356. 1 : 2-*Dicarboxylic Acids. Part IV.* The α-Ethyl-α′-methylsuccinic Acids and Their Derivatives.*

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The diastereoisomeric α-ethyl-α′-methylsuccinic acids and a number of their derivatives have been prepared for comparison with compounds obtained by the oxidation of derivatives of bacteriochlorophyll (preceding paper). Chromatographic behaviour and infrared spectra are recorded, and stereochemical configurations are assigned.

THE oxidation of bacteriochlorophyll derivatives has been postulated to yield substances derived from α-ethyl-α′-methylsuccinic acid and this has now been proved to be the case (Golden, Linstead, and Whitham [1]). This prompted the re-investigation of the two diastereoisomeric forms of this acid, which is described in the present paper.

The succinic acid can exist in the diastereoisomeric forms (I and II). Both of these give rise to anhydrides (III and (IV) and similar heterocyclic derivatives. The nomenclature is that used for the dihydrohæmatinic acids: [2] the classical terms *cis* and *trans* of the cyclic systems lead to the terms *cisoid* and *transoid* for the corresponding acids. As shown below, the *cis–cisoid*-series correspond to the higher-melting acid, which has been called " fumaroid " or " mesoid " by previous workers. The lower-melting *transoid*-acid has previously been called " maleinoid," " racemoid," or " DL." These earlier terms are best avoided. Both acids have been partially resolved by Berner and Leonardsen.[3]

The two diastereoisomerides, first prepared by Zelinsky [4] and Bischoff [5] and their collaborators, were thoroughly examined by von Auwers.[6] We prepared a mixture of

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* Part III, *J.*, 1954, 3730.

[1] Golden, Linstead, and Whitham, preceding paper.

[2] Ficken, Johns, and Linstead, *J.*, 1956, 2280.

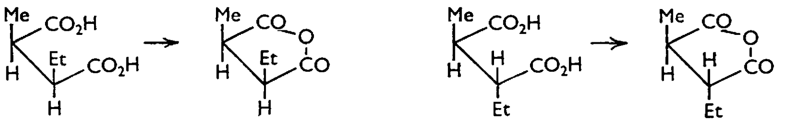
[3] Berner and Leonardsen, *Annalen*, 1939, **538**, 1.

[4] Zelinsky and Bitschichin, *Chem. Zentr.*, 1890, **11**, 43.

[5] Bischoff *et al.*, *Ber.*, 1889, **22**, 1817; 1890, **23**, 647; 1891, **24**, 1066.

[6] (*a*) von Auwers, *Annalen*, 1896, **292**, 132, 152; (*b*) von Auwers and Fritzweiler, *ibid.*, 1897, **298**, 147.

them by the hydrolysis of ethyl αβ-dicyano-α-ethylbutyrate.[7] The higher-melting (*cisoid*) acid was obtained by crystallisation and the residual mixed acids were converted into the mixed ammonium salts. Distillation then gave the *trans*-imide, which could be converted into the parent, low-melting acid by rapid hydrolysis with mineral acid. The melting points of the acids agreed with those recorded by von Auwers and the infrared spectra with those recorded by Schotte [8] (see Table).


(I) *cisoid*-acid (III) *cis*-anhydride (II) *transoid*-acid (IV) *trans*-anhydride

The *trans*-anhydride was obtained by treatment of the mixed acids with thionyl chloride followed by distillation; it yielded *transoid*-acid on hydrolysis. The *cis*-anhydride, which is easily inverted, was obtained by the method successful for *cis*(" *ms* ")-dimethylsuccinic anhydride, namely, treatment of the disodium salt of the acid with thionyl chloride in dry ether.[9] The *cis*-anhydride distilled unchanged under 10^{-6} mm. and on hydrolysis gave the *cisoid*-acid. The early report by Zelinsky and Bitschichin [4] that only one anhydride exists is incorrect, as already shown by von Auwers and Fritzweiler.[6b]

The ethylmethylsuccinimides, of special importance in relation to bacteriochlorophyll degradation, have not previously been described. It has been reported [6b] that the same *N*-phenylimide and *N*-tolylimide were obtained from both acids. The stable *trans*-imide, m. p. 61°, was readily obtained by dry distillation of the ammonium salts of either the *transoid*-acid or the mixed acids. The labile *cis*-imide was obtained by the method established by Linstead and Whalley [9] in the dimethyl series, catalytic hydrogenation of the corresponding maleimide. The *cis*-imide, m. p. 51°, sharply depressed the m. p. of its *trans*-isomeride. It differed markedly from it in infrared spectrum, and on hydrolysis gave the *cisoid*-acid. Table 1 summarises the properties of the two acids and their derivatives.

TABLE 1. *α-Ethyl-α'-methylsuccinic acids and their derivatives.*

	cis-cisoid-Series		*trans–transoid*-Series	
	Present work	Lit.	Present work	Lit.
Acid	M. p. 182°	180—182° (ref. 6*b*)	M. p. 102°	101—102° (ref. 6*b*)
Anhydride	B. p. 60°/10^{-6} mm. n_D^{21} 1·4482	118—119°/12 mm. (ref. 3)	B. p. 121°/15 mm. n_D^{21} 1·4459	114—115°/12 mm. (ref. 3)
Imide	M. p. 51°		M. p. 61—62°	
Di-*p*-bromophenacyl ester	M. p. 119°		M. p. 122°	

The configurations are assigned for three reasons. (i) The hydrogenation of methylethylmaleinimide may be presumed to give a *cis*-product, as in similar cases: this leads to a *cis*-configuration for the imide, m. p. 51°. (ii) Schotte [8] found, for a range of substituted succinic acids, that the lower-melting acid is *transoid* and has characteristic differences in the infrared spectrum, notably in the C=O stretching frequency which is a singlet for the *cisoid*- but a doublet for the *transoid*-form. On this basis our acid of m. p. 102° and its derivatives are *transoid*. (iii) The inversions of the heterocyclic derivatives reported below are parallel with those in the dimethylsuccinic series (where the configurations are certain) if the assignments given in Table 1 are correct.

The inversions of configurations are summarised in Table 2 and described in the Experimental section.

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[7] Braun, Keller, and Weissbach, *Annalen*, 1931, **490**, 179.
[8] Schotte, *Arkiv Kemi*, 1956, **9**, 397; cf. Schotte and Rosenberg, *ibid.*, 1954, **7**, 479; 1955, **8**, 16,
[9] Linstead and Whalley, *J.*, 1954, 3722.

TABLE 2.

Acids	Water or mineral acid at 180°	*cisoid* *transoid* } ⟶ Mixture
Anhydride [6b]	Heat	*cis* ⟶ *trans*
Imide	Heat, urea fusion	*cis* ⟶ *trans*

The greater stability of the *trans*-anhydride and imide is attributed, following Linstead and Whalley,[9] to the fact that they contain a zig-zag rather than a coiled conformation of the paraffin chain.

On paper chromotography, the *cis*- and *trans*-imides show small but definite differences from one another and from ethylmethylmaleinimide. The difference between the two acids on paper chromatograms is also small, but the two acids react differently with the indicator and are easily distinguished. Chromatographic separations of ethylmethylsuccinic acids from dihydrohæmatinic acids were easily effected both on paper and on silica gel.

The infrared spectra of the acids, di-*p*-bromophenacyl esters, anhydrides, and imides of the two series are recorded and discussed in the Experimental section. We also record the preparation of *cisoid*-α-ethyl-α′-methylsuccinamide and of the methyl ester of *trans*-dihydrohæmatinic imide (required for chromatographic experiments).

EXPERIMENTAL

Microanalyses by Miss J. Cuckney; infrared measurements by Mr. R. L. Erskine of this Department. Alumina for chromatography unless otherwise stated was Savory and Moore's, deactivated with water to Brockmann grade IV.

Preparation of α-Ethyl-α′-methylsuccinic Acids and their Derivatives.—Ethyl αβ-dicyano-α-ethylbutyrate, prepared [7] in 51% yield, had b. p. 198°/60 mm., n_{D}^{25} 1·4379. The ester (100 g.) was refluxed for 24 hr. with concentrated hydrochloric acid (600 c.c.). The clear solution was cooled at 0° overnight, then filtered from deposited solid, which was washed with 50% hydrochloric acid (20 c.c.) and recrystallised from water (yield, 19 g.; 23%; m. p. 182°). Recrystallisation from water or xylene gave needles of *cisoid*-ethylmethylsuccinic acid, m. p. 182°.

The aqueous liquors were extracted with ether for 24 hr. and the extract dried and concentrated, to give oily mixed acids (62·5 g., 76%). These (44·7 g.) were treated with aqueous ammonia (75 ml.; *d* 0·88) and left overnight. Distillation gave an aqueous solution of the *trans*-imide, which was extracted with ether for 24 hr. The extract was dried and concentrated, to give crude *trans*-imide (31·1 g., 79%). The imide partially solidified at 0° and was drained on a porous tile, leaving a white solid (16·9 g.), m. p. 49°. Sublimation and recrystallisation from water and light petroleum (b. p. 40—60°) gave pure trans-*α-ethyl-α′-methylsuccinimide*, m. p. 61—62° (Found: C, 59·8; H, 7·5; N, 9·9. $C_7H_{11}O_2N$ requires C, 59·85; H, 7·05; N, 10·2%). The infrared absorption and m. p. of this sample were identical with those of material prepared in the same manner from pure *transoid*-ethylmethylsuccinic acid.

trans-Ethylmethylsuccinimide (5 g.) was refluxed with concentrated hydrochloric acid (25 c.c.) for 3·5 hr., then cooled and extracted with ether. Concentration of the dried extract yielded a gum which crystallised on addition of water, to give a white solid (4·5 g., 79%), m. p. 99°. Extractive crystallisation from light petroleum (b. p. 40—60°) yielded pure *transoid*-ethylmethylsuccinic acid, m. p. 102°.

trans-*Anhydride.* Mixed ethylmethylsuccinic acids (17·8 g.) were refluxed for 90 min. with acetyl chloride (25 c.c.). Excess of acetyl chloride was removed and the residue distilled, giving a colourless liquid (13·8 g., 85·5%). Redistillation yielded the pure *trans*-ethylmethylsuccinic anhydride, b. p. 121°/15 mm., n_{D}^{21} 1·4459 (Found: C, 59·5; H, 6·8. Calc. for $C_7H_{10}O_3$: C, 59·1; H, 7·1%).

Hydrolysis of the anhydride (0·663 g.) with boiling water (0·5 c.c.) for 20 min. yielded (after ether-extraction) *transoid*-ethylmethylsuccinic acid (731 mg., 99%), m. p. 85° raised to 98° by extraction with light petroleum (b. p. 40—60°).

cis-*Anhydride.* A suspension of the finely ground, dry sodium salt, formed from the *cisoid*-acid (10 g.), in dry ether (100 c.c.), was treated with redistilled thionyl chloride (5 c.c.) in ether (20 c.c.) during 10 min. The mixture was left at room temperature for 12 hr., then filtered, and the solid washed with anhydrous ether. The filtrate was evaporated, which left a colourless liquid (7·84 g., 86%). This, on distillation at $60/10^{-6}$ mm., yielded pure *cis*-ethylmethylsuccinic anhydride, n_D^{21} 1·4482 (Found: C, 58·9; H, 7·2%).

Hydrolysis of the anhydride (243 mg.) with boiling water (0·5 c.c.) for 10 min. yielded (after ether-extraction) *cisoid*-ethylmethylsuccinic acid (257 mg., 95%), m. p. and mixed m. p. 179°.

Ethylmethylmaleinimide.—Ethyl α-ethylacetoacetate, b. p. 97°/18 mm., n_D^{19} 1·4235, was prepared from ethyl acetoacetate in 79% yield, converted into the cyanohydrin, hydrolysed, and dehydrated [10] to ethylmethylmaleic anhydride. The anhydride was converted into the imide by fusion with urea,[10] then sublimation and crystallisation from water gave the pure imide, m. p. 68°.

cis-*Ethylmethylsuccinimide.*—Pure ethylmethylmaleimide (996 mg.) in purified ethyl acetate (25 c.c.) was hydrogenated at atmospheric pressure in the presence of Adams catalyst (27 mg.) (uptake, 1 mol., complete in 5 hr.). Filtration and concentration yielded a solid, m. p. 50° (1·014 g., quantitative yield). Recrystallisation from light petroleum (b. p. 40—60°) gave leaflets, m. p. 51°, of cis-*α-ethyl-α-methylsuccinimide* (Found: C, 59·7; H, 7·6; N, 10·1. $C_7H_{11}O_2N$ requires C, 59·55; H, 7·85; N, 9·9%), mixed m. p. with the *trans*-imide 35°.

The *cis*-imide (63·1 mg.) was refluxed with concentrated hydrochloric acid (1 c.c.) for 1 hr. The cold solution was extracted with ether for 24 hr. The dried extract was concentrated, to yield *cisoid*-acid (71·3 mg., 99%), m. p. and mixed m. p. 176°.

p-*Bromophenacyl Esters.*—(*a*) To the *cisoid*-acid (250 mg.), dissolved in the minimum amount of 2N-sodium hydroxide and rendered just acid with 2N-hydrochloric acid, was added *p*-bromophenacyl bromide (870 mg.) in ethanol (7 c.c.). The solution was refluxed for 2 hr., then cooled; a white solid (814 mg., 94%), m. p. 119°, crystallised and was washed with water. Recrystallisation from ethanol gave the *di*-p-*bromophenacyl derivative* as needles, m. p. 119° (Found: C, 50·1; H, 4·3; Br, 28·9. $C_{23}H_{22}O_6Br_2$ requires C, 49·8; H, 4·0; Br, 28·8%).

(*b*) By the foregoing procedure the *transoid*-acid (250 mg.) yielded the corresponding di-*p*-bromophenacyl derivative (836 mg., 97%), m. p. 100°. Recrystallisation from methanol yielded needles of the *ester*, m. p. 122° (depressed to 106° on admixture with the *cisoid*-ester) (Found: C, 49·85; H, 4·2%).

The *S*-benzyl*iso*thiuronium, benzylamine, and piperidine salts of the ethylmethylsuccinic acids were too soluble for convenient preparation.

Conversion of cis-*Ethylmethylsuccinimide into the* trans-*Isomer.*—*cis*-Imide (300 mg.), mixed with urea (230 mg.), was kept at 155—165° for 3·5 hr. After cooling, the solid was dissolved in water and extracted with ether for 24 hr. The ethereal solution was filtered from urea, dried (Na_2SO_4), and evaporated, yielding white crystals (304 mg.), m. p. 51—52°. Sublimation yielded crystals (249 mg.), m. p. 53°, having infrared absorption identical with that of the *trans*-imide. Recrystallisation from light petroleum raised the m. p. to 60—61°.

Melting points of Mixtures of cisoid- *and* transoid-*Ethylmethylsuccinic Acids.*—Mixtures of the acids were prepared and their m. p. determined on an electric m. p. apparatus. The *cisoid*-acid was only slightly soluble in the acid melts.

cisoid (%)	0	11	28	36·5	46	56	64	73	82	90	95	100
M. p.	102°	98°	97°	95—96°	98°	100°	104°	124°	135°	157°	169°	182°

Interconversion of cisoid- *and* transoid-*Ethylmethylsuccinic Acids.*—Samples of *cisoid*- and *transoid*-acids (50 mg.) were heated (*a*) alone, (*b*) with water (2 c.c.), and (*c*) with concentrated hydrochloric acid (2 c.c.) at 180° for 72 hr. The products were evaporated to dryness over potassium hydroxide in a desiccator and their identity determined by paper chromatography and m. p.

(*a*) *cisoid*: Unchanged, m. p. 182°.

transoid: Gave a mixture of *cisoid*- and *transoid*-material; m. p. 71°. This on treatment with water (2 c.c.) and evaporation at room temperature melted at 95—97°, unchanged by further treatment with water; hence >50% of *transoid*-form.

(*b*) The *cisoid*- and the *transoid*-form both gave material of m. p. about 110—115°; hence an equilibrium mixture containing 30—35% of the *transoid*-form.

(*c*) The *cisoid*- and the *transoid*-form both gave low-melting mixtures of *cisoid*- and *transoid*-material. On treatment with water, as in (*a*), the m. p.s were raised to 95—97°; hence >50% of *transoid* material.

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[10] Muir and Neuberger, *Biochem. J.*, 1949, **45**, 164.

The low-melting crude products obtained in some of these experiments probably contain anhydrides.

Paper-chromatography of Acids and Imides.—Solutions of the pure compounds (1% in methanol) were spotted on paper and developed (descending method) with ethanol–water–ammonia (*d* 0·88) (80 : 15 : 5). All compounds showed clearly defined spots with negligible tailing; R_F ±0·02; relative values reproducible:

(a) *Imides*

Developed with *o*-tolidine by an adaptation of the method of Reindel and Hopper.[11]

	R_F
cis-Dihydrohæmatinimide	0·41
trans- ,,	0·45
trans-Dihydrohæmatinimide Me ester	0·77
cis-Ethylmethylsuccininimide	0·79
trans- ,,	0·81
Ethylmethylmaleinimide	0·87
Hæmatinimide	0·51
Benzylamine *	0·82

* Benzylamine salts of, *e.g.*, dihydrohæmatinimide, give a double spot.

Mixtures of *cis*- and *trans*-isomers form a double spot but do not separate clearly.

(b) *Acids*

Developed with ethanolic bromocresol-green, followed by lead acetate.

	R_F
Oxalic	0·00
Succinic	0·26
Malonic	0·17
transoid-Ethylmethylsuccinic	0·40
cisoid- ,,	0·43
Ethylmethylmaleic †	0·56
cisoid-Dihydrohæmatinic	0·12
transoid- ,,	0·11

† Anhydride dissolved in aqueous-methanolic ammonia.

The acids were also detectable by the imide spray (cf. *a*). *cis*- and *trans*-Isomers did not separate clearly, but the ethylmethylsuccinic acids were distinguishable by difference in the colour when freshly sprayed.

Partition Chromatography of cisoid-*Ethylmethylsuccinic and* cisoid-*Dihydrohæmatinic Acid.*—The acids (25 mg. of each) were dissolved together in ether saturated with water (5 c.c.) and chromatographed on silica gel saturated with water (20 × 1·5 cm.). The column was eluted with ether saturated with water, 3 ml. fractions being collected and identified by paper chromatography.

Fractions 1—2: nil. 3—6: *cisoid*-ethylmethylsuccinic acid (19·7 mg., 79%), m. p. 179°. 7—8: mixed acids (9·5 mg.). 9—20: *cisoid*-dihydrohæmatinic acid (11·8 mg., 47%), m. p. 180°. 21—40: traces only of acids. The total recovery was 82%. Addition of methanol failed to remove further acid. Use of ethyl acetate saturated with water, instead of ether, gave comparable results; benzene was ineffective.

Infrared Absorption of Ethylmethylsuccinic Derivatives.—(a) *Acids.* The *cisoid*- and the *transoid*-acid and their *p*-bromophenacyl esters gave characteristic curves and were readily distinguishable. Frequencies (cm.$^{-1}$) (in Nujol mulls) are tabulated (cf. Schotte[8]).

Acids			*p*-Bromophenacyl esters	
cisoid	*transoid*	Assignment	*cisoid*	*transoid*
1692 s	1715 s 1698 s	C=O stretching	1734 s	1745 s, 1736 s
1282 ms	Series	C=O stretching of carbonyl	1703 s	1706 s, 1694 s
952 m	937 m 897 m	OH out-of-plane bending	1586 ms	1587 s, 1570 w

(b) *Anhydrides.* The spectra of the ethylmethylsuccinic anhydrides showed marked differences, especially in the 7—9·5 and 12—14 μ regions. The C=O vibration frequencies (obtained in a liquid film) are tabulated; the values are typical for a five-membered anhydride ring (cf. ref. 12).

	cis	*trans*	Succinic anhydride[13]	Assignment
	1850 1777	1853 1779	1865 1782	C=O vibration
$\Delta\nu$	73	74	83	

(c) *Imides.* The imides possessed characteristic curves and were readily distinguishable from each other and from ethylmethylmaleinimide. The succinimides possessed a characteristic

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[11] Reindel and Hopper, *Chem. Ber.*, 1954, **87**, 1103.

[12] Bellamy, " Infra-red Spectra of Complex Molecules," Methuen, London, 1954.

[13] Randall, Fowler, Fuson, and Dangl, " Infra-red Determination of Organic Structures," Van Nostrand, New York, 1949.

band (*ca.* 1200 cm.$^{-1}$) not shown by the corresponding maleinimide. Frequencies (cm.$^{-1}$) in Nujol mulls are tabulated.

Ethylmethylmaleinimide	Ethylmethylsuccinimide cis	Ethylmethylsuccinimide trans	Assignment
3185 m	3165 m	3145 m	NH stretching
3012 m	3049 m	3040 m	
1764 s	1776 m	1770 m	Imide bands
1709 s	1698 s	1692 s	
—	1195 s	1185 s	Succinimide band

trans-*Dihydrohæmatinimide Methyl Ester.*—*trans*-Dihydrohæmatinimide (502 mg.) in ether (50 c.c.) was treated with excess of diazomethane in ether (50 c.c.). After 10 min. excess of diazomethane and ether were removed and the residue (534 mg., 99%) was transferred to a bulb tube. The clear oil was distilled, giving the *methyl ester*, b. p. 150°/0·5 mm., n_D^{18} 1·4910 (Found: C, 54·6; H, 6·6; N, 7·1. $C_9H_{13}O_4N$ requires C, 54·3; H, 6·6; N, 7·0%).

cisoid-α-*Ethyl*-α'-*methylsuccinamide* [with P. WALKER].—The *cis*-imide (200 mg.) was dissolved in 1 c.c. of aqueous ammonia (*d* 0·88) and kept at 0° for 2 days. The white crystals which separated were washed with water and with methanol. Recrystallisation from aqueous ammonia gave the cisoid-*amide* (40%), m. p. 340—342° (Found: N, 17·8. $C_7H_{14}O_2N_2$ requires N, 17·8%). Hydrolysis gave the *cisoid*-acid.

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