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THE STEREOISOMERS OF α, β, γ- TRIMETHYLGLUTARIC ACID

A Thesis

by

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History of Stereo-isomerism

Chevreul's definition, given in 1823, that a chemical species is a collection of individuals identical in the nature, the proportion, and the arrangement of the elements, was sufficiently demonstrated to justify its general acceptance. In 1844, however, an observation made by Mitscherlich seemed to contradict Chevreul's statement. In that year Biot (1) submitted to the Academie des Sciences a communication containing a note from Mitscherlich, which described as identical the properties manifested by sodium ammonium tartrate and its corresponding paratartrate or racemate, except that they differed in their effects upon polarized light. Mitscherlich's note concluded thus: "Yet, here the nature and number of the atoms, their arrangement and distances are the same in the two substances compared." Louis Pasteur (2), then a discerning student in the École Normale, sensed a contradiction of terms in this statement, and inferred that Mitscherlich must be in error, but not until 1860 was he ready to prove the truth of his deduction.

In the meantime, Pasteur strengthened his knowledge of crystal structure by diligently repeating the work of M. de la Provostaye (3) upon the crystalline forms of the salts of tartaric and racemic acids. In measuring the crystals he observed that while all the active tartrates studied had hemihedral faces, the racemates did not, and that while the tartrates in solution manifested rotative

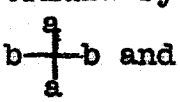
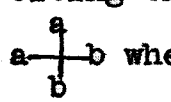
power, the racemates were optically inactive. He knew, moreover, that sometime previously, Herschel had shown that crystals having a certain arrangement of hemihedral faces deflected the plane of polarized light, and that other crystals having hemihedral faces in the reverse position deflected the plane of polarized light in the opposite direction.

Fortified with these data, Pasteur (2) undertook a closer examination of Biot's sodium ammonium salts. He found that not only the tartrate crystals were hemihedral, but, in this particular case, the racemate crystals were also hemihedral. He observed, moreover, that while all the tartrate crystals were hemihedral in the same way, the racemate crystals were hemihedral in two different ways. By a careful hand separation of the racemate into right and left hemihedral crystals, he obtained two forms of salts which in solution affected polarized light: the one rotating its plane to the right, the other to the left.

The contributions of Malus, Arago and Biot had already established the fact, that there is an actual relation between crystalline structure and the deviation of plane polarized light. Pasteur's investigation now compelled the recognition of a relation between the molecular structure of a substance and the external character of that substance, or — to modify Mitscherlich's statement — there is a difference in the spatial arrangement of the atoms of these isomeric molecules.

From the material evidence of right and left hemihedral crystals, Pasteur could only conclude that the molecules of the tartaric acids are asymmetric, in the sense that they are non-superable images: that the molecule of the left tartaric acid has its atoms arranged in an order inverse to that of the right; and that an equal mixture of the two forms the racemic or inactive variety. Later he identified a fourth variety which is optically inactive, but not racemic. From these conclusions Pasteur deduced two ways of recognizing molecular asymmetry: (1) by a non-superposable hemihedry, and (2) by the optical rotatory property of the substance in solution. Influenced by the fact that these two characteristics are manifested by many natural products, Pasteur stated that in order to synthesize an optically active compound, a natural product which is optically active must be used as the initial substance. This dictum, however, proved to be an unreliable rule, for—as was pointed out by LeBel in 1874—often the initial activity disappeared or changed in the course of a preparation. LeBel [4] offered a more dependable proposition based upon the orientation in space of atoms and atomic groups about the carbon atom. He pictured the carbon atom with its adjacent groups dispersed over a sphere, or at the vertices of a tetrahedron, or as material points in space. He made it clear that a carbon atom is asymmetric only when all the adjacent groups differ from one another.

In the same year (1874)—almost the same month—van't Hoff [5] published a memoir dealing with the same

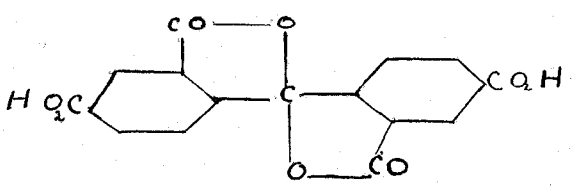
subject and in much the same way, but while LeBel based his principle on Pasteur's findings, van't Hoff built his theory on Kekule's concept of the quadrivalency of carbon. In 1863, Wislicenus had synthesized an ethylene lactic acid which he later discovered to be present with an analogous optically active acid in Liebig's paralactic acid. Upon thorough investigation, he discovered the existence of four of these isomeric acids. The fact that at the time no theory could explain the structural differences of these acids, drew from Wislicenus (6) the following statement: "If it is once granted that molecules can be structurally identical and yet possess dissimilar properties, it can only be explained on the ground that the difference is due to a different arrangement of their atoms in space." This remark inspired van't Hoff to investigate the nature of the difference in arrangement. Like LeBel he conceived the idea of a tetrahedral model, but he adhered to this idea more consistently than did LeBel. He justifies the need of a space formula by citing the theoretical possibility of such isomers as  and  when represented in one plane, while they have no existence in nature, and cannot be represented by space formulas. Both Le Bel and van't Hoff demonstrated their theory as applicable to numerous optically active organic compounds.

The theory of differentiation in atomic arrangement is not as original or revolutionary as it may seem. In 1869 Rosenthiehl had represented benzene by six tetrahedra, and

Paterno had explained the isomeric bromoethylenes by tetrahedral groupings. In 1873 Gaudin in his Architecture du Monde had expressed the same idea. Yet to Le Bel and van't Hoff is due the honor of having correlated the work of Pasteur and Paterno, and of having evolved from all previous data a logical and workable theory.

Theory of Stereo-isomerism

Le Bel and van't Hoff defined the condition necessary for asymmetric structure in organic compounds as the presence of four atoms or of four atomic groups, all structurally different and attached to the same so-called "asymmetric carbon atom." The subsequent discovery of compounds possessing no asymmetric carbon atom, but capable of being resolved into their enantiomorphously related isomers necessitated a more specific criterion of asymmetry. The diketo-dilactone of benzophenone 2, 4, 2', 4' tetracarboxylic acid [7] is an example of this need of a more comprehensive definition of asymmetry, for although this compound apparently possesses no asymmetric carbon atom, it has been resolved into its optical antipodes. Its formula

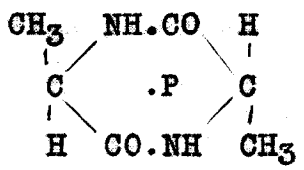


indicates two identical groups symmetrically arranged around the central carbon atom, but a space model would reveal the groups lying in different planes, a fact which destroys the apparent symmetry.

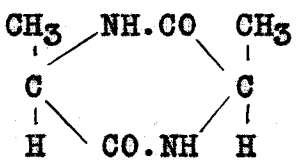
Elements of Symmetry

Modern theory considers a compound capable of optical activity when its spatial molecular arrangement lacks the following elements of symmetry:

(1) a center of symmetry; a point within the system through which straight lines may be drawn from any given group to an identical group. Such a point, P, is present in the trans diketodimethyl piperazine, I, and is lacking in its cis isomer, II.

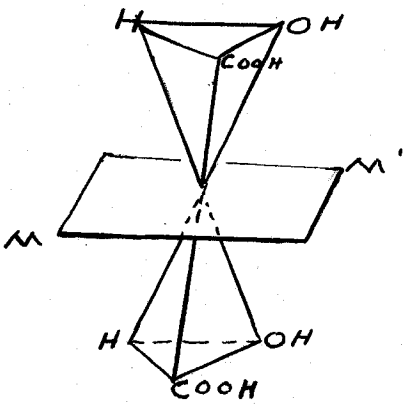


I trans-symmetrical



II cis-unsymmetrical

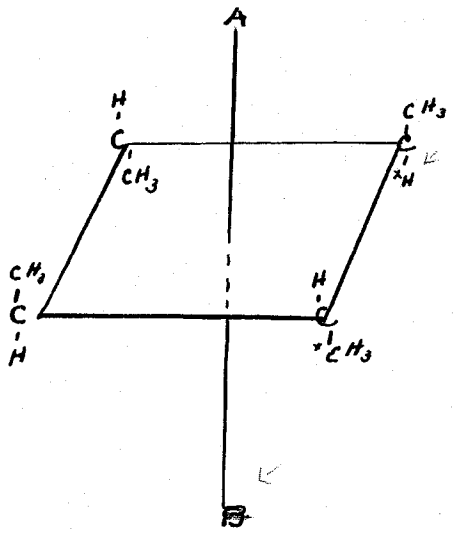
(2) a plane of symmetry; a plane which divides the system into two halves, that are mirror images. MM' exemplifies this element of symmetry, and divides meso tartaric acid symmetrically.



(3) An axis of symmetry:

(a) The ordinary axis of symmetry, which does not exclude the possibility of a separation of the compound into its optical antipodes, as is demonstrated by the resolution of cis 1:4 diketo-2:5 dimethyl piperazine shown above in II.

(b) The alternating axis of symmetry which excludes the possibility of optical resolution. Such an axis is represented by AB in the accompanying diagram.



If *CH_3 is rotated 90° in a plane parallel to that of the carbon atoms, it will arrive at the position occupied by *H, and be directly opposite its mirror image. This is true of all of the groups in the compound (9). The compound cannot be resolved even though it contains four asymmetric carbon atoms. This type of

symmetry may be classified under (2), where a plane of symmetry is passed diagonally through two vertices and perpendicular to the plane of the carbon ring, dividing the figure symmetrically.

Compounds having their groups dispersed about an atom of sulphur, tin, silicon, nitrogen, phosphorus or cobalt, and manifesting asymmetric arrangement, have been separated into their active forms. Thus it becomes evident that carbon, though very extensive in application, is only a special case of asymmetry. Louis Pasteur had a much broader conception of this phenomenon when he described "molecular" asymmetry as the prerequisite for optical activity, and so included all types of enantiomorphous compounds. Le Bel and van't Hoff, on the other hand, though formulating a limited theory, offered a method of more immediate value, at that time, for the prediction and identification of stereomeric forms.

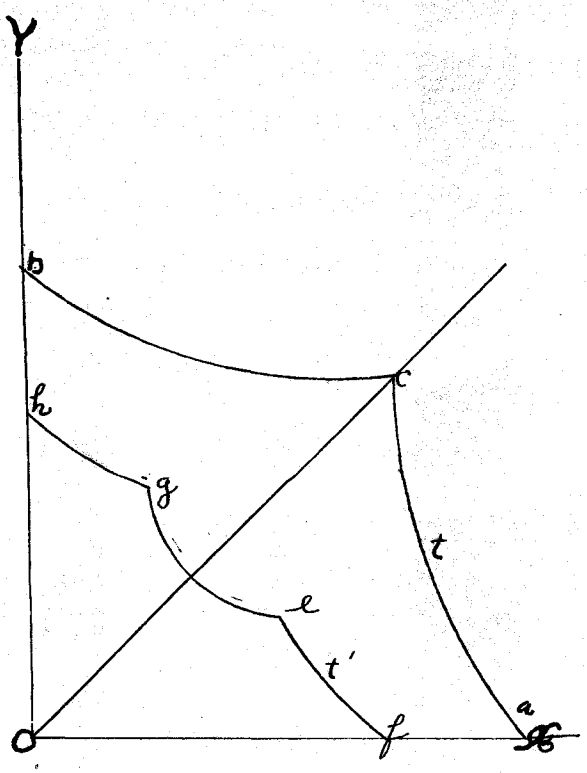
Solubility Relations

Kipping and Pope [10] classified externally compensated asymmetric substances as racemic compounds, racemic mixtures and pseudoracemic mixtures. They characterized the racemic compound as differeing widely in its crystallographic properties from its active components, and the pseudoracemic as similar in this respect to its active components.

The identification of an inactive substance as a racemic compound or mixture has been greatly facilitated by the solubility and freezing point relations as presented by

Bakhuis Roozeboom. Kenrieks [11] collected data for the change in solubility relations of the active and racemic ammonium bimalates, upon the addition of crystals of the active forms. Roozeboom [12] used this information in constructing the phase diagram for a three component system of water, d- and l- forms, and proposed it as a method for determining whether an inactive substance is a racemic compound or a racemic mixture.

The accompanying diagram represents upon the X and Y axes respectively the amounts of d- and l- forms in solution. The curves bc and ca express the solubilities of the two components at a temperature t. If a racemate forms at a temperature t', the curve takes the form hgef, the portion ge representing the racemate, and hg and ef, the two enantiomorphs.

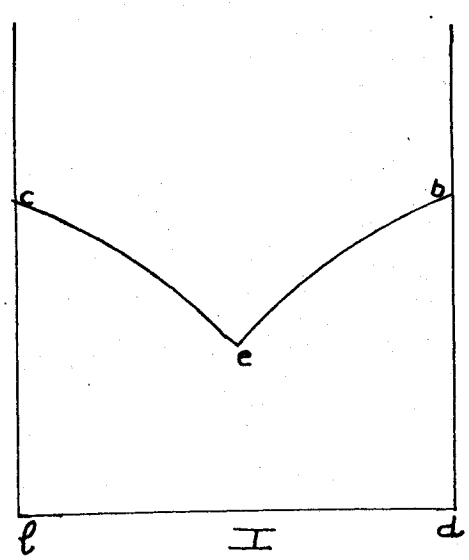


If the inactive solution contains an equimolecular mixture of dextro and laevo forms in contact with active solid, the solubility will not alter if one or other enantiomorph is added. If the inactive solution contains a racemate, the addition of another solid phase will alter the solubility relation and the solution will prove optically

active upon polariscopic investigation.

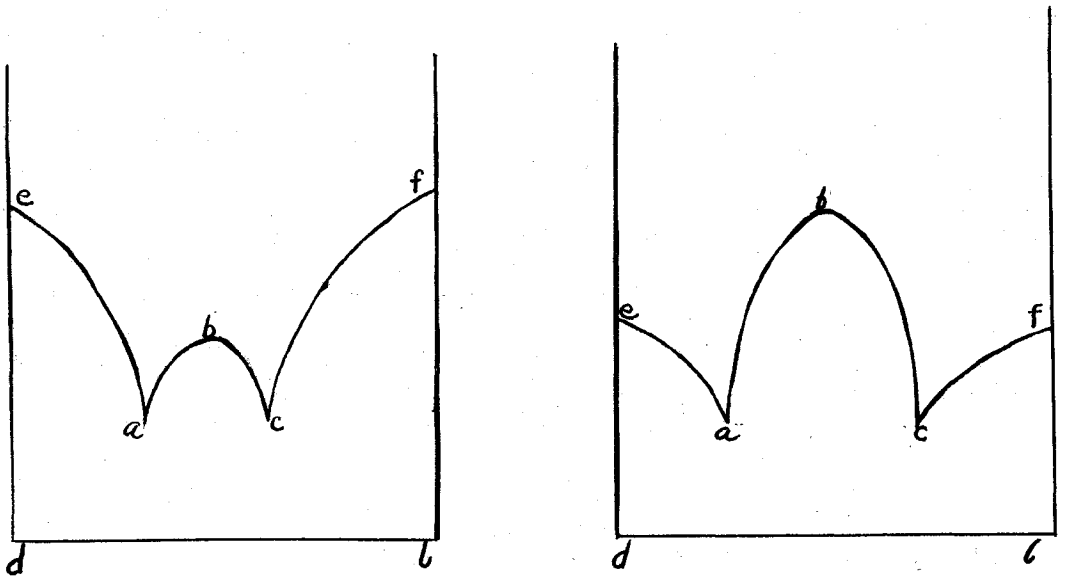
Freezing Point Relation

Another valuable criterion of the nature of an inactive resolvable substance is based on the freezing point relations and explained by the phase rule method of Bakhuis Roozeboom (12). If the freezing point of the doubtful substance is determined and then compared with the mixed freezing point of the doubtful substance, and one of the enantiomorphs, the following rule applies: (1) a rise in freezing point indicates a mixture, and (2) a lowering in freezing point indicates a racemic compound. A study of the freezing point curves clarifies these relations:



(1) If c represents the concentration of the l-form, and if small quantities of the d-form are added, the temperature lowers until equimolecular amounts are present, at e. If more of the d-form is added the freezing point will rise until it attains its original value.

(2) If b represents the freezing point of a racemic compound, and e and f the freezing point of the enantiomorphs, the curves of the accompanying phase diagram indicate the change in the freezing point of the racemoid upon the addition of either enantiomorph.



In diagram II is shown the freezing point curve when the racemoid freezes at a temperature lower than do the enantiomorphs; and in III, when the racemoid freezes at a higher temperature.

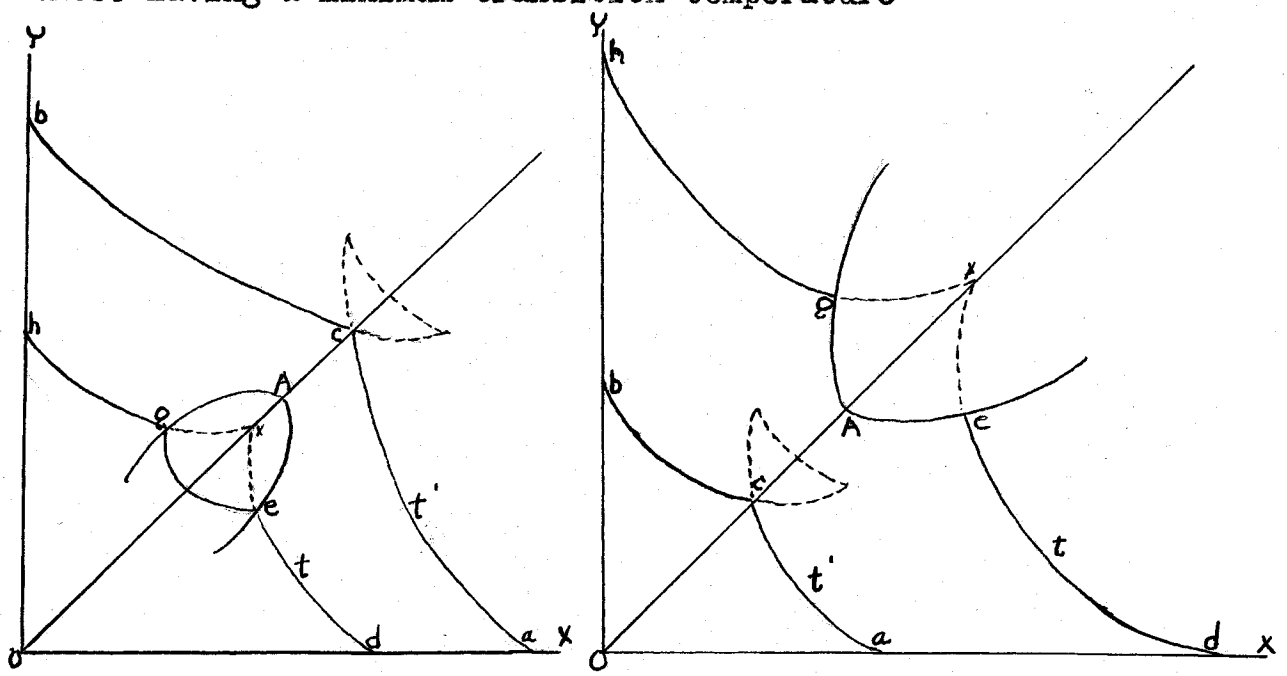
Optical Resolution

Fission of a racemoid is one of the oldest and most important phases of stereochemistry. Pasteur in his original researches outlined three methods of resolution of externally compensated compounds, and later workers have added but little to his methods.

(a) The first method, fission by simple crystallization is applicable only when the transition temperature of the compound lies near the crystallization temperature. If the transition temperature is said to be a "maximum", then above

that temperature the racemate cannot exist as such, but changes into an agglomerate of dextro and laevo particles. If on the other hand, the transition temperature is said to be a "minimum", then below that temperature, the racemate cannot exist as such.

The mixed crystals appearing under these conditions may be separated by hand into dextro and laevo forms. By imposing Roozeboom's phase diagram (12) for the transition state upon his solubility diagram, we obtain a set of very elucidating curves (13). Diagram I applies to racemates having a maximum transition temperature, and diagram II, to those having a minimum transition temperature



The curve, bca, is the solubility isotherm at a temperature t', of the three phases in equilibrium, namely solvent and two solid phases, the dextro and laevo forms.

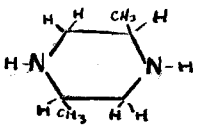
The curve hged is the solubility isotherm at a temperature t, where the racemate ge forms. f represents the optical inactivity of the solution which is saturated with respect to the racemate. x is an optically inactive point in a metastable region and represents an equilibrium between a mixture of the active components in solution, and the racemic substance. At A, the transition point, all phases may exist in equilibrium, but in case I the racemate cannot exist above this point, while in case II it cannot exist below it. Ag represents all solutions which with an increase in temperature are saturated with respect to the racemate and the laevo component; and similarly Ae represents all solutions saturated with respect to the racemate and the dextro component.

(b) The second method, <u>fission by living organisms</u>, is specific and has the added disadvantage of a loss of one half of the material in the selective consumption by the bacteria.

(c) <u>Fission by chemical means</u> is the third and most general method. Here is effected the combination of a racemic acid with an optically active base, or of a racemic base with an optically active acid. The d- and l- tartaric acids [14] and the d- and l- malic acids have been used extensively in the fission of racemic bases, but in recent times camphor sulphonic acid and bromo-camphor sulphonic acids [15]—both synthetic products—have been used to great advantage because of their great optical activity and high molecular weights. The naturally occurring alkaloids,

cinchonine, strychnine, brucine, etc. had no rival synthetic bases, until the recent preparation of d- phenyl ethyl amine [16] and hydroxy-hydrindamine [17]. Compounds resolved by these natural or synthetic substances may in their turn, serve in the resolution of other externally compensated compounds. Thus d,d_1 -dimethyl succinic acid [30] was resolved by triethylene diamine cobalic bromide, $Co(NH_2.CH_2.CH_2.NH_2)_3Br_3$, an active substance, previously resolved by its d-bromo tartrate [18].

By the addition of an active acid or base to a racemoid, salts of the types, d-acid l-base and l-acid d-base, form. Since the new substances are not enantiomorphous, their physical properties will differ, and a separation may therefore be accomplished. The efficiency of the most common method of separation, fractional crystallization, may be increased by special manipulation, varying with the cases considered. For certain compounds, the precipitation of the less soluble form takes place readily when only one half of the required amount of the active agent is added to the racemoid, the more soluble form of the racemoid remaining in solution. Another effective modification of fractional precipitation consists in discontinuing an esterification when only one half of the time required to complete the reaction has expired. Within this time the more reactive form separates as an ester, α-ethoxy propionic acid after a partial esterification with d-menthol [19] separated in the dextro form, the laevo remaining in solution. "Seeding" of a racemoid, or even the addition of a crystal of

the same system as that to which the active forms belong, hastens separation of one of the enantiomorphs. Certain compounds, which according to theory are resolvable, have resisted all attempts to separate them. Stoehr (20) prepared a compound, 2:5 dimethyl piperazine,  , which he described as existing in cis and trans forms. In order to establish the formulas of this compound, Pope and Peachey (21) undertook its resolution. They carried out an exhaustive series of fractional crystallizations of both cis and trans forms, combined with such optically active compounds as sodium ammonium d-tartrate, several active camphor sulphonic acids, camphor sulphanates, etc. but met with no success. Other compounds of this type are being studied.

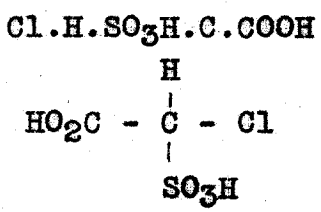
The resolution of a compound is rendered difficult or impossible by the following conditions:

(1) formation of an oil or syrup instead of crystals when subjected to fractional crystallization. This may be due to presence of impurities, improper solvent or coexistence of several isomeric forms.

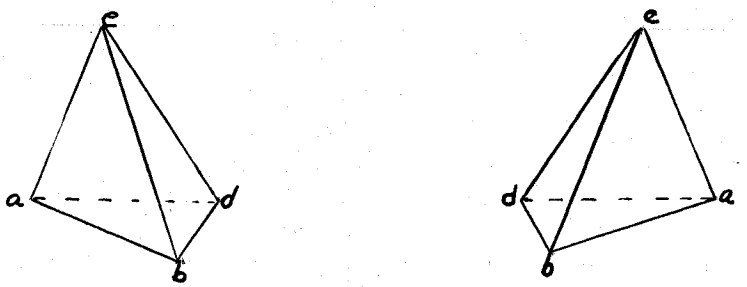
(2) lack of a sufficient difference in solubility, which condition allows both forms to be precipitated simultaneously.

(3) formation of partial racemoids (22) in the precipitate: that is, the optically active compound unites with the racemoid as a whole, and not with the separate enantiomorphs. In certain cases, the partial racemoid, at the transition temperature, will change into two different compounds, which, however, are not mirror images.

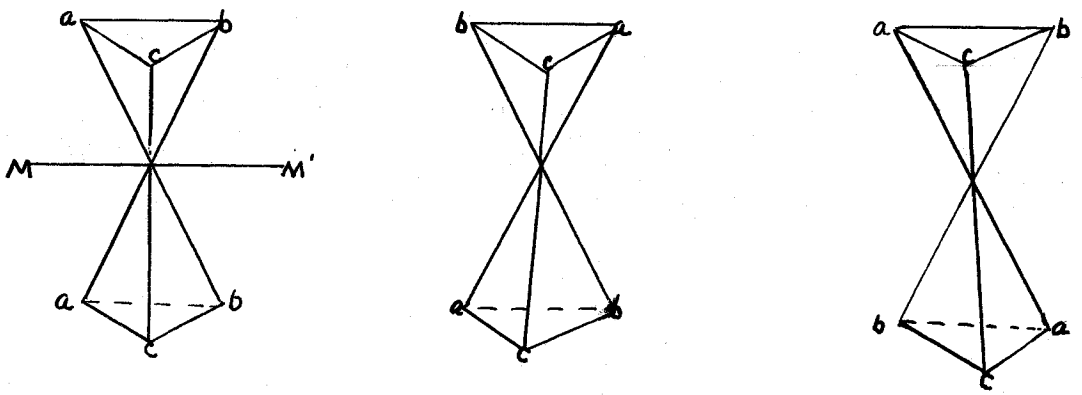
Types of Optically Active Compounds

A certain degree of molecular complexity was formerly considered as a pre-requisite for the manifestation of optical activity by enantiomorphous substances. Many unsuccessful attempts to resolve compound containing a single asymmetric carbon atom seemed to verify this theory. Chloro-sulpho-acetic acid,[23]  was reported resolved by means of strychnine and cinchonine, but Pope and Read [24] were unable to duplicate the resolution. In 1914 these two chemists reported an investigation of chloro-iodo methyl sulphonic acid [25], $Cl.I.CH.SO_3H$, whereby they proved conclusively that a compound containing a single carbon atom, to which are attached four different inorganic groups, is possessed of optical activity. Their data were not sufficiently quantitative to furnish standard values for the constants of rotation of chloro-iodo-methyl sulphonic acid. Within the last year, Read and McMath [26] have effected the complete resolution of this compound by the use of l-hydroxy-hydrindamine, and have determined its constants of resolution. Fluoro-chloro-bromo acetic acid, F.Cl.BrC.COOH, was reported by Swarts [27] as optically active, but the speedy decomposition of the free acid necessitated determining the rotation of the strychnine salt. An acid of greater complexity, but containing only <u>one</u> asymmetric carbon atom is dimethyl

glutaconic acid. It can exist in two isomeric forms, the "cis" or labile type, and the "trans" or stable type. The dimethyl glutaconic acid (28), $COOH.CHCH_3.CCH_3:CCH_3.COOH$ in the stable form has been resolved by several precipitations of its strychnine acid salt. The resolution of these simple compounds is in agreement with stereochemical predictions, according to which there exist dextro- and laevo- forms which by external compensation give the racemoid.



The system investigated by Louis Pasteur was more complex, two asymmetric carbon atoms being present. Such a structure accounts for two optically active forms, producing a racemoid, and for an inactive or meso form.



When, however, the two asymmetric carbon atoms differ structurally, this type of compound exists in two racemic forms.

The meso form is an internally compensated form, the upper and lower halves being mirror images. Forms II and III are mirror images, and when mixed in equal quantities, are externally compensated and optically inactive. Pasteur succeeded in isolating all three forms of tartaric acid (29). Derivatives of tartaric acids have been resolved, and some interesting methods employed: α, α' -dimethyl succinic acid (30), by means of triethylene diamine cobaltic salts; α -methyl succinic acid (31) through the use of quinine, which after forming a partial racemate, changed into active quinine salts above the transition point: and asparagine, upon the introduction of a crystal of glycocoll precipitated the less soluble form.

α, β -dimethyl glutaric acid, $COOH.(H.C.CH_3)_2.CH_2.COOH$, has a history and properties similar to the trimethylated glutaric acid, which is the subject of this research. Montemartini (32) obtained two acids from a condensation of ethyl sodium methyl malonate and chloro-butyrate. One was crystalline, melting at 63° and identified as α -methyl adipic acid: the other was a syrup, whose analysis indicated a dimethyl glutaric acid. Blaise (33) later prepared a solid acid, which from its synthesis and analysis he identified as α, β -dimethyl glutaric acid, melting at 82-83°. Thorpe and Young (34), in 1903, prepared an α, β -dimethyl glutaric acid, and obtained a syrup similar to that of Montemartini. Under no condition could they effect the crystallization of the acid. Finally, they prepared the anhydride and then the imide, a crystalline compound melting at 113°.

A crystalline acid was derived from the hydrolysis of the imide, and melted sharply at 87°. Thorpe and Young designated their acid as the "cis" form, and expressed a belief that it was identical with the α, β dimethyl glutaric acid prepared by Blaise. In the mother liquors, a syrup remained having the composition of a dimethyl glutaric acid, which under no condition would crystallize.

Still greater complexity is present in compounds of three asymmetric carbon atoms. If we designate the spatial configuration by + and -, and the carbon atoms by A, B and C, we obtain these modifications:

+ A	- A	+ A	- A	+ A	- A	- A	+ A
+ B	- B	+ B	- B	- B	+ B	+ B	- B
+ C	- C	- C	+ C	+ C	- C	+ C	- C
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)

Forms (1) and (2); (3) and (4); (5) and (6); and (7) and (8) are enantiomorphous pairs, and therefore produce racemoids.

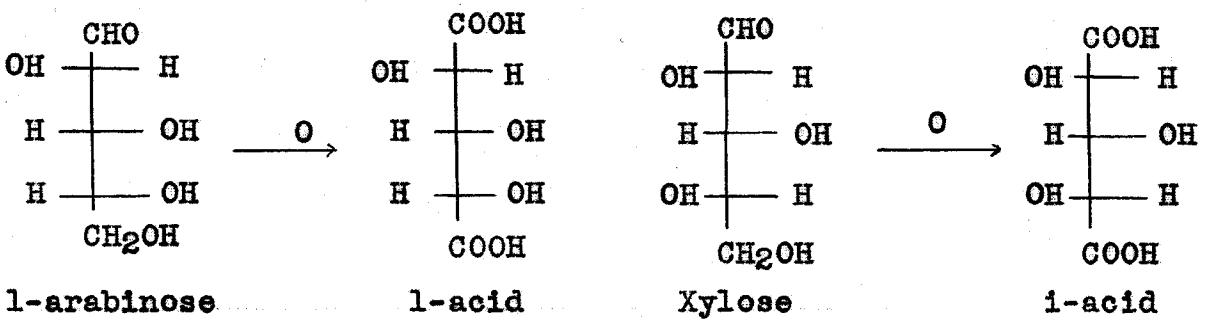
A special case of three carbon asymmetry, one with which this investigation is especially concerned, occurs when the two end groups have an identical structure. When these end groups have the same spatial arrangement, the central carbon is no longer asymmetric, and only two active forms are possible:

+ A	- A
o B	o B
+ A dextro	- A laevo

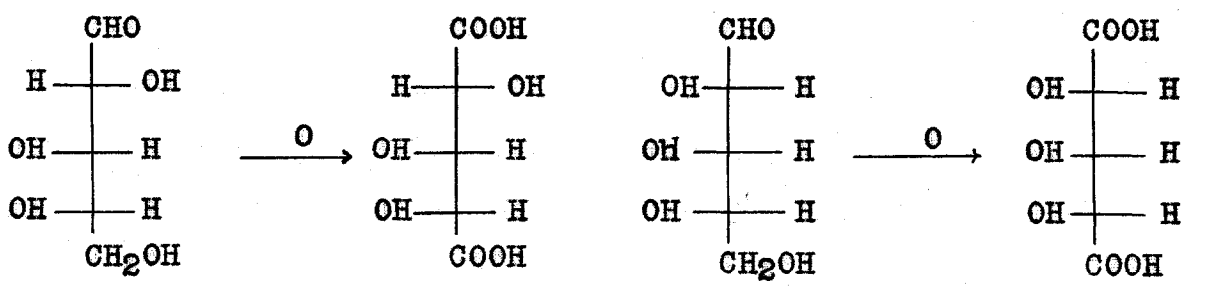
When the end groups have a different configuration, they neutralize each other's rotatory effect. The grouping around the central carbon atom is unsymmetrical, but does not convey optical activity to the compound. This phenomenon is called "pseudoasymmetry." Since two spatial arrangements of the groups around the central carbon atom are possible, two inactive or meso forms exist:

+ A	+ A
+ B	- B .
- A	- A
meso	meso

Trioxyglutaric acid is the only example of a pseudo-asymmetric compound possessed of three asymmetric carbon atoms known to exist in its four stereomeric forms. The structure of these compounds, moreover, has been greatly elucidated by the method of their preparation. Certain pentoses, whose formulas had been determined were oxidized by nitric acid and the resulting dicarboxylic acids isolated. Thus



l-arabinose l-acid Xylose i-acid



d-arabinose d-acid ribose i-acid

The following briefly tells the history of these acids.

Acid	Investigator	Melting Point	$[\alpha]_D^{20}$
l-trioxyglutaric	Kiliani and Fischer(35)	127°	-22.7°
d-trioxyglutaric	Ruff (37)	127°	+22.8°
r-trioxyglutaric	Ruff (37)	154.5°	
i-trioxyglutaric	Fischer (36)	145.5°	
i-trioxyglutaric	Fischer and Pilaty(38)	170°-171°	

Trimethyl Glutaric Acids

Chemical theory indicates the existence of four different position isomers of the trimethylglutaric acids. Four such acids have been isolated. They are:

(1) α, α, α ——————→ $COOH.C(CH_3)_2.CH_2.CHCH_3.COOH$ (39)

(2) α, α, β ——————→ $COOH.C(CH_3)_2.CHCH_3.CH_2.COOH$ (40)

(3) α, β, β ——————→ $COOH.CHCH_3.C(CH_3)_2.CH_2.COOH$ (41)

(4) α, β, α ——————→ $COOH.(CHCH_3)_3COOH$ (42)(43)

Recently α, β, α-(also called α, β, γ-) trimethylglutaric acid has been the subject of chemical controversy. F. E. Ray (42)(43) in an effort to identify an acid of doubtful structure prepared by Noyes and Skinner (44) and described by them as α, β, β trimethylglutaric acid, synthesized an acid whose analysis conformed to that of a trimethylglutaric acid, and whose method of preparation indicated the α, β, γ isomer. It melted at 134°.

Michael and Ross [45] in a study "On the Course of Addition of Sodium Enol Alkyl Malonic Esters to Alpha-Beta Unsaturated Esters" describe their preparation of an acid, which from analytical data they believed to be α,β,γ-trimethylglutaric acid. This acid was a syrup which resisted all attempts at crystallization. An imide [46] of this acid was prepared and isolated in crystalline form, melting at 90°. Upon hydrolysis it yielded a crystalline trimethylglutaric acid with a melting range of 115°-125°, and described by Micahel and Ross as the "cis" form. From the mother liquors a syrup was separated, and analyzed as a trimethylglutaric acid. This syrup, they designated as the "trans" α,β,γ,- trimethylglutaric acid, considering it as a single distinct form.

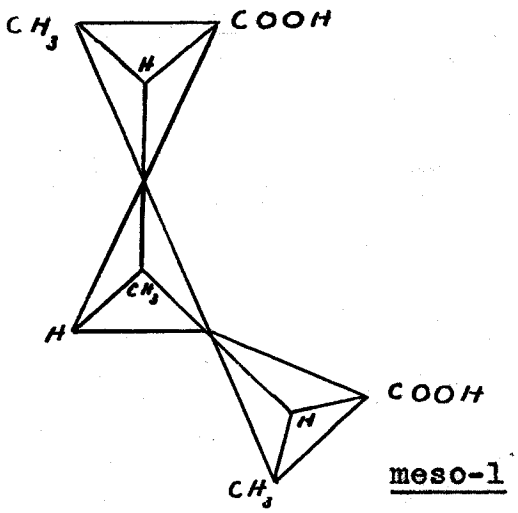
The different results obtained by F. E. Ray and by Michael and Ross influenced the latter to assume that Ray's acid was α,β,- dimethylglutaric acid, because the acid α,β,γ,-trimethyl-r-carboxyglutaric acid from which it was derived melted at 144°, and α,β,- dimethyl-r-carboxyglutaric ester was known to melt at 144°-145°. Ray [47] pointed out that α,β,- dimethylglutaric acid [46] obtained from α,β,γ-dimethyl-r-carboxyglutaric acid melted at 87°, while his acid melted at 134°. The existence of the four possible stereo-isomers of α,β,γ trimethylglutaric acid indicated by stereochemical theory, was suggested by F. E. Ray, and the possible identity of Ray's acid with that of Michael and Ross proposed. In a final retort, Michael and Ross [48]

advanced the criticism that Ray had prepared the tiglic ester used in his process from ethyl methyl malonic ester prepared by the ethylation and methylation of malonic ester, thus rendering a pure product improbable.

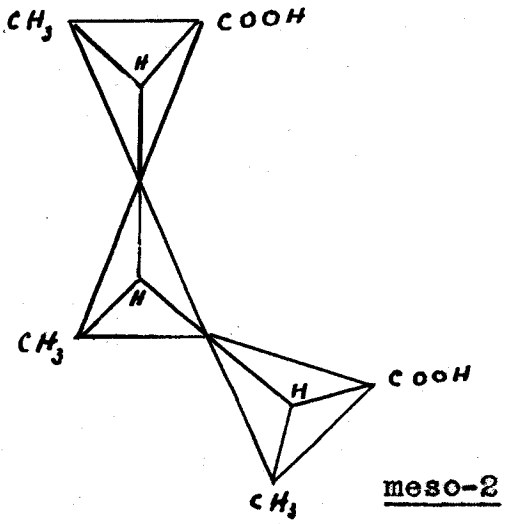
We offer no criticism on the method employed by Michael and Ross in separating "cis" and "trans" acids, for its effectiveness has been attested to by many successful applications (46). The readiness of their compound to form anhydrides is explained by the theory of Walden and Bischoff(49). On the basis of "mechanical" effects rather than "positive-negative" effects, Walden and Bischoff suggest that the same radical can act in different ways, depending on its position in the system of which it is a part: thus in certain cases, as the succinic and glutaric acids, the methyl group facilitates ring closure, while in other cases it impedes ring closure. To this we may add that the anhydride formations of the various stereomers occur with different velocities, so that the more reactive stereomer forms its anhydride first. This relation was demonstrated by Thorpe and Young (46) who found that by sustaining a sufficiently high temperature they would eventually obtain their entire acid as an anhydride. This last observation may explain the wide range in the melting point of Michael and Thorpe's "cis" acid, two or more stereomers with similar velocities of reaction being present.

A consideration of the acids previously separated into the "cis" and "trans" forms shows that there are only two possible inactive forms of each of these acids: $\alpha,\alpha,$-dimethyl and $\alpha,\alpha,\beta,\beta,$ -tetramethyl-glutaric acids have one racemic and

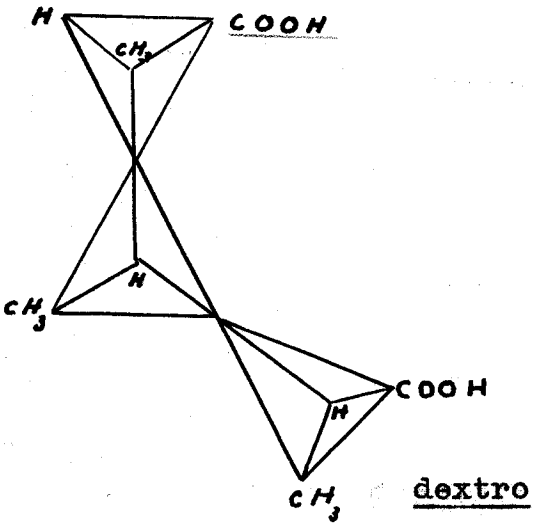
one meso form: α,β -dimethyl and α -methyl-β -isopropyl have each two racemoids. The other methylated acids, α,α,α' : α,α,β: α,β,β and α,α cannot be separated in this manner, since at most, they have only one racemic form. α,β,γ -trimethyl-glutaric acid is a more complicated case than any of the methylated glutaric acids heretofore prepared, for it has three stereomers, two of which are meso and one racemic, a condition analogous to the trioxyglutaric acids.



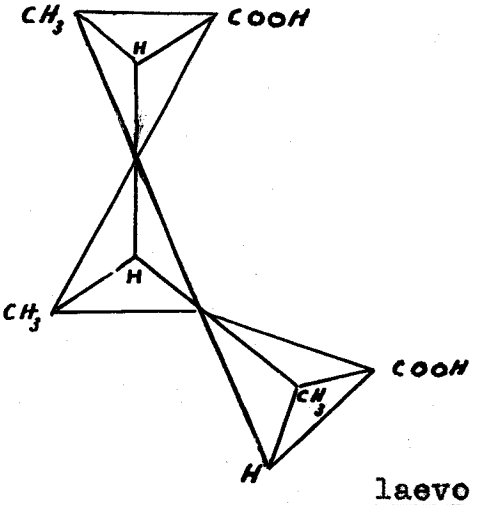
meso-1



meso-2



dextro



laevo

Although stereochemistry indicates the possibility of the two meso and one racemic α,β,γ -trimethylglutaric acids, it may happen that all forms cannot be isolated. According to a theory proposed by Michael (50) a preponderance of one isomer may result in a mixture of isomers due to its lack of free energy. That is, the greater the free energy, as determined by the heat of combustion, the less stable the compound. Hence it will change more readily to the stable form. A sufficient difference in free energy, therefore, could cause the elimination of the less stable form.

In our own research we have endeavored to gain information concerning the disputed points of α,β,γ- trimethyl glutaric acid. Each phase that we have investigated is reviewed separately, in the following:

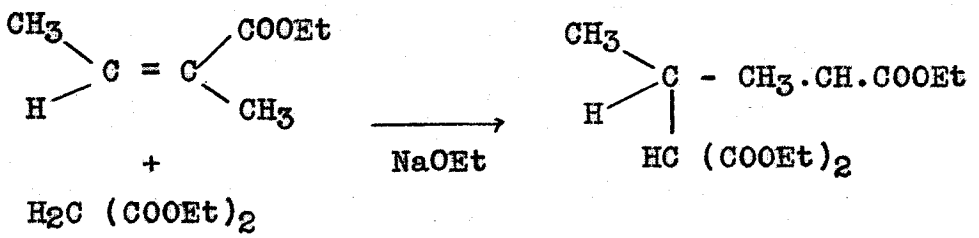
(1) The early attempts of F. E. Ray to synthesize α,β,γ -trimethyl-glutaric acid, from one mol of acetaldehyde and two mols of malonic ester and methylation of the product, were unsuccessful due to the formation of α,β,γ -trimethyl α,γ -dicarboxyglutaric acid

$$CH_3.CHO + 2H_2C(COOEt)_2 \longrightarrow (COOEt)_2CH.CHCH_3.CH(COOEt)_2$$

On decomposition the tetracarboxylic acid always gave a liquid of wide boiling range. The composition of the liquid had never been determined. We obtained some of this liquid by heating α,β,γ -trimethyl- α,γ -dicarboxyglutaric acid, melting point 190° (prepared by Paul E. Burchfield). A silver salt analysis excluded the possibility of a trimethyl glutaric acid. Qualitative tests showed that the original acid had

decomposed into formic, acetic, and butyric acids.

(2) In the preparation of our α,β,γ-trimethyl-glutaric acid we effected a condensation of tiglic and malonic esters, using sodium ethylate as the condensing agent.



The tiglic ester used in our reaction was in part an ester prepared from secondary butyl carbinol, and in part an ester prepared from tiglic acid, an Eastman product, which after recrystallization from water melted at 63°-64°. The physical properties of the two esters were almost identical and the final products prepared from them were the same.

The previous investigations found the use of cyano-acetic ester much more efficient than malonic ester. We used malonic ester and obtained yields as high as those formerly prepared from the cyano derivative. We used the same proportions of esters with 1/6 mole sodium ethylate but we also employed a very rigid technique to exclude all moisture.

(3) A portion of $\alpha,\beta,$ -dimethyl-r-carboxyglutaric ester was hydrolyzed and the resulting acid isolated in crystalline form, having a melting point of 144°. Since Michael and Ross assumed F. E. Ray's compound to be this acid, we ran a mixed melting point of it with a portion of F. E. Ray's α,β,γ trimethyl-r-dicarboxyglutaric acid. The drop in its melting point proved their lack of identity.

(4) The α,β -dimethyl-glutaric ester was methylated. On distillation under reduced pressure, a fifty percent yield of the α,β,γ trimethyl-glutaric ester was obtained; the remaining fifty percent had retrogressed into the original esters. The trimethylated ester gave in every case a variation of one degree in the boiling point. To exclude any doubt as to the success of our methylation we checked our results by determination of density and refractive indices and by silver salt analyses of the corresponding acids. After hydrolysis by lengthy refluxing with excess potassium hydroxide, α,β,γ-trimethyl-γ-carboxyglutaric acid formed. Carbon dioxide was eliminated when the compound was heated and α,β,γ-trimethyl-glutaric acid formed.

$$COOH.(CHCH_3)_2.CCH_3(COOH)_2 - CO_2 \longrightarrow COOH(CHCH_3)_3COOH$$

After the acid was subjected to vacuum distillation and boiled with bone black, it appeared as a very light colored syrup. After ten days drying in a desiccator the acid did not crystallize, nor could crystallization be induced in any way. This was quite reasonable because three different stereomers were present. We prepared the anhydride, and imide, of a portion of our acid and then isolated a "cis" acid, melting point 110°-125°, and recovered a syrup, the so-called "trans" acid, from the mother liquors. Both substances were analogous to those obtained by Michael and Ross.

(5) Our inability to effect the crystallization of the original acid prepared by us, or of the smaller portion of the "trans" acid, gave evidence of the presence of more

than one chemical individual. Silver salt analyses of both products identified them as trimethyl glutaric acids. We accordingly attempted the separation of the stereoisomers. A marked variation in a physical property of a derivative of a compound is necessary, before stereomeric separation can be accomplished. The fact that the ethyl ester varied but one degree in its boiling point offered but little hope of separation by fractional distillation of an ester. The other alternative was fractional crystallization, so a search for the proper derivative was undertaken. The anilic acid could be crystallized, but not very satisfactorily. An attempted separation with a solid amine [52] (Bettie's) proved unsuccessful. After an investigation of the salts of many of the metals, potassium acid glutarate was chosen as the most satisfactory material for recrystallization. The acid salt formed supersaturated solutions with water and with 99% alcohol, and was insoluble in higher alcohols. Absolute alcohol was found to be the proper solvent.

By a series of crystallizations we separated the acid salt into three fractions. A small amount of each fraction, slowly recrystallized from absolute alcohol, in a desiccator gave rosettes of fine crystalline needles, which showed no structural difference. Upon hydrolysis of each fraction of the salt a thick syrup resulted. Seeding with crystals of the "cis" acid and of F. E. Ray's acid, friction, various solvents were all ineffective in our attempts to crystallize the fractions of the acids.

The difference in solubility was not great enough to effect a complete separation of the stereomers. It was thought, however, that the active form could be isolated. Accordingly, the resolution of each fraction into the enantiomorphous isomers was attempted. Sufficient strychnine was added to convert 1/2 of the acid into its acid salt, in order to precipitate only the least soluble form. The strychnine acid salt separated as a heavy oily substance, which by lengthy stirring was worked into a viscous white mass. This semi-solid was recrystallized from ether and ligroin. The acid in the original solution which was not precipitated as a strychnine salt was recovered as a syrup.

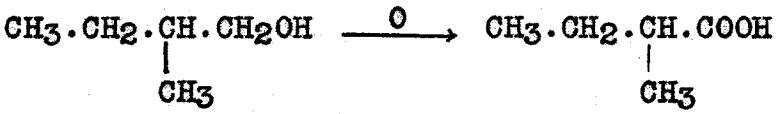
Solutions of the acid salts when examined in the polariscope showed varying optical activity. After the strychnine was precipitated with dilute ammonia, the various fractions of the acid were recovered but did not crystallize. The head fraction, however, showed a tendency to crystallize from absolute ether. The various fractions of acid also gave evidence of optical rotation, but this property diminished as the solubility of the corresponding potassium salt had increased.

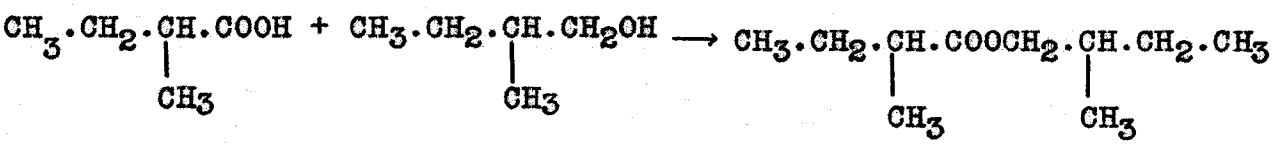
In order to identify the various fractions of the acid by means of crystalline derivatives, we prepared the corresponding anilides. The anilide of the head fraction showed a specific rotation, + 2.1, and melted sharply at 180°. We concluded that since in the purification of the anilide,

the compound was recrystallized four or five times, the anilide of the pure dextro stereomer was isolated. The middle fraction of our acid formed an anilide which sintered at 200-205°, and showed a negligible rotation. This was the anilide of a meso form. It is interesting to note that the meso forms of α, β, γ -trioxyglutaric acid also melt at a temperature considerably higher than do the optical forms. The tail fraction contained accumulated impurities and so could not be crystallized. It manifested a laevo rotation when examined polarimetrically. Our anilides differ from the anilide of F. E. Ray's meso acid. Consequently there exist two meso forms and two enantiomorphous forms, and this demonstrates that the "cis" and "trans" acids of Michael and Ross are not distinct chemical compounds.

EXPERIMENTAL PART

Amyl valerate was prepared from d-amyl alcohol, which after fractional distillation boiled at 127.54°C/760 mm. To a cooled mixture of 230 cm^3 of d-amyl alcohol and 460 grams of 50% sulphuric acid, 230 grams of sodium dichromate was added in small portions. In order to prevent volatilization of the product formed, the temperature was kept below 50°C. The d-amyl alcohol was oxidized to valeric acid, which in turn reacted with d-amyl alcohol, forming amyl valerate. When the oxidation was complete, the material was steam distilled. The amyl valerate was a heavy oil, which was subjected to alkaline hydrolysis without further purification. The yield of amyl valerate was 180 grams.





Ethylmethylacetic acid was obtained from the hydrolysis of amyl valerate. One hundred and eighty grams of amyl valerate and 100 grams of sodium hydroxide in 50% solution were refluxed together for three hours. A small quantity of ethyl alcohol added to the mixture increased the miscibility of the water and ester layers. When the hydrolysis was complete, the acid was extracted with ether, and dried over calcium chloride. The fraction distilling between 174-175°C was

retained. Its refractive index was 1.703. The yield was 75 grams.

$$CH_3.CH_2.\underset{\displaystyle CH_3}{\overset{|}{C}}H.COOC_5H_{11} + NaOH \longrightarrow CH_3.CH_2.\underset{\displaystyle CH_3}{\overset{|}{C}}H.COONa + C_5H_{11}OH$$

$$CH_3.CH_2.\underset{\displaystyle CH_3}{\overset{|}{C}}H.COONa + H_2SO_4 \longrightarrow CH_3.CH_2.\underset{\displaystyle CH_3}{\overset{|}{C}}H.COOH + NaHSO_4$$

Ethyl α -bromoethylmethyl acetate: the acid was changed to the chloride, brominated and esterified in one operation. One hundred and sixty grams of phosphorus pentachloride was placed in a flask. To this was added dropwise 72 grams of ethylmethylacetic acid, the flask being shaken occasionally as the acid was added. Time was allowed to permit the escape of the HCl evolved. During the operation all of the pentachloride dissolved.

$$C_4H_9COOH + PCl_5 \longrightarrow C_4H_9COCl + POCl_3 + HCl$$

Eighty-five grams of bromine was added dropwise to the chloride, the flask being shaken constantly. The hydrogen bromide evolved was collected in potassium hydroxide solution. The reaction mixture was allowed to stand until hydrogen bromide was no longer given off.

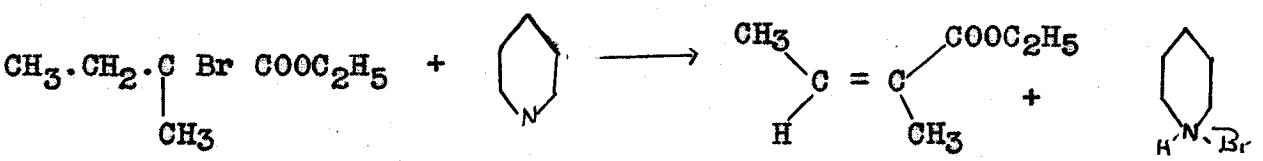
Eighty grams of ethyl alcohol (excess) were slowly introduced into the reaction mixture, which was allowed to stand several hours to complete the esterification

$$C_4H_8Br.COCl + C_2H_5OH \longrightarrow C_4H_8BrCOOC_2H_5 + HCl.$$

The ester was poured over cracked ice to remove the excess

alcohol and the soluble impurities. The ester was salted out, extracted with ether, and dried over sodium sulphate. Ethyl α -bromoethylmethyl acetate distilled 72°-96°/18 mm.

Tiglic ester was prepared from the amyl valerate. Ethyl α -bromoethylmethyl acetate was unsaturated by refluxing for 6 hours with 70 grams of quinoline, boiling at 103-120°C/16-18 mm. Quinoline hydrogen bromide separated as a semi-solid mass, when the reaction mixture cooled. The liquid layer was decanted and distilled under reduced pressure: the fraction boiling at 55°-68°C/14 mm. was retained. The yield was 50 grams. A total of 117 grams of tiglic ester was prepared in this manner.



Constants of tiglic ester prepared from amyl valerate.

	Theoretical	Found
Specific gravity	0.9427 (19.5°)	0.9454 (22.8)
Index of Refraction	1.4298 (25°)	1.4178 1.4175
Molecular weight	128.12	

Molecular refractivity:

(a) Calculated	7 C's = 7 x 2.418	=	16.926
	12 H's = 12 x 1.100	=	13.200
	O =		1.643
	O_2 =		2.211
			33.980
	Double bond		1.733
			35.713

(b) From experimental data in Lorentz-Lorenz formula

$$M_o = \frac{1}{0.9454} \times \frac{\frac{1.4178^2 - 1}{2}}{\frac{1.4178^2 + 2}{}} \times 128.12 = 34.51.$$

This discrepancy in the molecular refractivity indicated that at this stage of the preparation the compound was not pure.

Silver tiglate for analysis: eighteen grams of tiglic ester was refluxed with 50 grams of potassium hydroxide, 50% solution, and 25 cm^3 ethyl alcohol. After one hour 25 cm^3 water was added and 25 cm^3 alcohol distilled off, to permit a higher boiling point. After two hours of refluxing, the solution was cooled and acidified. The tiglic acid was extracted with ether, and the extract condensed. Crystals of tiglic acid separated.

Yield of tiglic acid - 3 grams

Melting point: found 63°C (after one crystallization)

standard 64.5°C.

Freshly distilled ammonium hydroxide was added to the 3 grams of tiglic acid. To prevent the solution of the silver salt, any excess ammonia was evaporated. An equivalent of silver nitrate was added, and silver tiglate precipitated. This salt was filtered off, washed with distilled water and dried in the oven at 110°C.

Analysis: subs. 0.2690; Ag, 0.1402

calc. for $AgC_5H_7O_2$: Ag, 52.1. Found, 51.9

Tiglic Ester from Tiglic Acid: one hundred and fifty grams of tiglic acid — an Eastman product with a melting range 62°-63° after one recrystallization — was converted to the silver salt, as explained above. An attempt to bring about a reaction between silver tiglate and ethyl bromide was unsuccessful. Thereupon, a large excess of ethyl iodide was added to 25 grams of dry silver tiglate. A vigorous reaction took place almost immediately. during which an abundant yellow precipitate of sodium iodide formed. The liquid portion was extracted with ether, and the ether evaporated. The remaining liquid was distilled under reduced pressure, 46-47°/8 mm. A total of 142 grams of tiglic ester was prepared by this method.

Comparative data of tiglic esters

	B.P.	n_D	Mol. Ref.	Density	Silver Salt
Standard	152°/ 760 mm.	1.4218	35.71	0.9427 (19.5°)	52.1%
Preparation from tiglic acid	151.2°/ 740.2mm.	1.4352	36.30	0.9356 (25°)	
Preparation from amyl valerate	142°-152°/ 754.8mm.	1.4178	34.51	0.9454 (25°)	51.9%

Tiglic ester was now condensed with malonic ester in the presence of sodium ethylate. The malonic ester used was an Eastman product, which boiled at 192°C/753.2 mm. The sodium ethylate was prepared as follows: ethyl alcohol - 100% - was obtained by a further dehydration of 99% alcohol, magnesium methylate being used as the dehydrating agent. All apparatus used in the distillation of the absolute alcohol was thoroughly

dried by baking, and all moisture was excluded during reaction. Eight cubic centimeters of absolute alcohol were distilled directly into the reaction flask, which was then quickly attached to an upright condenser, previously dried by a current of warm, dry air. Three and a half grams of freshly cut sodium was added through the condenser.

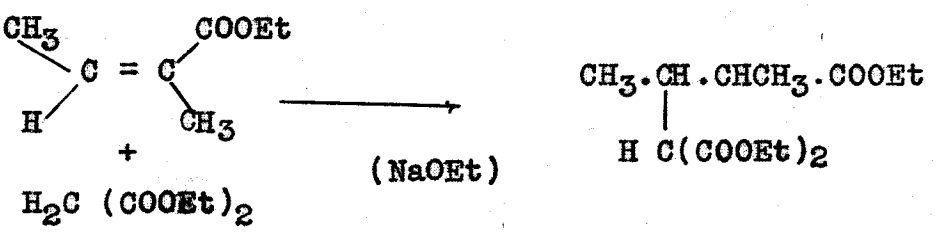
α,β -dimethyl-γ-carboxyglutaric ester: After all of the sodium had dissolved, 96 grams of tiglic ester and 200 grams of malonic ester were added through the condenser, which was then closed with a freshly charged calcium chloride tube. The esters were refluxed for 20 hours, but subsequent runs of only 6 hours gave equally satisfactory results.

It was observed that when the conditions were not absolutely anhydrous, a gelatinous substance appeared, on the addition of the esters, but when no moisture was present, the esters remained clear and unchanged in appearance. When the condensation of the esters had been effected, two distinct layers appeared (possibly due to the sodium malonate not being soluble in the very heavy ester formed). When the liquid was distilled under reduced pressure (6-7 mm.) α,β -dimethyl-γ-carboxyglutaric ester boiled at 152°-154°. The yield was 90 grams. A total of 206.5 grams of α,β -dimethyl-γ-carboxyglutaric ester was prepared in this manner.

Comparative data of α,β-dimethyl-γ-carboxyglutaric ester

	Prepared from Tiglic I	Prepared from Tiglic II
Molecular weight	288.19	Same
Density	1.049	1.055
Refractive Index	1.4339	1.4378
Molecular Refractivity		
(a) Calculated from atomic refractivities	71.81	Same
(b) Found by Lorentz-Lorenz	71.58	71.36

Condensation:



Analysis: subs, 0.1090; H_2O, 0.0780; CO_2, 0.2318

Calc. for $C_{14}H_{24}O_6$: H 8.33; C 58.33

Found H 7.98 C 58.07

α,β -dimethyl-γ-carboxyglutaric acid was isolated in order to determine the identity of the ester. Twenty grams of α β -dimethyl-γ-carboxyglutaric ester was hydrolyzed, and the acid was separated in crystalline form. After six recrystallizations it melted at 144°C.

Methylation of α,β -dimethyl-γ-carboxyglutaric ester was accomplished only under anhydrous conditions. All apparatus was dried as for the malonic-tiglic condensation, and all

damp air was excluded from contact with the reagents. Six grams of sodium was added, through a reflux condenser, to 15 cm^3 of anhydrous alcohol (dried over magnesium methylate) contained in a three necked flask. The alcohol was stirred constantly. When all of the sodium had dissolved, 64 grams of α,β-dimethyl-γ-carboxyglutaric ester and 40 grams of methyl iodide (excess) were added dropwise. The mixture was refluxed for three hours, being stirred constantly.

Yield - 35 grams of α,β,γ-trimethyl-γ-carboxyglutaric ester

Boiling Point 164°-165°/6 mm.

Refractive Index 1.4392

Molecular Weight 302.21

Molecular Refractivity: found (Lorentz-Lorenz)	75.96
" " : calculated (atomic refractivities)	76.47
" " α,β,γ-trimethyl-γ- carboxyglutaric ester	75.760
α,β-dimethyl-γ- carboxyglutaric ester	71.360
CH_2 (found) =	4.400
CH_2 (calculated) =	4.618

This close agreement between the calculated and experimental increase in the molecular refractivity gave evidence that the third methyl group had entered the compound.

Subs. 0.2114 g. H_2O, 0.1557; CO_2, 0.4579

Calc'd. for $C_{15}H_{26}O_6$: H, 8.60; C, 59.60

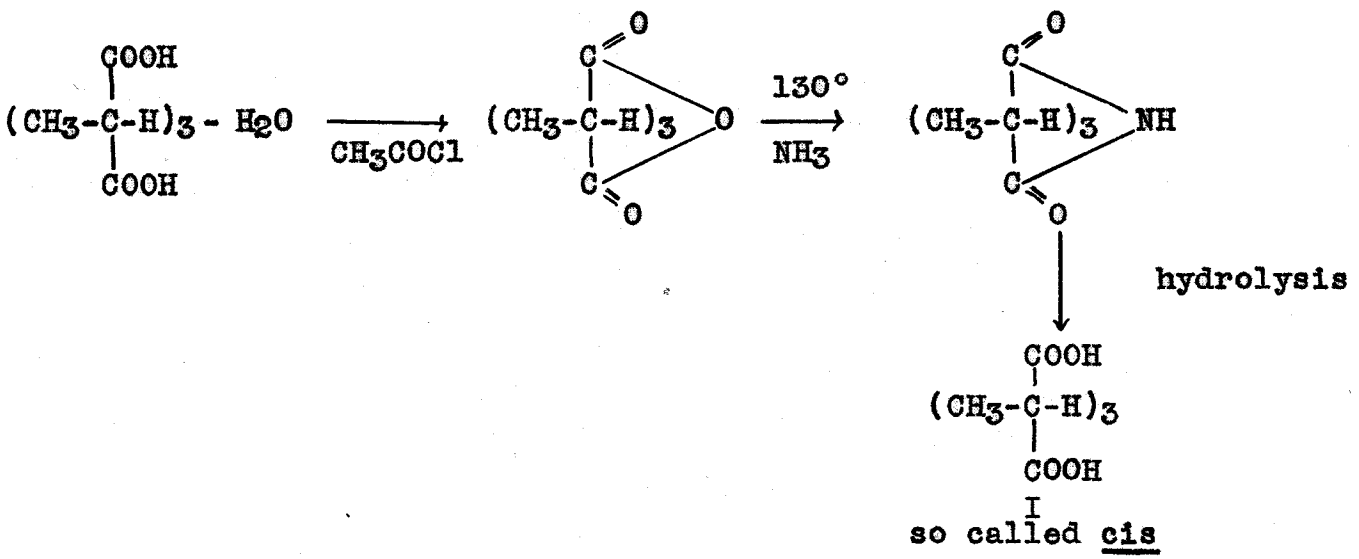
Found H, 8.13; C, 59.12.

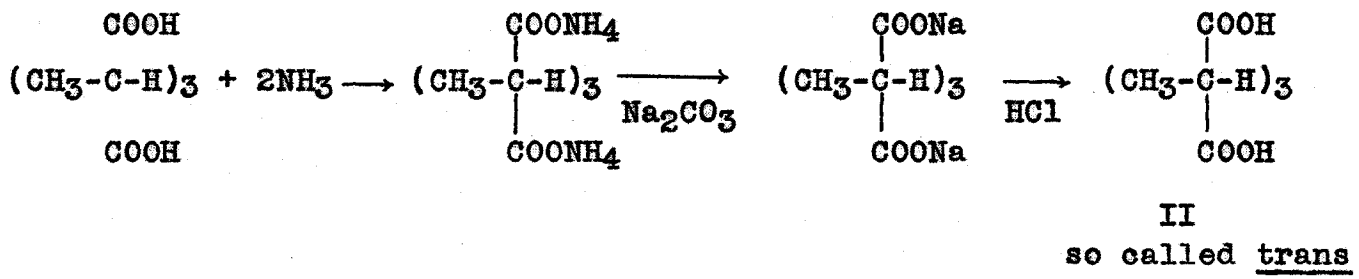
α,β,γ trimethylglutaric acid: α,β,γ-trimethyl-carboxyglutaric ester was subjected to alkaline hydrolysis, one hundred grams of this ester being refluxed 64 hours with 40 grams of 50% caustic potash solution. Occasionally a little water was added to the mixture, and an equal volume of liquid distilled off and tested for alcohol. When the hydrolysis was complete, as evidenced by the absence of alcohol in the distillate, the mixture was acidified, and the α,β,γ trimethyl-γ-carboxyglutaric acid was extracted with freshly distilled, alcohol free ether. The ether extract was dried over calcium chloride, and the ether was removed. The acid was heated for 30 minutes between 150-160°, whereupon carbon dioxide was evolved. The resulting α,β,γ-trimethylglutaric was distilled at 170-183°/3 mm. and yielded 35 grams. The total amount of this acid prepared was 88.1 grams. α,β,γ-trimethylglutaric acid was a heavy syrup, which could not be induced to crystallize.

Anal. subs. 0.2515: Ag, 0.1380

Calc'd for $Ag_2C_8H_{12}O_4$: Ag, 55.64. Found: 55.3.

Ten grams of α,β,γ-trimethylglutaric acid was converted into the anhydride by several treatments with acetyl chloride. The acetic acid which formed was removed by distillation under reduced pressure. The anhydride was converted into the imide (55) by passing dry ammonia gas into the anhydride for one hour at 130°C. The mixture was dissolved in dilute hydrochloric acid, and extracted with ether. The extract was washed with sodium carbonate to remove any unchanged acid.





Upon evaporation of the ether solution, α,β,γ-trimethylglutarimide crystallized in long white needles. The imide was hydrolyzed with 20% caustic potash and the socalled "cis" α,β,γ-trimethylglutaric acid (see page 46) was separated in crystalline form. After four crystallizations, it melted 110°-125°C. This "cis" acid was obtained in relatively small amounts, when compared to the syrup residue. The limited quantity prevented further recrystallizations.

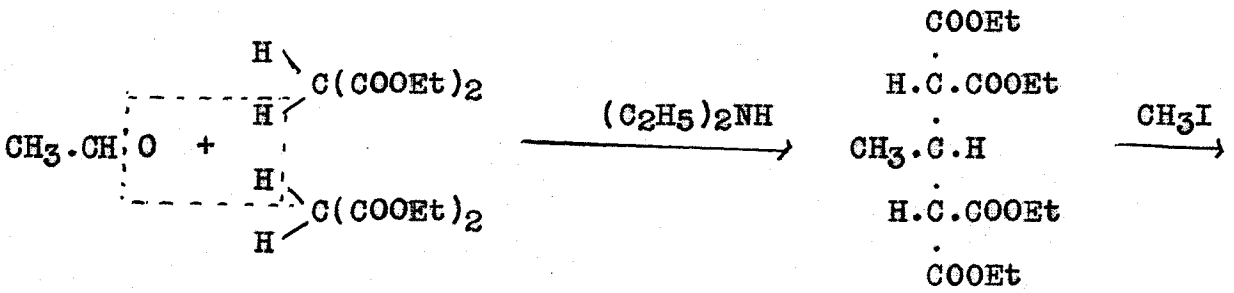
The sodium carbonate was acidified and extracted with ether. A syrup identified by a silver salt analysis as $C_8H_{14}O_4$ was separated. The syrup corresponded to the product similarly obtained by Michael and Ross, and called by them "trans" trimethylglutaric acid. This material contained some

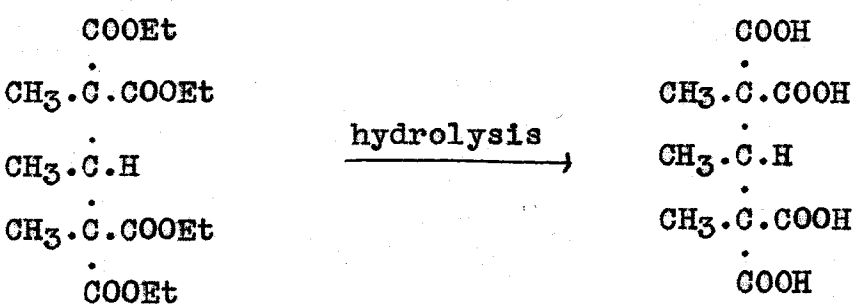
impurities as shown by the analysis.

Anal: subs. 0.062; Ag, 0.034

calc'd for $Ag_2C_8H_{12}O_4$: Ag, 55.64. Found, 54.7.

<u>α,β,γ-trimethyl- α,γ -dicarboxyglutaric ester</u> had been prepared (see page 26) by the condensation of one mole of acetaldehyde and two moles of ethyl malonic ester, according to the Knoevenagel synthesis followed by the methylation of the product. The symmetrical α,β,γ -trimethyl- α,γ-dicarboxyglutaric acid was obtained by hydrolysis, and melted with decomposition at 190°.





Anal: subs. 0.096, Ag 0.059

Calc'd for $Ag_4C_{10}H_{10}O_8$: Ag 62.3 Found 62.2.

Five grams of α,β,γ-trimethyl- α,γ -dicarboxyglutaric acid was rapidly decomposed when heated on the oil bath at 190-230°. After the decomposition, a clear mobile

liquid remained, which had a boiling range of 140-200°/760 mm. It was evidently a mixture. This liquid responded to the test for formic acid (57), and to the iodoform test for the CH_3CO group. A strong odor of butyric acid was perceptible when concentrated sulphuric acid was added.

On the assumption based on these qualitative tests, that the α,β,γ-trimethyl- α,γ-dicarboxyglutaric acid had decomposed into lower fatty acids, the molecular weight was calculated for a monobasic acid, from the data obtained by a silver salt analysis.

Anal: subs. 0.0735 Ag, 0.042

Ag Found, 57.8

$0.042:0.073 = 108:x$

$x = 187.5$ M.W. of silver salt

$187.5 - 107.88 + 1.008 = 80.628$ M.W. of monobasic acid.

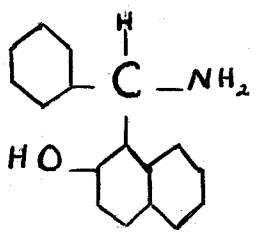
It is evident from the boiling point that this decomposition product is not α,β,γ-trimethylglutaric acid. Moreover, the equivalent weight of α,β,γ-trimethylglutaric is 87. Hence it is clear that some product of lower molecular weight is formed.

α,β,γ-trimethylglutaranilic acid (56) was prepared in an effort to find a derivative suitable for fractional crystallization. The anhydride of α,β,γ trimethylglutaric acid was dissolved in benzene and treated with an excess of freshly distilled aniline. The excess aniline and benzene were removed by distilling under reduced pressure. After several day's drying in a desiccator, a semi-solid mass appeared. The oily

mother liquor was absorbed on a porous plate, and a crystalline compound separated. After four recrystallizations it softened at 123° and melted at 131°, but it was not suitable for fractional crystallization, because of the uncrystallizable material in the mother liquor.

Metallic salts of trimethylglutaric acid were investigated for a derivative suitable for recrystallization. A neutral solution of the ammonium salt reacted as indicated with the following reagents. Mercurous nitrate, ferric chloride, and silver nitrate formed abundant precipitates which were insoluble in both cold and hot water. Uranyl acetate gave no precipitate in cold solution, and only a sparse precipitate in hot. Lead acetate, stannous, stannic, barium, magnesium, bismuth, mercuric, sodium, potassium and zinc chlorides did not precipitate in water solutions.

An organic salt of α,β,γ-trimethylglutaric acid was sought from the interaction of α,β,γ-trimethylglutaric acid on Betti's amine (52),



Equivalent amounts of α,β,γ-trimethylglutaric acid and Betti's amine in acetone solution were mixed, and allowed to stand until a solid separated. When recrystallized from alcohol, the solid melted at 140° - 142°. Betti's amine melts at 125°C, but from alkaline solution it forms a complex, melting at 144°C. A mixed melting point of our product with

some of this complex melted at 144°C, thus establishing their identity. No neutralization had occurred, but the amine had rearranged in this weak acid medium.

Potassium acid glutarate was formed when one equivalent of standardized potassium hydroxide solution was added to two equivalents of α,β,γ-trimethylglutaric acid. Upon evaporation there remained a viscous syrup which did not crystallize. It was heated with benzene to remove traces of moisture. By long mixing, it was worked into a semi-solid crystalline mass, which on being heated with acetone precipitated white crystals, traces of ester being dissolved by the acetone.

An investigation of the possible solvents of this salt gave the following results: the potassium acid glutarate was only slightly soluble in cold absolute alcohol, while it was very soluble in hot. It readily formed supersaturated solutions with cold water, and with cold 99% ethyl alcohol. It was practically insoluble in higher alcohols. Absolute ethyl alcohol was therefore chosen as a suitable solvent for the recrystallization of the potassium acid glutarate. The analysis showed that this salt had crystallized with one molecule of water.

Anal: subs. 0.0308 Residue as K_2SO_4 = 0.0095

Calc'd as $K_2C_8H_{12}O_4$: K 15.5 Found 13.9

Calc'd as $K_2C_8H_{12}O_4.H_2O$: K 13.3 Found 13.9

Potassium acid α,β,γ -trimethylglutarate was fractionally crystallized from hot absolute alcohol. Three crystalline fractions were separated, each having been recrystallized four times. The crystals of these fractions had no evident differentiating property. They all were fine needle crystals with a high refringence and an index of refraction below 1.470. Each fraction was separately converted into the acid, which in each instance was a clear syrup that could not be crystallized. It was thus evident that the difference in solubility of the stereoisomers was not great enough to permit their separation as distinct forms. When, after drying two weeks in an evacuated desiccator, the acid showed no tendency to crystallize, an attempt was made to isolate an optically active form of the acid.

The optical resolution of α,β,γ -trimethylglutaric acid was undertaken with strychnine, a laevorotatory base, as the resolving agent. One fourth of an equivalent of strychnine was dissolved in chloroform and added to one equivalent of α,β,γ -trimethylglutaric acid, also dissolved in chloroform. A heavy oily layer separated. The chloroform was evaporated, and the resulting heavy oil treated with ligroin, whereupon some unchanged acid present in the oily layer was removed. The heavy oil was let stand over night, and then "worked up" into a semi-crystalline mass. In the presence of anhydrous ether, crystals of strychnine and glutarate separated, the unchanged acid remaining in solution. (This strychnine salt,

unlike strychine, was readily soluble in water). Several fractions were obtained in this manner from the original three fractions of acid. Solutions in chloroform of the various fractions of the strychnine salts were prepared and their rotations determined. The acid was then isolated by precipitation of the strychnine salt with cold dilute ammonia. The acid was extracted with ether from the various fractions, but could not be crystallized. The head fraction, however, showed a tendency to crystallize. The optical rotation of the acid fractions in chloroform was determined, and it became evident that two enantiomorphs existed.

Crystalline derivatives, the anilides, of these syrup fractions of acid were prepared. One tenth gram of acid and 0.6 cm^3 of aniline were refluxed at 150° for an hour and a half. The anilides were purified by several recrystallizations from 50% alcohol, and their melting points were determined. The interpretations of these values have been given (see page 32).

		$[\alpha]_D^{20}$ free acid	anilide
Fraction 1	a	+ 2.1	180° melts sharply (dextro)
	b	0	185° sinters
2	a	0	185° sinters
	b	0.26	200-205° (meso)
3	a	0	182°-
	b	-5.51	no anilide

SUMMARY

This investigation offers evidence that trimethylglutaric acid exists in three stereomeric forms, and that its classification by Michael and Ross as two forms, "cis" and "trans" is unwarranted. This statement is substantiated by the isolation of the dextro form as an anilide, and by the identification of the meso form through its anilide. This meso form differs from the meso form prepared by F. E. Ray. The suggestion of Michael and Ross that Ray's acid is a dimethylated glutaric acid has been shown to be untenable. Lastly, the decomposition product of α, β, γ -trimethyl- α,γ-carboxyglutaric acid is a mixture of lower fatty acids, and not α, β, γ -trimethylglutaric acid.

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