melting at $119-121^{\circ}$, was precipitated.

Anilic acid, prepared from the anhydride, and recrystallised from benzene, melted at 101-102°. On analysis:

0.1441 gave 0.3672 CO₂ and 0.1098 H₂O. C = 69.48; H = 8.47. 0.2649 gave 12 c.c. nitrogen at 18° and 764 mm. N = 5.26. $C_{16}H_{23}O_3N$ requires C = 69.31; H = 8.66; N = 5.05 per cent.

Mutual Conversion of the cis- and trans-Acids. (1) Action of Hydrochloric Acid.—When either isomeride was heated with strong hydrochloric acid for 10 hours at 180° in sealed tubes, a mixture of the two, containing about 95 per cent. of the *trans*-acid, was obtained. These results form a striking contrast with the corresponding experiments on the s-diisopropyl acids, where it was shown that the *cis*-acid was not changed in the slightest degree by the action of hydrochloric acid at 180° , and is only to a very small extent converted into the *trans*form at $220-230^{\circ}$.

(2) Action of Acetic Anhydride.--The trans-acid (or anhydride) is completely converted into the cis-anhydride by being heated for 5 hours in sealed tubes with acetic anhydride.

H. aa₁-Propylisopropylsuccinic Acids.

The investigation of these acids, as will be explained later, was undertaken for the express purpose of determining the influence of the 'propylisopropyl' combination upon the electrical conductivities of two stereoisomeric 'succinic' acids.

trans- aa_1 -Propylisopropylsuccinic acid is a beautiful, crystalline powder, which, after recrystallisation from a mixture of benzene and light petroleum, melts at 192–194°. On analysis:

0.1861 gave 0.4048 CO₂ and 0.1529 H₂O. C=59.33; H=9.13. C₁₀H₁₈O₄ requires C=59.40; H=8.91 per cent.

Silver Salt.

0.1572 yielded, on ignition, 0.0816 Ag. Ag = 52.11.

 $C_{10}H_{16}O_4Ag_2$ requires Ag = 51.92 per cent.

Calcium Salt is anhydrous. On analysis: 0.3104, on ignition, gave 0.0519 CaO. CaO = 16.71.

 $C_{10}H_{16}O_4Ca$ requires CaO = 16.66 per cent.

Anhydride, prepared as usual. A colourless liquid which distilled at $265-272^{\circ}$ under 742 mm. pressure. On analysis :

0.1179 gave 0.2811 CO₂ and 0.0942 H₂O. C = 65.02; H = 8.88. $C_{10}H_{16}O_{3}$ requires C = 65.21; H = 8.69 per cent.

The oil dissolved in a hot 50 per cent. sodium hydroxide solution, giving the sodium salt of the original *trans*-acid.

Anilic acid, prepared from the anhydride and aniline, melted at 147-149° after recrystallisation from dilute alcohol. On analysis:

0.1928 gave 8.75 c.c. nitrogen at 13° and 749 mm. N = 5.26. C₁₆H₂₈O₃N requires N = 5.05 per cent.

(b) cis-s-Propylisopropylsuccinic acid crystallised in small plates with silvery lustre from a mixture of chloroform and light petroleum. It melted at 151-152°. On analysis:

0.2011 gave 0.4360 CO₂ and 0.1631 H₂O. C = 59.13; H = 8.91. C₁₀H₁₈O₄ requires C = 59.40; H = 8.91 per cent.

Silver Salt.

0.1552, on ignition, gave 0.0807 Ag. Ag = 52.00. C₁₀H₁₆O₄Ag₂ requires Ag = 51.92 per cent.

Calcium Salt, $C_{10}H_{16}O_4Ca, 2H_2O_6$ On analysis :

0.6221 lost 0.0828 H_2O at 150°. $H_2O = 13.31$.

0.3326 anhydrous salt gave 0.0551 CaO. CaO = 16.51.

Calculated, $H_{2}O = 13.04$; CaO (in anhydrous salt) = 16.66 per cent.

Anhydride.—A colourless liquid which distilled at 265—275° under 742 mm. pressure. On analysis :

0.1028 gave 0.2449 CO_2 and 0.0824 H_2O . C = 64.99; H = 8.91. $C_{10}H_{16}O_3$ requires C = 65.21; H = 8.69 per cent.

The oil dissolved in a hot 50 per cent. solution of sodium hydroxide, yielding the sodium salt of the original *cis*-acid.

Anilic acid from anhydride and aniline. This, as distinguished from all anilic acids of substituted succinic acids which we have hitherto examined, is a liquid. All attempts to induce solidification failed.

Mutual Conversion of the cis- and trans-Acids. (1) Action of Hydrochloric Acid.—On heating either the cis- or trans-acid in sealed tubes with hydrochloric acid at 200° , about half of it is converted into the isomeric form.

(2) Action of Acetic Anhydride.—As in the case of the other acids described in the paper, the *trans*-modification can be quantitatively converted into the *cis*-anhydride by being heated in sealed tubes with acetic anhydride at 150° .

K. Dissociation Constants of the Acids.

The study of the dissociation constants of the acids we have described in the foregoing sections of this paper has yielded such remarkable results that we feel justified in discussing them separately at some length.

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Considering the constants of the 'succinic' series as a whole, it may be pointed out that the replacement of one hydrogen in the molecule of succinic acid by an alkyl radicle is invariably accompanied by an increase in electrical conductivity, and, therefore, of the dissociation constant. Thus:

				10000
Succinic acid				0.0068
Monomethy lsu	ccinic a	d	•••••	0.0085
Monoethyl	,,	,, .		0.0085
Monopropyl	,,	, ,	••••	0.00886
Monoisopropyl	,,	,,	••••••••••••	0.0076

It will also be noted that whereas the 'normal' radicles appear to have much the same influence on the conductivity, an "iso"-grouping raises it to a much smaller extent. The substitution of a second hydrogen by an alkyl radicle may occur in one of two possible ways according as the second alkyl replaces a hydrogen attached to the same or to a different carbon atom as that to which the first alkyl was attached. Only one example of the first-named type of acid, namely, as-dimethylsuccinic acid, has so far been studied from this point of view, and its constant (0.0080) is practically the same as that of the monomethyl acid. On the other hand, quite a number of s- or aa1-dialkylsuccinic acids have been investigated, all of which, of course, exist in two stereoisomeric forms. Experience shows that the substitution of the second hydrogen by alkyl in such cases invariably increases the dissociation constant to a much greater extent than did the first alkyl substitution increase that of succinic acid, and, further, that two stereoisomerides in each case generally have nearly the same constants. Thus:

	trans-Acid.	cis-Acid.
s-Dimethylsuccinic	0.0196	0.0123
s-Diethylsuccinic	0.0245	0.0201
aa1-Methylethylsuccinic	0.0207	0.0201
aa1-Methylallylsuccinic	0.0243	0.0233
aa ₁ -Ethylallylsuccinic	0.0269	0.0359

In the case of tri- or tetra-substituted acids, our present knowledge is limited to the methyl compounds; the constants of these, however (trimethyl- =0.032 and tetramethyl- =0.033), show still the tendency of successive alkyl substitutions to increase the conductivities in the series.

On determining the constants of our s-diisopropyl acids we were astonished to find, not only that that of the *cis*-acid was very much

^{*} The values for 100k quoted in this and following table are those which appear to be the most probable according to determinations made by Walden, Walker, ourselves, and others.

greater than that of any other previously known member of the series, but also that it was over *twenty* times as great as that of the isomeric *trans*-acid. The actual numbers obtained were :

trans-s-Diisopropylsuccinic Acid (temp. 25°).

v.	μ_v .	m.	100k.
256	53.7	0.1535	0.01081
512	73.15	0.2090	0.01088
1024	98.86	0.2824	0.01077
2048	129.7	0.3691	0.01057
	<i>K</i>	- 0.0108	

cis-s-Diisopropylsuccinic Acid (temp. 25°).

v.	μ_v .	m.	100k.
128	146.8	0.4191	0.2368
256	183.6	0.5246	0.2262
512	233.8	0.6395	0.2209
1024	262.4	0.7491	0.2183
	K =	0·2300.	

In the first place, it will be observed that the value of k for our *cis*acid approximates to that given by Auwers for the acid he obtained from ethyl a-bromoisovalerate (0.2938), but that, whereas his values diminished considerably on dilution (see p. 655), ours remain nearly The chemical properties of the two acids (his and ours) are constant. so much alike that we are not disposed to doubt their identity. But since the trans-acid is now shown to have a constant less than onetwentieth that of the cis-isomeride, Auwers' conductivity results can hardly be explained on the supposition that he was dealing with a mixture of the two in which the cis-form predominated. As a matter of fact, we made a mixture of 9 parts of the cis-acid with 1 part of the trans-acid, and although the mixture melted in the neighbourhood of 178° (the temperature given by Auwers as the melting point of his acid), its "dissociation constant" (if such a term can be strictly applied to a variable quantity) was always much lower than that of the pure cis-acid, thus :

Mixture of 90 per cent. cis- with 10 per cent. trans-s-Diisopropylsuccinic Acids (temp. 25°).

<i>v</i> .	μ_v .	m.	100k.
384	152.2	0.4342	0.0869
768	181.1	0.5174	0.0722
1536	211.1	0.6028	0.0596
3072	215.5	0.6157	0.0321

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The chief interest, however, connected with these results is the indication they afford that the constants of two stereisomeric saturated acids may differ very greatly. Professor J. Walker has in a private communication drawn our attention to the fact that the constant for maleic acid (k=1.17) is thirteen times as great as that of fumaric acid (k=0.093). But the two cases are in no wise parallel, for the stereoisomerism of two s-dialkylsuccinic acids is of a totally different character from that of maleic and fumaric acids, although it must be confessed that the conventional use of the terms *trans*- and *cis*- in the case of the former is misleading.

Our experiments on the conductivities of the two s-dipropylsuccinic acids yielded the following numbers :

/ m				<i>/</i> .	~ × ~ \	
trong_g_/la	mannal	001000000	And	tomn	- Jho	۱.
$v_1 a_{110} \circ \sigma_2 D a_1$	$v \nu i v \nu u q u$	0000000000	1000	UCHID.	40	
	r - r - v					

v.	μ_{v}	m.	100k.
256	78 . 7 8	0.2250	0.02552
512	106.1	0.3031	0.02380
1024	144.4	0.4126	0.02337
2048	163.6	0.4675	0.02287
	K	= 0.025	

cis-s-Dipropylsuccinic Acid (temp. 25°).

v.	μ_v .	m.	100k.
128	77.41	0.2212	0.04908
256	103.91	0.2966	0.04883
512	136.41	0·389 3	0.04857
1024	173.5	0.4957	0.04759
	K	= 0.049.	

There is nothing extraordinary about these results, for although there is a marked difference between the constants of the two stereoisomerides, it is not abnormal. Thinking that the exceptional behaviour of the s-diisopropyl acids might be connected with the isopropyl grouping, we determined to examine aa_1 -methylisopropyl- and aa_1 -propylisopropyl-succinic acids. Professor Perkin was kind enough to furnish us with specimens of the two inactive isomerides of the former,* whilst those of the latter were of our own preparation. Conductivity determinations gave the following results:

* The $\alpha \alpha_1$ -methylisopropylsuccinic acids were described in a paper by W. H. Bentley, W. H. Perkin, jun., and J. F. Thorpe (Trans., 1896, **69**, 270).

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trans-aa₁-Methylisopropylsuccinic Acid (m. p. 174-175°).

v.	μ_v	т.	100k.
161.7	51.75	0.1478	0.01543
$323 \cdot 4$	70.45	0.2013	0.01570
646.8	95.75	0.2735	0.01590
1293.6	$127 \cdot 1$	0.3633	0.01602
	K = 0	0.0158.	

cis-aa₁-Methylisopropylsuccinic Acid (m. p. 125-126°).

v_{*}	μ_v .	m.	100k.
90.8	75.35	0.2154	0.0652
181.6	101.98	0.2913	0.0659
363.2	$135 \cdot 2$	0.3862	0.0669
726.4	173.8	0.4957	0.0671
	K =	0.066	

trans-aa₁-Propylisopropylsuccinic Acid (temp. 25°).

v.	μ_{v} .	m.	100k.
256	61.74	0.1764	0.0149
512	82.85	0.2367	0.0144
1024	112.7	0.3219	0.0147
2048	143.6	0.4103	0.0139
	K = 0	0.0147.	

cis-aa₁-Propylisopropylsuccinic Acid (temp. 25°).

v.	μ_v .	m.	100k.
128	62.63	0.1790	0.0297
256	83.90	0.2397	0.0295
512 104.5	104.5	0.3200	0.0294
1024	$145 \cdot 4$	0.4164	0.0290
	K = 0	0.0295.	

Thus, we find in the case of the aa_1 -methylisopropyl acids that the constant of the *cis*- is four times that of the *trans*-isomeride, whereas there is no greater difference between the two stereoisomeric aa_1 -propylisopropyl acids than there is between the corresponding twos-dipropyl acids. Hence it would seem that the peculiar behaviour of the two diisopropyl acids is in some measure due to the additive effect of the two isopropyl groups. In order to see whether this was wholly so or not, we prepared and determined the constants of the methyl hydrogen salts of the two s-diisopropyl acids. We were astonished to find that the masking of one of the carboxyl groups, whilst it only lowered the constant of the *trans*-acid by about 40 per cent., reduced that of the *cis*-acid to one-twentieth of its original value. Thus:

Methyl Hydrogen trans-s-Diisopropylsuccinate.

v.	μ_v .	m.	100k.
380	50.37	0.1439	0.00636
760	68.64	0.1961	0.00629
1520	91.40	0.5611	0.00616
3 04 0	118.1	0.3453	0.00599
	K=	= 0.0063	

Methyl Hydrogen cis-s-Diisopropylsuccinate.

v.	μ_{v}	m.	100k.
238	52.87	0.1210	0.01129
476	73.08	0.2087	0.01153
952	98.26	0.2807	0.01153
1904	130.6	0.3731	0.01166
	<i>K</i> =	= 0·0115.	

The foregoing results, which for the sake of reference we have tabulated at the end of this paper, indicate that the connection between the dissociation constant and constitution of an organic acid is not so direct as many would have us believe it to be. Professor Walker has recently stated (Trans., 1900, 77, 398) that the increase in the constant of succinic (or glutaric) acid when the hydrogens are successively replaced by alkyl groups, is not due to the primary effect of the substitution, but rather to an increase in the proximity of the two carboxyl groups. Adopting the Perkin-Bouveault formula for camphoric acid, which represents it as a succinic derivative, as follows:

 $\begin{array}{c} CMe_2\\ H_2C & CMe \cdot CO_2H\\ H_2C & -CH \cdot CO_2H \end{array},$

he accounts for its small dissociation constant (0.0025) by saying that the rigidity of the ring formation prevents the approximation of the carboxyl radicles, and thus allows the primary effect of substitution to become manifest. The view that the proximity of the carboxyl radicles in succinic acid increases as the hydrogen is successively replaced by alkyl groups, is supported by the fact that the tendency to anhydride formation is more marked as the number of alkyl-substituted groups increases, but our results show that such considerations do not wholly explain the facts. Since our experience is that *cis-s*-di-

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propylsuccinic acid yields an anhydride with acetyl chloride if anything more readily than does the *cis-s*-diisopropyl acid, it can hardly be contended that the two carboxyl radicles in the latter are nearer each other than they are in the former, and yet the constant of the latter is nearly five times as great as that of the former. We hope shortly to publish, in conjunction with Dr. Sudborough, important evidence on these matters derived from a study of the methyl hydrogen salts of substituted succinic acids, but the facts recorded in our present communication are sufficient to show that the subject calls for much further investigation before any general principle can legitimately be deduced.

Acid.	Trans.	Cis.	Approx. ratio.
s-Dipropylsuccinic αα ₁ -Propylisopropylsuccinic αα ₁ -Methylisopropylsuccinic s-Diisopropylsuccinic Methyl hydrogen s-diisopropylsuccinate	0.025 0.0147 0.0158 0.0108 0.0063	$\begin{array}{c} 0.049\\ 0.0295\\ 0.066\\ 0.2300\\ 0.0115\end{array}$	$ \begin{array}{c} 1:2\\ 1:2\\ 1:4\\ 1:20\\ 1:2 \end{array} $

Table of Dissociation Constants.

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