

STERIC CORRELATIONS BY THE QUASI-RACEMATE METHOD

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Abstract—The quasi-racemate method for steric correlation of optically active compounds is presented and discussed. The work performed in this field by the Uppsala school is reviewed with special reference to the correlation of the amino acids and the terpenes to the glyceraldehyde system.

KNOWLEDGE of the steric relationships is indispensable for the understanding of many reaction mechanisms, not least in biological systems, and also for the theory of optical activity. The work in this field has attracted renewed interest since the problem of the absolute configuration has been solved. From the chemist's point of view, the optical activity in itself is perhaps of secondary interest; it is important as a physical constant for characterizing a compound, but the main interest is attached to the geometrical form of the molecules, which often exerts a decisive influence on the possibilities of reaction in asymmetric systems. The quasi-racemate method, which is based on the power of the asymmetric molecules to form molecular compounds or solid solutions must not be regarded only as a control or a complement to the classical methods. It also offers possibilities for the development and deepening of our knowledge of reactions in asymmetric systems.

It is well known that a pair of enantiomorphs often crystallize together to give a racemic compound, a true racemate, which manifests itself in the melting-point diagram as a special curve branch with a maximum at 50 per cent. The enantiomorphs seldom give a continuous series of solid solutions (a pseudo-racemate) or a eutectic mixture (a conglomerate). The true racemate is a molecular compound, characterized by a special crystal lattice, where the (+)- and (−)-molecules occupy different positions; often they are arranged in pairs having a centre of symmetry. In this way the lattice obtains a higher symmetry and a higher stability than when the enantiomorphs crystallize separately.

Centnerszwer reported¹ that (+)-chlorosuccinic acid and (−)-bromosuccinic acid give a molecular compound in the ratio 1 : 1, which must be regarded as a kind of racemate. Delépine independently took up the question of the existence of such molecular compounds for general discussion² and later Timmermans realized that they could be utilized for studying steric relationships.³ In older literature, different names were used for such compounds, but now the term quasi-racemate or quasi-racemic compound, introduced by the present author,⁴ seems to be generally accepted.

A quasi-racemate may thus be defined as a molecular compound, which can be derived from a true racemate by a not too extensive change in the structure of one of the components. Like a true racemate it manifests itself in the melting point diagram

¹ M. Centnerszwer, *Z. Physik. Chem.* **29**, 715 (1899).

² M. Delépine, *Bull. Soc. Chim. Fr.* [4] **29**, 656 (1921).

³ J. Timmermans, *Rec. Trav. Chim.* **48**, 890 (1929).

⁴ A. Fredga, *The Svedberg 1884-30/8 1944* p. 261. Uppsala and Stockholm (1944).

as a special curve branch with a maximum at 50 mole-per cent, but as the components have different melting-points, the diagram is not symmetrical. Its formation is of course due to the tendency to form a more symmetrical and more stable lattice. Some aspects on this question have been discussed by Hägg.⁵

The possibilities for the formation of a quasi-racemate may depend upon a number of factors. Already the tendencies to form true racemic compounds may be very different, even for closely related substances, and it is obvious that both sterical and polar factors must be taken into consideration. It is sometimes stated that strong

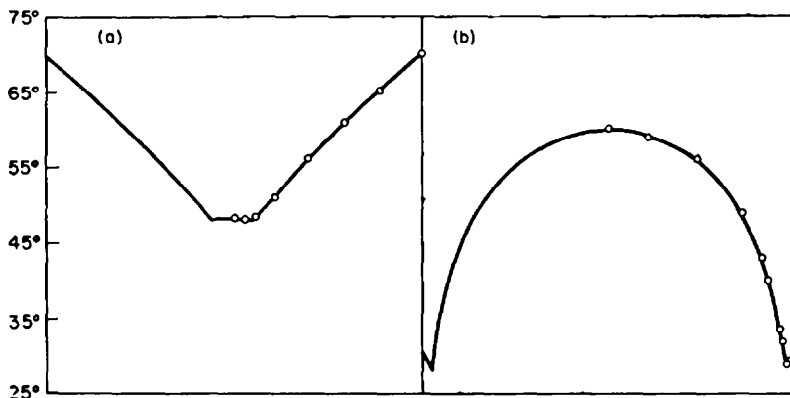


FIG. 1. (a) (+)- and (-)-Ethylxanthopropionic acid.
(b) (+)- and (-)-Ethylxantho-n-butyric acid.

polar forces are necessary for the formation of true racemates,^{6,7} and this may be true to a certain extent, but in the author's opinion the influence of this factor is somewhat overrated. For instance, Matell has found⁸ that the methyl ester of the β -phenyl- β -hydroxy-pivalic acid gives a true racemate while the free acid is a eutectic mixture of the enantiomorphs; from experience, the ester should be less polar than the acid. The present author has examined two homologues, α -ethylxanthopropionic acid and α -ethylxantho-n-butyric acid, where the polar forces must be very similar in nature.⁴ In the first case (Fig. 1a), the racemate melts considerably lower than the enantiomorphs and only indicates its presence within a very limited part of the diagram. The higher homologue behaves in an opposite manner, the molecular compound completely dominating the diagram (Fig. 1b).

It is difficult to give an adequate measure of the racemate-forming tendency; it would be more correct to express it in terms of energy, but the determination of the energy changes in question is very laborious, especially as the enantiomorphs are often accessible only in small quantities. For practical purposes, one can often use the difference in melting point between the racemate and the enantiomorphs; a high melting-point of the racemate means a stable molecular compound. Petterson has pointed out⁹ that the extent of the middle branch of the curve or the height of the maximum, reckoned from the eutectic points (compare Fig. 1a and b) may be used as a measure of the racemate forming tendency.

⁵ G. Hägg, *The Svedberg 1844-30/8-1944* p. 140. Uppsala and Stockholm (1944).

⁶ P. Landrieu, *Bull. Soc. Chim. Fr.* [4] 31, 1217 (1922).

⁷ J. D. M. Ross and I. C. Sommerville, *J. Chem. Soc.* 2770 (1926).

⁸ M. Matell, *Arkiv. Kemi* 1, 455 (1950).

⁹ K. Petterson, *Arkiv. Kemi* 10, 297 (1956).

It seems justified to assume that a substance, which forms a very stable true racemate, should also have a strong tendency to form quasi-racemates, and from experience this assumption holds good.

It may be asked how great the structural difference between the two components may be, that the power of forming quasi-racemates may not be lost. A first indication is given by the power of different atoms or atomic groups to replace one another in isomorphous mixtures. It has been found, however, that quasi-racemates are obtained in many cases, where the enantiomorphs of analogous configuration are not isomorphous. In several cases, quasi-racemates were obtained between the lowest optically active members of homologous series. Also a hydrogen atom in one of the components may be replaced by bromine or iodine¹⁰ if the molecule is not too small.

In many cases, the question arises, whether a molecular compound between two optically active substances is really to be considered as a quasi-racemate. In the first place, it is necessary to make clear which atoms or groups in the two components should be regarded as corresponding to each other. Also, each component should form a molecular compound only with one antipode of the other. If compounds are formed with both antipodes (which is very unusual) the case must be examined very thoroughly. In addition, crystallographic relationships should be sought for between the quasi-racemate and the true racemates of the components. It may even happen, that the quasi-racemate is isomorphous with an unstable form of one of the true racemates. It is often simpler to investigate, with the aid of melting-point curves, if the quasi-racemate forms solid solutions with one of the true racemates, but X-ray diagrams may often render good service. The X-ray methods are also very useful if the quasi-racemates melt incongruently (maximum overlapped by a descending curve branch as in Fig. 13) or when the components tend to decompose or racemise on heating.

In special cases, other physico-chemical methods may be resorted to (solubility determinations, examination of crystals under the polarising microscope etc.). Rosenberg and Schotte have found that a quasi-racemate may give rise to special frequencies in the I.R.-spectrum of the solid phase.¹¹

If two compounds are too different in structure to give a quasi-racemate, the question of configuration may be solved by comparing both with a suitably chosen third substance. Another method is to introduce a common substituent in both substances (without affecting the centre of asymmetry); the structural difference is thus rendered less prominent. Similar methods may be employed if the two compounds, on account of their physical properties (low melting-point, poor crystallization power etc.) do not lend themselves to the recording of melting point diagrams. For instance, low-melting acids may be studied as amides.^{12,13}

In cases, where no quasi-racemate is formed, it may happen that the antipodes with corresponding configuration give solid solutions (mixed crystals), easily detectable in the melting point diagram. If finally an optically active substance gives curves of the common eutectic type with both enantiomorphs of another, though a quasi-racemate could be expected, these diagrams are rather similar but in most cases not quite identical. It seems that if there is a difference, the eutectic temperature is always

¹⁰ A. Fredga, To be published.

¹¹ A. Rosenberg and L. Schotte, *Arkiv. Kemi* **8**, 143 (1955).

¹² K. Mislow and M. Heffler, *J. Amer. Chem. Soc.* **74**, 3668 (1952).

¹³ K. Pettersson, *Arkiv. Kemi* **9**, 509 (1956); **10**, 283 (1956).

lower when the components have opposite configurations. The experimental material is, however, too small to permit any definite conclusions.

Timmermans, who in 1929 drew attention to this method of correlating configurations, has investigated a great number of systems and also reviewed the work in this field up to 1951.¹⁴ In recent years, very interesting contributions have been made by Mislow *et al.*, who have, among other things, investigated atropisomeric substances.^{12,15,16} The present article deals with the work performed in Uppsala and gives examples of the mode of procedures in different cases.

Organic compounds of sulphur and selenium

It is well known that analogous compounds of sulphur and selenium are often isomorphous and a number of such pairs have been tested in 1934–1943.¹⁷ In some cases the enantiomorphs with corresponding configuration were isomorphous, in others they were not, but in all cases quasi-racemates were obtained. For such compounds, the method is thus very appropriate and the steric correlation presents no difficulties. As an example, the diagrams for the acids I and II are given. In



the first case, the racemate melts lower than the enantiomorphs (Fig. 2a), in the second much higher (Fig. 2b). The curve representing the quasi-racemate (Fig. 2c) looks like a sort of compromise between the two types. Such curves of intermediate type are often obtained when the components of the quasi-racemate are closely related in structure; another example is found in Fig. 11. When the structural difference is greater, the quasi-racemate may manifest itself only within a very limited part of the diagram, even if both components display a strong tendency to form true racemates.

Amino acids

The steric connections of hydroxy- and amino acids were studied (1924–1935) by Freudenberg and collaborators,¹⁸ who made use of optical methods (“Verschiebungsregel”). They concluded that the naturally occurring amino acids most probably possess L-configuration. The quasi-racemate method seems not directly applicable for the correlation of these acids; they are too unlike in respect of the polar properties. Most amino acids occur in the crystal lattice as zwitter-ions and melt with decomposition, and a molecular compound between an amino and a hydroxy acid could be interpretable as a salt. By the introduction of a suitably chosen common substituent at the hydroxy and amino groups, however, it is possible to increase the structural

¹⁴ J. Timmermans, *J. Chim. Phys.* **49**, 162 (1953).

¹⁵ K. Mislow, *Trans. New York Acad. Sci.* [II] **19**, 298 (1957).

¹⁶ K. Mislow and W. C. Meluch, *J. Amer. Chem. Soc.* **78**, 5920 (1956); K. Mislow and M. Siegel, *Ibid.* **80**, 473 (1958).

¹⁷ A. Fredga, *Arkiv. Kemi, Mineral. Geol.* **11B**, No. 43 (1934); **12B**, No. 22 (1936); **12A**, No. 27 (1938); **17A**, No. 17 (1943). *Svensk Kem. Tid.* **49**, 124, 139 (1937); *J. Prakt. Chem.* [2] **150**, 124 (1938).

¹⁸ K. Freudenberg and F. Rhino, *Ber.* **57**, 1547 (1924); K. Freudenberg and A. Noé, *Ibid.* **58**, 2399 (1925); K. Freudenberg and M. Meister, *Liebigs Ann.* **518**, 86 (1935).

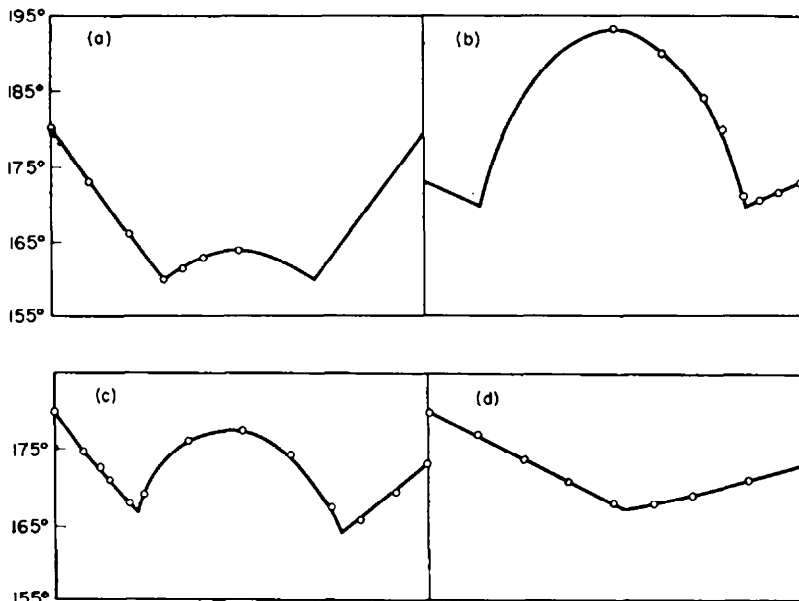


FIG. 2. (a) (+)- and (-)-I. (b) (+)- and (-)-II. (c) (+)-I and (-)-II. (d) (+)-I and (+)-II.

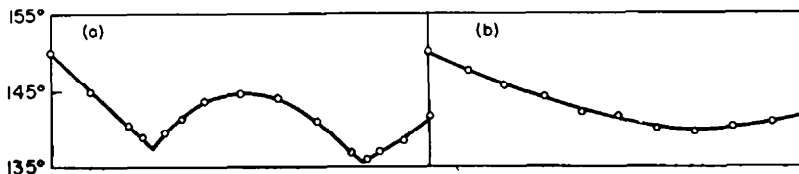
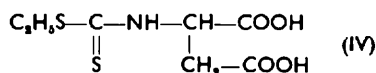
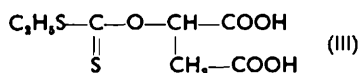
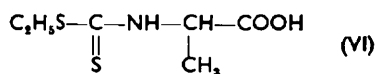
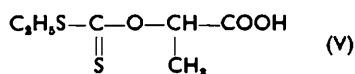


FIG. 3. (a) (+)-III and (-)-IV. (b) (+)-III and (+)-IV.

similarity of the molecules and at the same time suppress the basic character of the amino group. For the correlation of malic acid and aspartic acid, the author selected the compounds III and IV, which are easily prepared from the parent acids without



affecting the centres of asymmetry. The melting point diagrams (Fig. 3) are very typical: in one case a quasi-racemic compound and in the other a curve indicating far-reaching miscibility in the solid state.¹⁹ From the diagrams, it could be deduced that L-(-)-malic acid and natural(+)-aspartic acid have corresponding configurations. In the same manner, it was established, with the aid of the acids V and VI,²⁰ that L-(+)-lactic acid has the same configuration as natural (+)-alanine (Fig. 4). In this



case, the acids with the same configuration give a curve of the common eutectic type.*

* Matell has later found that also the 2,4-dinitrophenyl group can be used as common substituent for correlating alanine and lactic acid.²⁰

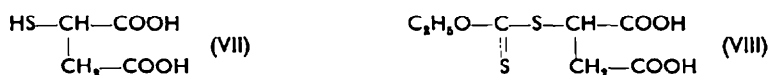
¹⁹ A. Fredga, *Svensk Kem. Tid.* 53, 221 (1941).

²⁰ A. Fredga, *Svensk Kem. Tid.* 54, 26 (1942).

As expected, the results were in accordance with those obtained by Freudenberg, and the configuration of the amino acids could thus be regarded as definitely settled. Later the problem attracted renewed interest and additional evidence was produced by several authors.²¹

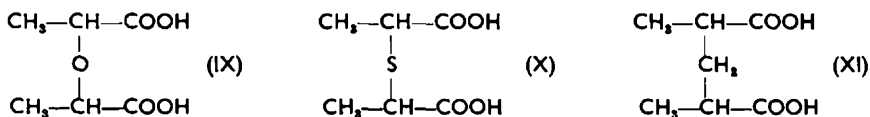
Mercaptosubstituted acids

The conditions for a direct comparison between hydroxy and mercapto acids are not very favourable. The atomic radii of oxygen and sulphur are too unlike and the difference in the external dimensions of the molecules is thus rather great. For the correlation of malic acid and mercaptosuccinic acid (VII), two derivatives were selected, *viz.* the acid III mentioned above and the ethylxantho-succinic acid (VIII). The acids III and VIII are isomeric and differ only in the relative positions of a



sulphur and an oxygen atom. Fig. 5 shows that the acids with the *same* direction of optical rotation give a quasi-racemate and must therefore be assigned *opposite* configurations. The acid VIII is easily connected to VII by chemical methods, and the final result was that malic acid and mercaptosuccinic acid with the same direction of rotation have also the same configuration.²²

Lactic acid and α -mercaptopropionic (thiolactic) acid, which have low melting points, were correlated with the aid of two derivatives, dilactic acid (IX) and thiodipropionic acid (X). These acids gave certainly no molecular compounds, but since



the atomic radius of carbon lies between those of oxygen and sulphur, it might be expected that both acids would give quasi-racemates with $\alpha\alpha'$ -dimethylglutaric acid (XI). The latter acid has a very strong tendency to racemate formation and in addition it forms so-called anomalous racemates, *i.e.* compounds between the enantiomorphs in other ratios than 1 : 1. (–)-Dilactic acid and (+)-dimethylglutaric acid gave a quasi-racemate (Fig. 6) but also a compound in the ratio 3 : 1 (75 per cent of dimethylglutaric acid.) The thiodipropionic acid gave under the same conditions a very pronounced maximum at 50 per cent and another molecular compound, represented by a very small curve branch in the vicinity of one of the eutectics. The composition of this compound, which melts incongruently, could not be derived from the diagram, but probably it is an analogue of the compound 3 : 1 mentioned above. The final result was, that L-(+)-lactic acid and (–)- α -mercaptopropionic acid have analogous configurations.²³

The dimethylglutaric acid could also be correlated to the monomethylglutaric acid,²⁴ and even in this case a compound in the ratio 3 : 1 is formed in addition to the normal quasi-racemate (Fig. 7).

²¹ P. Brewster, E. D. Hughes, C. K. Ingold, and P. A. D. S. Rao, *Nature, Lond.* **166**, 178 (1950); D. P. Shoemaker, J. Donohue, V. Schomaker and R. B. Corey, *J. Amer. Chem. Soc.* **72**, 2328 (1950).

²² A. Fredga, *Arkiv. Kemi, Mineral. Geol.* **14B** nr. 27 (1941).

²³ A. Fredga, *Arkiv. Kemi, Mineral. Geol.* **14B** nr. 12 (1940).

²⁴ A. Fredga, *Arkiv. Kemi, Mineral. Geol.* **24A** nr. 32 (1947).

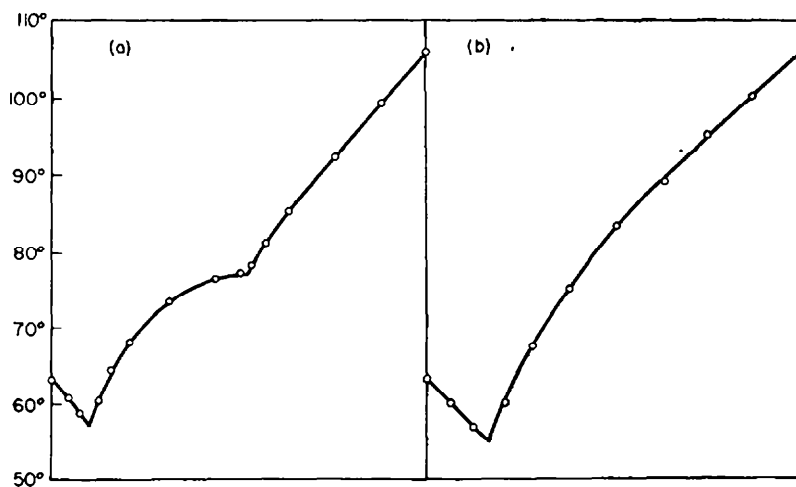


FIG. 4. (a) (+)-V and (+)-VI. (b) (-)-V and (+)-VI.

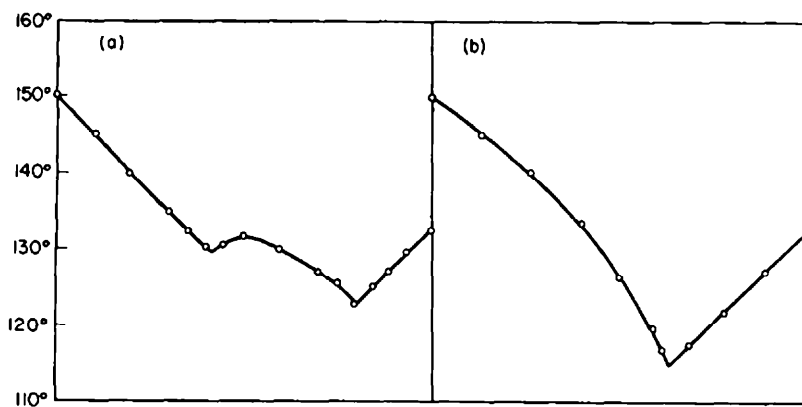


FIG. 5. (a) (+)-III and (+)-VIII. (b) (+)-III and (-)-VIII.

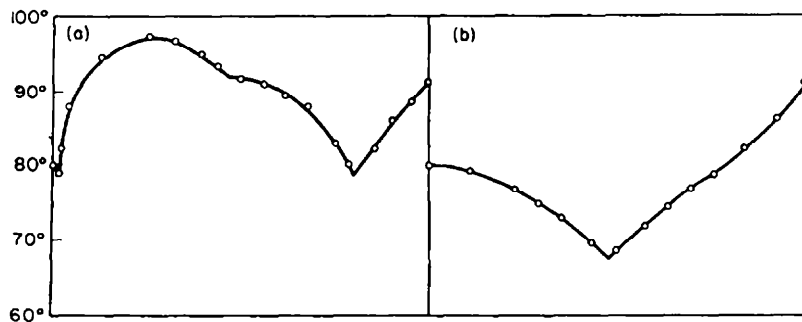
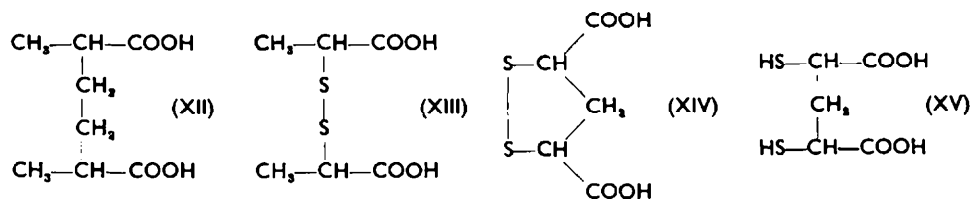


FIG. 6. (a) (-)-IX and (+)-XI. (b) (+)-IX and (+)-XI.

Attempts to correlate $\alpha\alpha'$ -dimethyladipic acid (XII) and dithiodipropionic acid (XIII) met with no success.²⁵ Probably these acids have rather different conformations on account of the dihedral angle of the disulphide group which is about 90° . In the



cyclic acid XIV investigated by Schotte, the ring must tend to assume a planar conformation and the dihedral angle must be much smaller than usual (X-ray studies on another acid with the same ring indicate²⁶ that it is about 20°). It is interesting

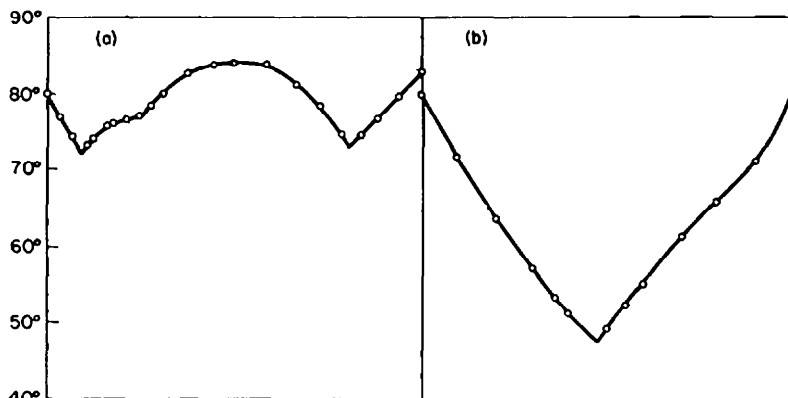


FIG. 7. (a) (—) Dimethylglutaric acid (XI) and (+)-methylglutaric acid.
(b) (—) Dimethylglutaric acid and (—)-methylglutaric acid.

to note that in this case a quasi-racemate is obtained with the thiophane-dicarboxylic acid (I) mentioned earlier. On reduction, the acid XIV gives $\alpha\alpha'$ -dimercaptoglutaric acid (XV) which by quasi-racemate formation was connected to dimethylglutaric acid (XI). The acids I and XIV could thus be connected to the glyceraldehyde system.²⁷

Alkylsuccinic acids

It is known that CH_2 and S in organic compounds may replace each other in isomorphous mixtures, and we have seen above that they can do it in quasi-racemate formation. Mercapto succinic acid was thus tested against methylsuccinic acid and the enantiomorphs with opposite directions of rotation gave a compound 1:1 (Fig. 8a). Acids of the same mode of rotation gave a diagram indicating mutual but not unlimited miscibility in the solid state (Fig. 8b); obviously we have in the latter case a curve of the kind designated by Roozeboom as type 4. It is interesting to note that the two racemic acids give a very similar diagram indicating solid solutions.²⁸

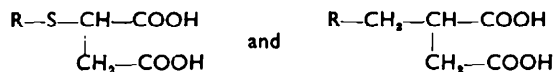
²⁵ I. Hedlund, *Arkiv. Kemi* 8, 89 (1955).

²⁶ O. Foss and O. Tjomsland, *Acta Chem. Scand.* 11, 1426 (1957).

²⁷ L. Schotte, *Arkiv. Kemi* 9, 441 (1956).

²⁸ A. Fredga, *Arkiv. Kemi, Mineral. Geol.* 15B, No. 23 (2942).

Matell²⁹ has extended this investigation to acids of the types:



where R represents n-alkyl groups from CH₃ to C₅H₁₁. For R = CH₃ he obtained curves very similar to those in Fig. 8. With growing chain length, the tendency to form quasi-racemates decreases and from R = C₄H₉ no molecular compounds were formed. An explanation for this behaviour cannot be given as yet. It is also remarkable that no quasi-racemate was obtained for R = iso-C₃H₇.

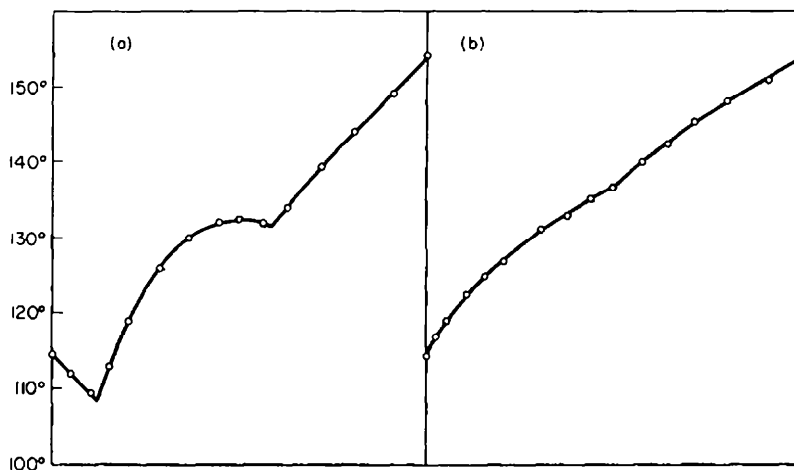


FIG. 8. (a) (-)-Mercaptosuccinic acid (VII) and (-)-methylsuccinic acid.
(b) (+)-Mercaptosuccinic acid and (-)-methylsuccinic acid.

The lower alkylsuccinic acids were thus correlated to the alkyl-sulphide-succinic acids, and the latter acids were easily connected with mercaptosuccinic acid by direct synthesis. The relative configurations of the alkylsuccinic acids could further be checked by quasi-racemate formation between adjacent members of the homologous series, and in this way also the n-pentyl- and n-hexylsuccinic acids could be correlated. As expected all alkylsuccinic acids with the same mode of rotation have the same configuration.

Investigations by the present author and collaborators^{30,31} show that alkylsuccinic acids with branched alkyl groups can be connected to the unbranched acids and Porath found it possible to connect α -methyl- α -ethyl-succinic acid³² and α -methyl- α -isopropyl-succinic acid.³³ To the author's knowledge, the latter acid represents the first correlation of an asymmetric quaternary carbon atom to the system of glyceraldehyde.

Halosuccinic acids

Several cases are known, where a methyl group can replace chlorine or bromine in isomorphous mixtures. When optically active methylsuccinic acid is mixed with

²⁹ M. Matell, *Arkiv. Kemi* 5, 17 (1952).

³⁰ A. Fredga and U. Sahlberg, *Arkiv. Kemi, Mineral. Geol.* 18A nr. 16 (1944).

³¹ A. Fredga and E. Leskinen, *Arkiv. Kemi, Mineral. Geol.* 19B nr. 1 (1944).

³² J. Porath, *Arkiv. Kemi* 3, 163 (1951).

³³ J. Porath, *Arkiv. Kemi* 1, 385 (1949).

halosuccinic acid of *opposite* mode of rotation, the melting point sinks towards a eutectic (Fig. 9a and c). If, on the other hand, halosuccinic acid of the *same* mode of rotation is added, the melting point rises, indicating that the halosuccinic acid enters into solid solution (Fig. 9b and d). We have here diagrams of Roozeboom's type 4, and it is justified to conclude that the antipodes, which form solid solutions have corresponding configuration.⁴ The non-appearance of quasi-racemic compounds in

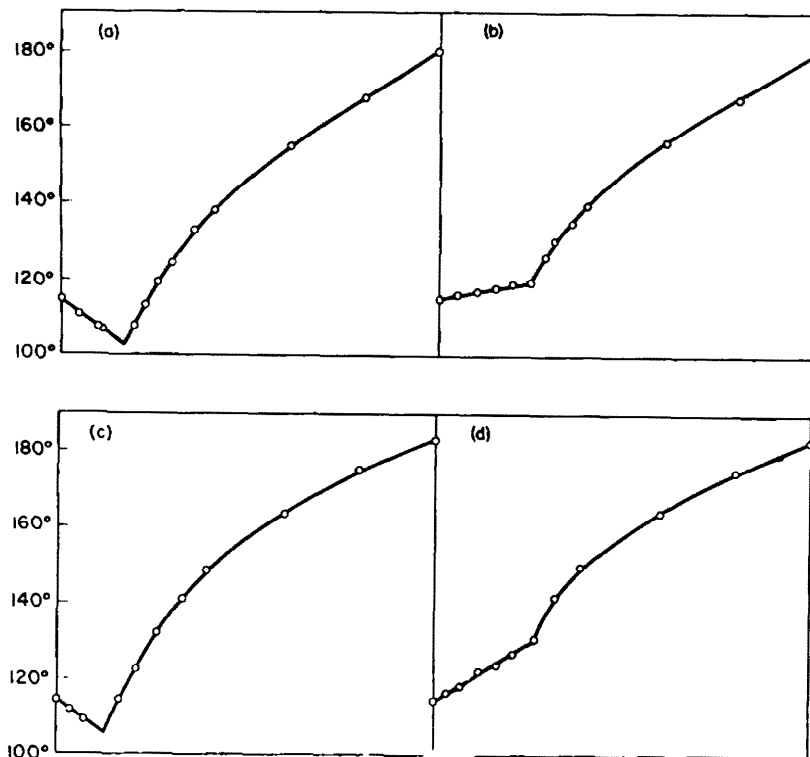


FIG. 9. (a) (+)-Methylsuccinic acid and (-)-Chlorosuccinic acid.
 (b) (-)-Methylsuccinic acid and (-)-Chlorosuccinic acid.
 (c) (+)-Methylsuccinic acid and (-)-Bromosuccinic acid.
 (d) (-)-Methylsuccinic acid and (-)-Bromosuccinic acid.

this case is certainly due to the poor racemate-forming tendency of the halosuccinic acids.

The results of the work related above are summarized in Charts 1 and 2. The latter chart shows the configuration of the dextro-rotatory alkylsuccinic acid; as seen from the chart, most acids could be related to the others in two or more ways.

Special interest is connected with the steric relations of alkylsuccinic and alkylglutaric acids, since such acids are often obtained on oxidative degradation of natural products, e.g. terpenes. As seen from Chart 1, methylsuccinic acid could be related to malic acid and methylglutaric acid to lactic acid, in both cases by the aid of mercapto acids. Confirmation by another route was desirable, especially as (+)-methylsuccinic acid and (+)-methylglutaric acid were found to possess opposite configurations. It was therefore important that (+)-isopropylglutaric acid could be degraded to

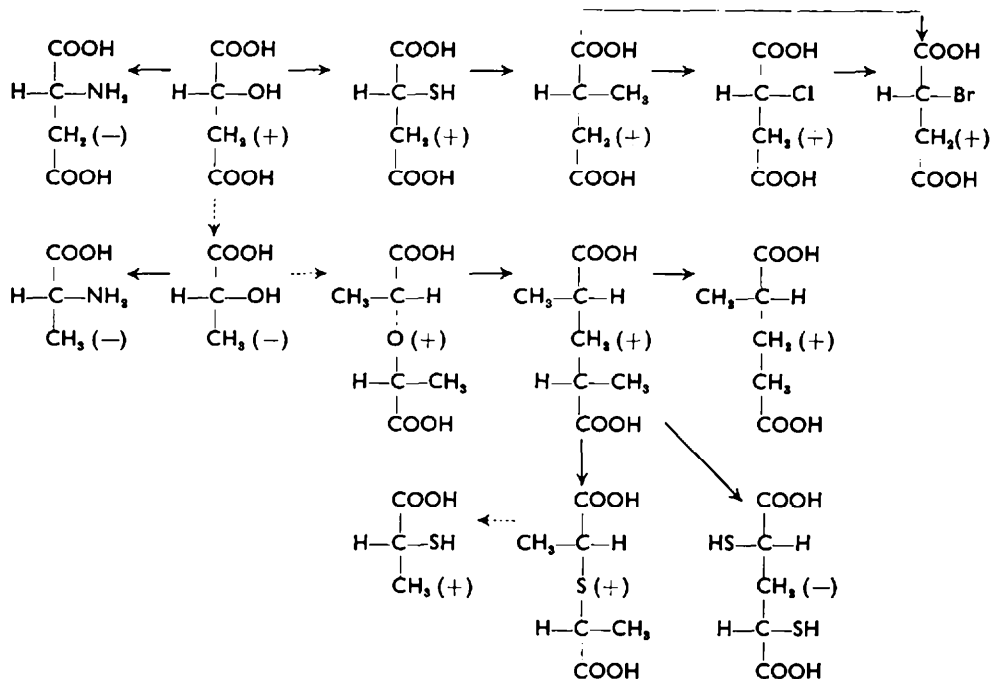
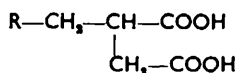
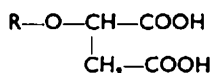


CHART 1. Fundamental correlations by the quasi-racemate method. Broken piles indicate chemical correlations by previous authors.

(-)-isopropylsuccinic acid.³⁴ This fact affords additional support to the conclusions regarding the methylsubstituted acids, but unfortunately the isopropylglutaric acid could not be related to the methyl derivative by the quasi-racemate method. Decisive evidence has later been produced by James,³⁵ who obtained both methylsubstituted acids by controlled degradation of the side chain of a steroid molecule.

A direct confirmation of the absolute configuration of the alkylsuccinic acids appeared possible by studying acids of the types:



The former are obtained by O-alkylation of malic acid and their steric relations are known. A preliminary study indicated that acids, which should possess opposite configurations give in fact quasi-racemates of rather low stability, while the acids with corresponding configurations have a certain tendency to form solid solutions. However, the examination of these systems was very tedious as the melts crystallize rather slowly and the samples were found to be very hygroscopic. The final investigation of the systems was therefore postponed; a preliminary diagram for the system O-methyl-malic acid-ethylsuccinic acid is given in Fig. 10.

In recent years, Freudenberg has determined the configuration of the alkylsuccinic acids by a purely chemical method, using the lactone of dihydroshikimic acid.³⁶ His results are in accordance with those found in Uppsala.

³⁴ A. Fredga and J. K. Miettinen, *Acta Chem. Scand.* 1, 371 (1947).

³⁵ V. H. T. James, *Chem. & Ind.* 1388 (1953); *J. Chem. Soc.* 637 (1955).

³⁶ K. Freudenberg, *Monatsh.* 85, 537 (1954); and quoted references.

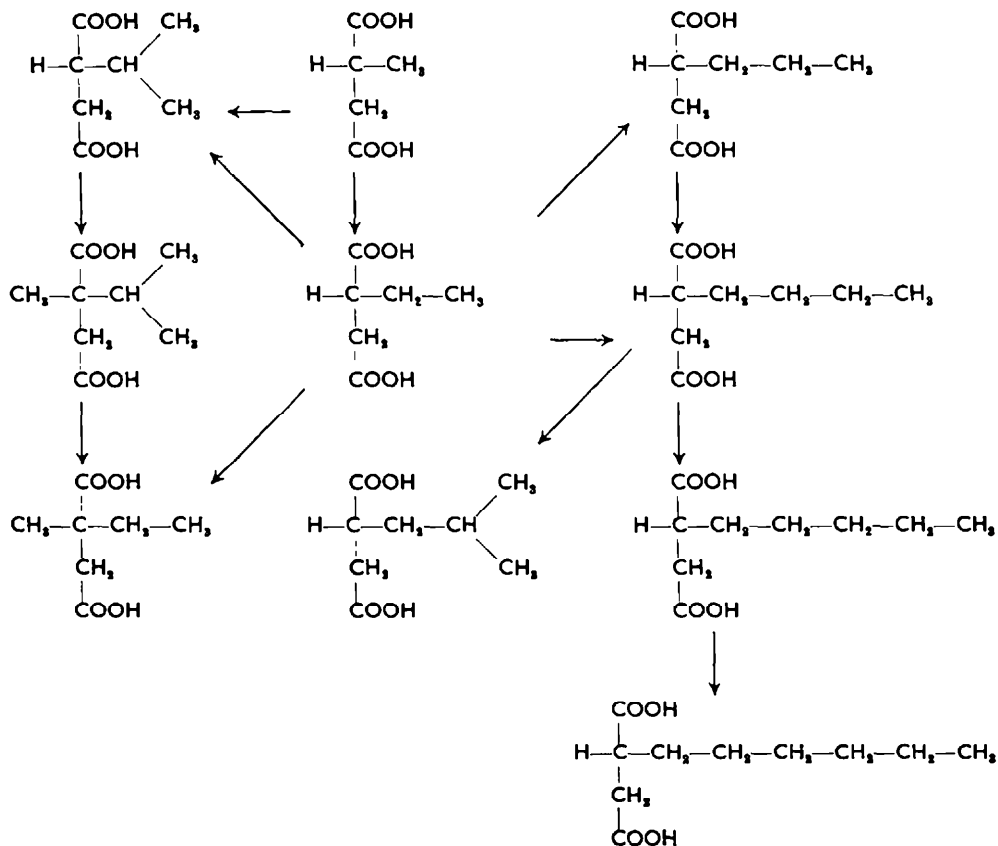


CHART 2. Configurations of dextro-rotatory alkylsuccinic acids correlated by the quasi-racemate method.

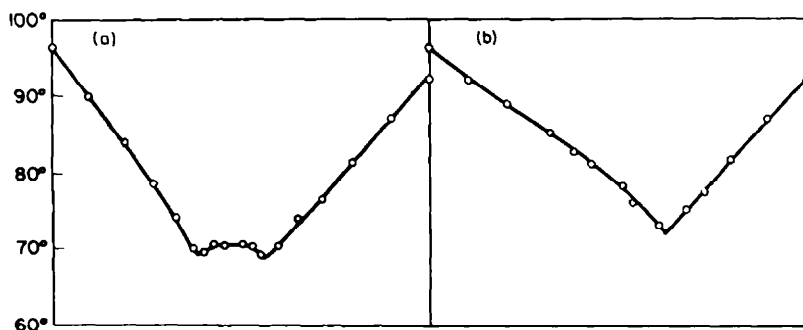


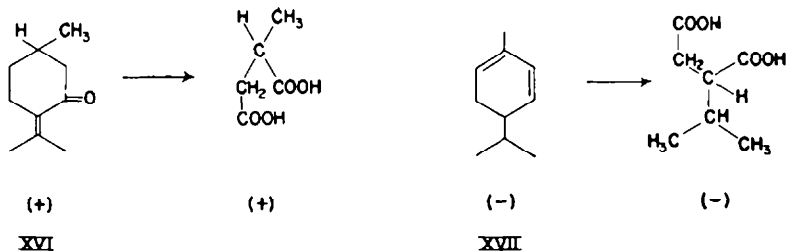
FIG. 10. (a) (-)-O-Methyl-malic acid and (+)-ethylsuccinic acid.
(b) (-)-O-Methyl-malic acid and (-)-ethylsuccinic acid.

Terpenes and related compounds

In 1941, Hückel gave a review of the steric relations inside the terpene group.³⁷ When the alkylsuccinic acids had been related to the glyceraldehyde system, the road

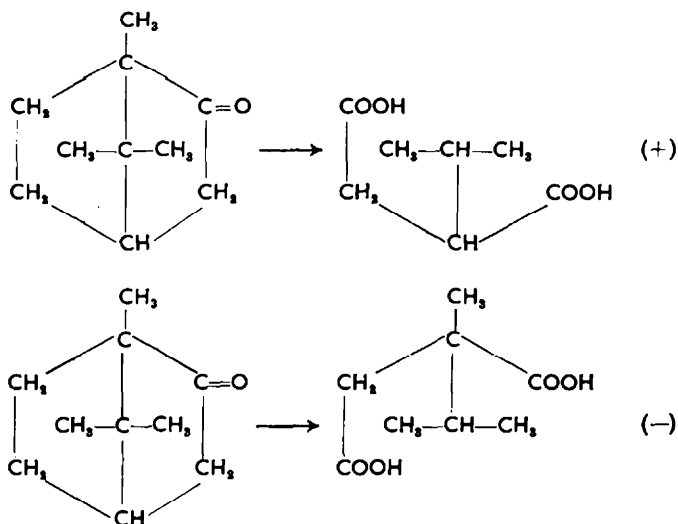
³⁷ W. Hückel, *J. Prakt. Chem.* [2] 157, 225 (1941).

was open for connecting the terpenes to this system, and here the preparative work of previous authors could be utilized. For instance, von Braun and Jostes had connected (+)-pulegone (XVI) with (+)-methylsuccinic acid by oxidative degradation.³⁸ On comparison with Chart 2 we find that the methyl group of the pulegone must be situated above the plane of the paper. In another case, Henry and Paget had obtained (–)-isopropylsuccinic acid from (–)-phellandrene (XVII).³⁹ Here we find that the



isopropyl group of the phellandrene must be situated above the plane of the paper.

It was also possible to connect the camphor molecule in this way. Different parts of this molecule could be connected with (+)-isopropylsuccinic acid and (–)-methylisopropylsuccinic acid as indicated below:



The first route, leading to the configuration at C_4 is rather complicated; (+)-camphor and (+)-fenchone are both related to (+)- α -pinene and the relative configurations at C_4 are known. On degradation of (+)-fenchone, Wallach obtained (–)-isopropyl-glutaric acid, which as we have seen above, is sterically related to (+)-isopropylsuccinic acid.^{39,40}

The configuration at C_1 was determined by Porath in a more direct way from camphoronic acid.⁴¹ The two methods give consistent results: if the (+)-camphor is

³⁸ J. von Braun and F. Jostes, *Ber. Dtsch. Chem. Ges.* 59, 1444 (1926).

³⁹ T. A. Henry and H. Paget, *J. Chem. Soc.* 70 (1928).

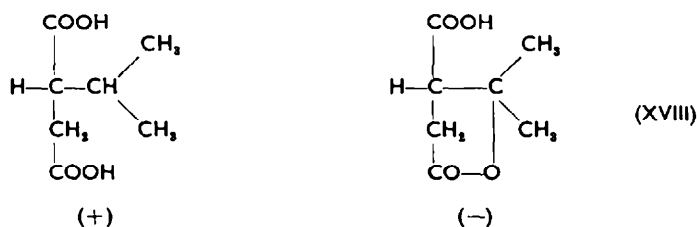
⁴⁰ O. Wallach, *Liebigs Ann.* 369, 63 (1909); 379, 182 (1911).

⁴¹ J. Porath, *Arkiv. Kemi* 1, 525 (1950).

written as above, the bridge must be situated behind the plane of the paper. A scheme of the absolute configurations of the principal terpenoid compounds has been given by Birch, who has also extended it to compounds of the carene group.⁴²

Various natural products related to alkylsuccinic acids

Only a few examples can be given. Oxidation of (+)-isopropylsuccinic acid gives (-)-terebic acid (XVIII) of corresponding configuration.⁴³

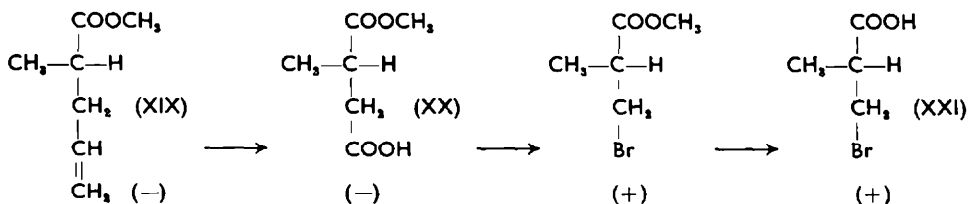


By the aid of terebic acid, Crombie and Harper could establish the configuration of two cyclopropane derivatives, caronic acid and chrysanthemum acid.⁴⁴

A small but important group of natural products is represented by isoleucine, methyl-ethylacetic acid and the anti-iso acids. These compounds were related to methylsuccinic acid by Ställberg-Stenhagen and Stenhagen.⁴⁵ They prepared (+)-methyl-allylacetic acid, which could be oxidized to (-)-methylsuccinic acid. On the other hand catalytic hydrogenation yielded (+)-methyl-propylacetic acid, which had been related to methyl-ethylacetic acid by Levene *et al.*⁴⁶ The configuration of isoleucine has later been confirmed by Trommel.⁴⁷

Ställberg-Stenhagen has also prepared the optically active half-ester of β -methylglutaric acid and connected it to methyl-succinic acid.⁴⁸ The half-ester has found extensive use for synthesis of optically active long-chain compounds, e.g. tuberculo-stearic acid.⁴⁹

Ställberg has recently found that careful oxidation of methyl methyl-allylacetate (XIX) gives a good yield of the half-ester of methylsuccinic acid (XX), which can be used for synthesis of various α -methylsubstituted acids, e.g. by Kolbe's electro-synthesis.⁵⁰ The Hunsdiecker reaction gave the ester of optically active β -bromoisobutyric acid (XXI), which can also be used for synthetic purposes.⁵¹



⁴² A. J. Birch, *Ann. Repts. on Progress Chem.* **47**, 192 (1950).

⁴³ A. Fredga, *Svensk Papperstidn.* **50**, No. 11B, 91 (1947).

⁴⁴ L. Crombie and S. H. Harper, *J. Chem. Soc.* 470 (1954).

⁴⁵ S. Ställberg-Stenhagen and E. Stenhagen, *Arkiv. Kemi, Mineral. Geol.* **24B**, No. 9 (1947)

⁴⁶ P. A. Levene and R. E. Marker, *J. Biol. Chem.* **91**, 77 (1931); **98**, 1 (1932).

⁴⁷ J. Trommel, *Proc. Acad. Sci. Amst.* **B 57**, 364 (1954).

⁴⁸ S. Ställberg-Stenhagen, *Arkiv. Kemi, Mineral. Geol.* **25A**, No. 10 (1947).

⁴⁹ S. Ställberg-Stenhagen, *Arkiv. Kemi, Mineral. Geol.* **26A**, No. 12 (1948).

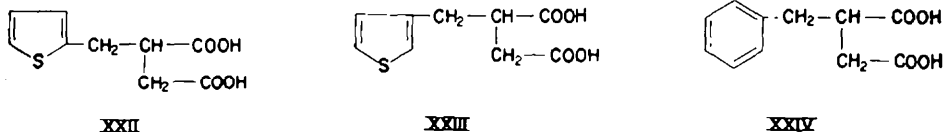
⁵⁰ G. Ställberg, *Arkiv. Kemi* **12**, 79 (1957); **12**, 153 (1958).

⁵¹ G. Ställberg, *Arkiv. Kemi* **12**, 95 (1957).

It is well-known that the methylsuccinic acid has been used for correlating steroid compounds to the glyceraldehyde system.

Thiophene derivatives

Optically active thiophene derivatives can usually be correlated to the analogous phenyl compounds. For instance, the two thenylsuccinic acids (XXII) and (XXIII) give quasi-racemates with benzylsuccinic acid (XXIV) and with each other.^{62,63} In



this case, the three racemates and the three quasi-racemates are all isomorphous and the curves representing the quasi-racemates are of an intermediate type. An example is given in Fig. 11. Other thiophene derivatives have been investigated and connected to the phenyl compounds by Pettersson and by Gronowitz, e.g. 2- and 3-thienylsuccinic acid and the thiophene analogues of mandelic acid.^{9,64,65-67}

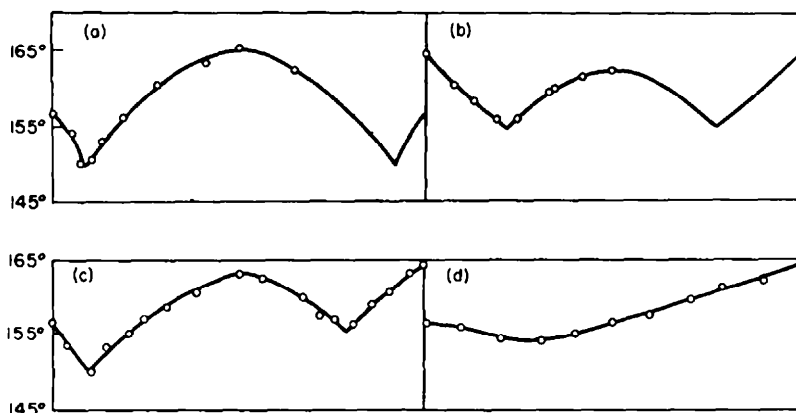


FIG. 11. (a) (+)- and (-)-XXII. (b) (+)- and (-)-XXIV. (c) (+)-XXII and (-)-XXIV. (d) (+)-XXII and (+)-XXIV.

By desulphurization with Raney nickel, the optically active thiophene derivatives can be converted into aliphatic compounds whose configuration is known previously. We have here a way to determine the absolute configuration of thiophene and benzene derivatives. Thus benzylsuccinic and phenylsuccinic acid were correlated to the alkylsuccinic acids.^{68,66} The configuration of mandelic acid could be confirmed by correlation with α -hydroxycaproic acid.⁶⁷

Synthetic plant growth regulators

The best-known natural growth regulator, indole-3-acetic acid or heteroauxin, is optically inactive and has no asymmetric carbon atom. Kögl found, however,

⁶² A. Fredga and O. Palm, *Arkiv Kemi, Mineral. Geol.* **26A**, No. 26 (1949).

⁶³ S. Gronowitz and S. Larsson, *Arkiv. Kemi* **8**, 567 (1955).

⁶⁴ K. Pettersson, *Arkiv Kemi* **7**, 39 (1954).

⁶⁵ K. Pettersson, *Arkiv Kemi* **7**, 347 (1954).

⁶⁶ S. Gronowitz, *Arkiv Kemi* **11**, 361 (1957).

⁶⁷ S. Gronowitz, *Arkiv Kemi* **13**, 87 (1958); **13**, 231 (1958).

⁶⁸ A. Fredga, *Arkiv Kemi* **6**, 277 (1953).

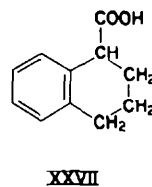
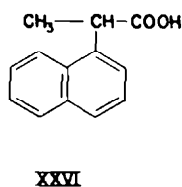
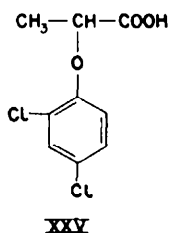
that the enantiomorphs of the next homologue, α -(indole-3) propionic acid, show an obvious difference in auxin activity.⁶⁹ Later he attributed this effect to different diffusion velocity in the plant.⁶⁰ Similar observations on optically active synthetic growth regulators were reported by several authors and now numerous compounds of this type have been studied. In some cases, the difference between the enantiomorphs is rather small, in others one form may have a very strong auxin effect while the antipode is practically inactive or even an anti-auxin. The difference may also vary considerably with the test method used, and even if differences in transport velocity may play a role in certain cases, the steric effect is certainly more complicated. It is obvious that this effect must be important for the understanding of the growth-regulating mechanism; the optically active compounds form a more subtle and more specialized instrument than the natural heteroauxin.

The synthetic growth regulators studied in Uppsala belong to three different types.

(1) α -Aryloxy-carboxylic acids, e.g. 2,4-dichlorophenoxy-propionic acid (XXV). (A certain effect is also found if the oxygen is replaced by NH, S or CH₂).

(2) α -Aryl-carboxylic acids, e.g. α -(1-naphthyl) propionic acid (XXVI). This group also includes the indole-3-propionic acid.

(3) Certain bicyclic acids with partially hydrated ring system, e.g. indane-3-carboxylic acid or 1,2,3,4-tetrahydro-1-naphthoic acid (XXVII).



In the first group, mainly investigated by Matell⁶¹⁻⁶³, the tendency to form quasi-racemates is very pronounced. All acids investigated could be correlated to one or more of the others and the possibilities of cross-checking are numerous. For instance the unsubstituted phenoxypropionic acid gives quasi-racemates with the acids having F, Cl, Br, I and CH₃ in para-position to the oxygen^{10,62} and also with the 2-naphthoxypropionic acid. The latter acid gives quasi-racemates with many other acids, among them 1-naphthoxy-, 2,4-dichlorophenoxy- and 3,4-dichlorophenoxy-propionic acid. These acids represent very interesting material for studying different types of diagrams and the decreasing stability of the quasi-racemates when the difference between the components increases. The absolute configuration was determined by the aid of the 2,4-dinitrophenoxy-propionic acid, which could be synthesized either from optically active lactic acid and 2,4-dinitrochlorobenzene or from phenoxypropionic acid by nitration. In all cases, the forms having higher auxin activity than their enantiomorphs were sterically related to D-(—)-lactic acid. The same holds good for

⁶⁰ F. Kögl, *Naturwissenschaften* 25, 465 (1937).

⁶¹ F. Kögl and B. Verkaaik, *Z. physiol. Chem.* 280, 167 (1944).

⁶² M. Matell, *Stereochemical Studies on Plant Growth Substances*. Thesis, Uppsala (1953). Also in *Kgl. Lantbruks-Högskis Ann.* 20, 205 (1953); and quoted references.

⁶³ M. Matell, *Arkiv Kemi* 7, 437 (1954).

⁶⁴ M. Matell, *Arkiv Kemi* 8, 79 (1955).

the 2,4,5-trichloroanilino-propionic acid, which could be correlated to the trichlorophenoxy compound;⁶⁴ these acids form a very beautiful example of a quasi-racemate diagram (Fig. 12). It should perhaps be pointed out that arylamino acids having greater auxin effect than their enantiomorphs are sterically related to the "unnatural" amino acids.

The acids of the second group have been studied principally by Sjöberg.⁶⁵ By the quasi-racemate method they could be correlated to each other and to the hydratropic (α -phenylpropionic) acid, whose configuration has been established by several

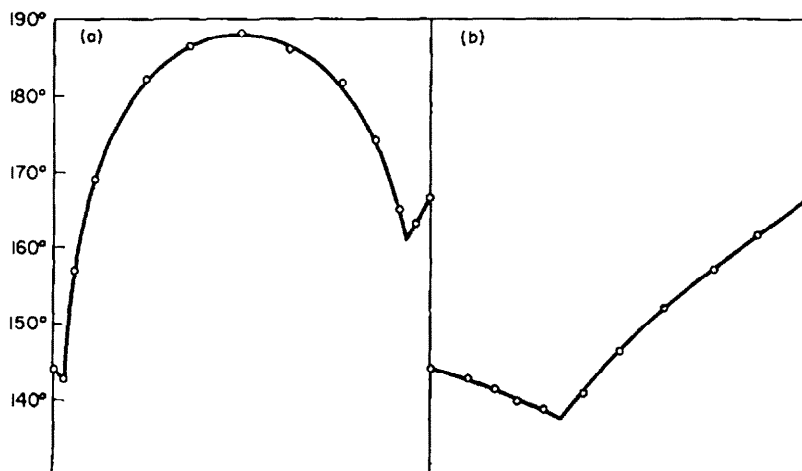


FIG. 12. (a) (—)Trichlorophenoxy-propionic acid and (+)-trichloroanilino-propionic acid.
(b) (+)-Trichlorophenoxy-propionic acid and (+)-trichloroanilino-propionic acid.

authors (Chart 3). An example of the diagrams is given in Fig. 13: the maximum is overlapped and the curve may at first sight be mistaken for a diagram of the simple eutectic type. A more thorough investigation revealed the existence of a separate curve branch and the existence of the quasi-racemate could be confirmed by X-ray analysis.

The absolute configuration could be checked by degradation of the (+)-thionaphthyl-2-propionic acid. On desulphurization with Raney nickel and subsequent ozonization it yielded (+)- α -methylglutaric acid. The forms having greater biological activity have analogous configuration and are all dextrorotatory (in ethanol solution). The acid XXVI forms a racemate of unusual stability, melting 80° higher than the enantiomorphs, and this acid has a central position in the chart.

Some bicyclic acids of the third group have by synthetic methods been correlated to phenylsuccinic acid.⁶⁶⁻⁶⁹

In the first and second group it is obvious that the higher biological effect is connected with a certain sterical configuration, and in the author's opinion conclusions as to the configuration of the antipodes of such acids can be drawn from the

⁶⁴ A. Fredga, *Arkiv Kemi* 11, 23 (1957).

⁶⁵ B. Sjöberg, *Arkiv Kemi* 13, 1 (1958); and quoted references.

⁶⁶ A. Fredga, *Chem. Ber.* 89, 322 (1956).

⁶⁷ L. Westman, *Arkiv Kemi* 12, 161 (1958).

⁶⁸ T. Mitsui, *J. Agr. Chem. Soc. Japan* 25, 526 (1952).

⁶⁹ K. Kawazu, T. Fujita and T. Mitsui, *J. Amer. Chem. Soc.* 81, 932 (1959).

⁷⁰ M. Matell, *Arkiv Kemi* 6, 355 (1953).

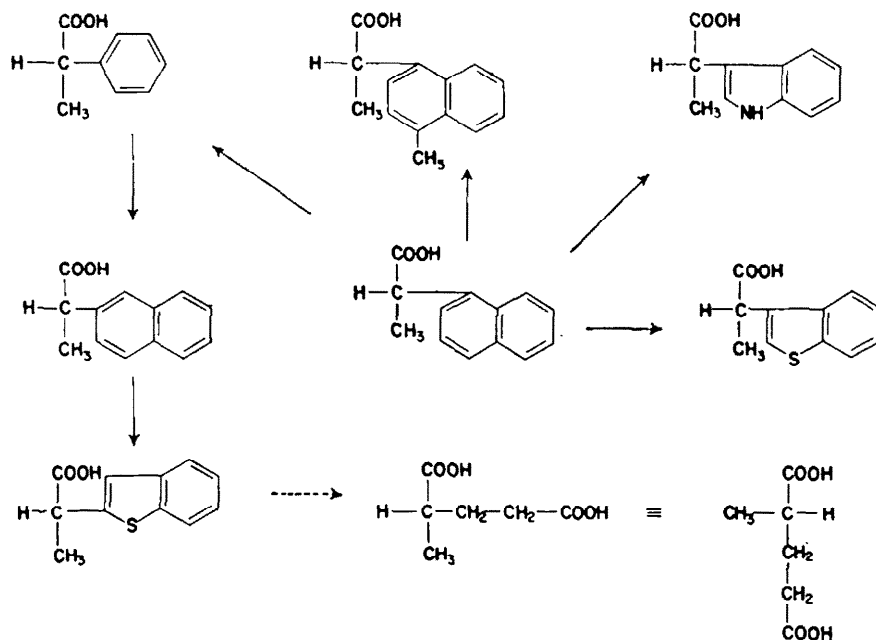


CHART 3. Configurations of dextrorotatory arylpropionic acids correlated by the quasi-racemate method. The broken pile indicates chemical correlation by degradation.

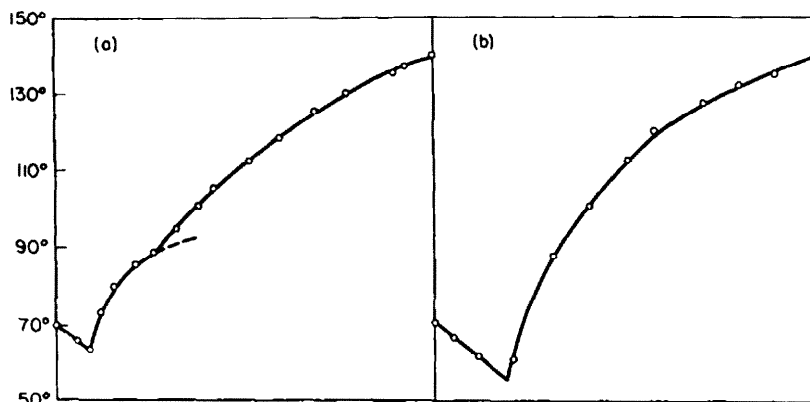


FIG. 13. (a) (-)- α -(Naphthyl-1) propionic acid (XXVI) and (+)- α -(indole-3) propionic acid, (b) (+)- α -(Naphthyl-1) propionic acid and (+)- α -(indole-3) propionic acid (B. Sjöberg).

difference in biological activity. The material of acids of the third group is still too scanty to permit any general conclusions.

As seen above, the quasi-racemate method is often used in combination with purely chemical methods, and such investigations will certainly play an important rôle in future work. Here sulphur compounds may render good service. Sulphur-containing groups are easily introduced in various molecules and afterwards the sulphur can be removed in different ways, e.g. by Raney nickel. Sulphur-containing asymmetric systems of known configuration can also be used for synthesizing larger molecules, with which sulphur-free systems may give quasi-racemates.

In the author's opinion, the quasi-racemate method is very reliable; when it gives an answer to a question of configuration, this answer is trustworthy. On the other hand, it often happens that no quasi-racemate is obtained though the possibilities may be judged as favourable. Nature keeps its secrets. It cannot be denied, that the work with this method has an element of gambling, but this makes it more thrilling and the odds are fair.

It must, however, be borne in mind that not every molecular compound between optically active substances can be regarded as a quasi-racemate. For a better understanding of the conditions for formation of racemates and quasi-racemates, a systematic investigation of the crystal structures of such compounds would be of great interest. Such studies might also throw light upon the sterical and polar factors responsible for the formation of molecular compounds and also upon the general conditions for interaction between asymmetric molecules. In this direction some work has been done, but much remains to do.