

The Steric Relationships of Optically Active *α*-iso-Propylglutaric Acid, Fenchone and Camphor

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The steric relationships of *α*-iso-propylglutaric acid are of considerable interest inasmuch as this acid is formed on the degradation of several terpenoid compounds, *e. g.* fenchone. The pure optically active forms have recently been described by one of us¹, and the next step is then to connect them sterically with the active *α*-iso-propylsuccinic acid. This might be accomplished in a purely chemical way by degrading the glutaric acid without loss of activity.

Barbier and Loquin have given a practical method for degradation of carboxylic acids². The ester of the acid is treated with organomagnesium compound and the resulting ketone or tertiary alcohol is oxidised, thus giving a new acid with one less carbon atom. Wieland has introduced the method into steroid chemistry³, and Bouvet has utilized it for double-sided degradation of dicarboxylic acids⁴. For one-sided degradation of a dicarboxylic acid it is not directly applicable.

Komppa and Rohrmann have investigated the reaction of organomagnesium compound with glutaric anhydride and some of its derivatives^{5, 6}. Compounds of the types (I—III)* were formed. By reaction of one mole of Grignard reagent, (I) is the chief product formed, and with two moles (II) is obtained for the most part. Still larger amounts of magnesium compound give principally (III). On oxidation, all these compounds may be supposed to yield succinic acid.

If the glutaric anhydride carries a substituent in one of the *α*-positions, the molecule is not symmetrical, and two sets of compounds (I—III) might be formed. The carbonyl group adjacent to the substituent will, however, probably react with a much lower velocity owing to sterical hindrance. The corresponding set of compounds will then appear in rather poor yield; on

* Formulas p. 377.

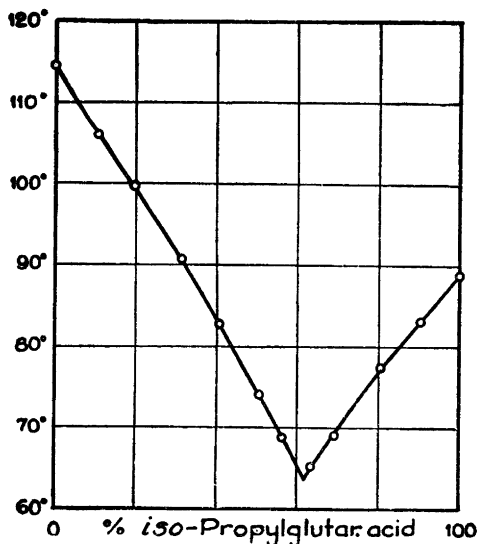


Fig. 1. (+)-*iso*-Propylglutaric acid and (+)-methylglutaric acid.

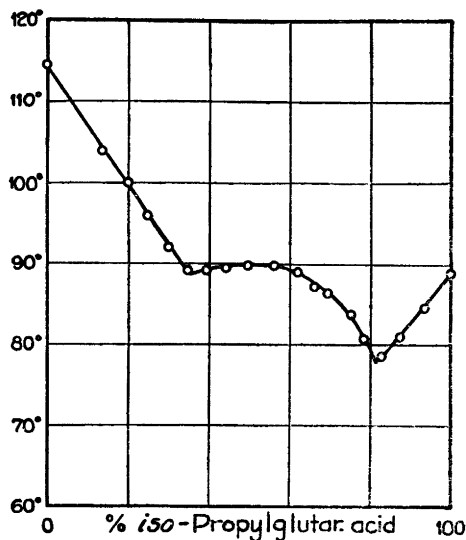


Fig. 2. (-)-*iso*-Propylglutaric acid and (+)-methylglutaric acid.

oxidation, α -substituted succinic acid and a minor quantity of succinic acid might be formed.

On treating the anhydride of α -*iso*-propylglutaric acid with methyl magnesium iodide and subsequent oxidation of the reaction products with chromic acid, α -*iso*-propylsuccinic acid was obtained. As no succinic acid was detected, the reaction can in this case be utilized for one-sided degradation of the substituted glutaric acid.

When the experiment was repeated with the anhydride of *dextro*-rotatory α -*iso*-propylglutaric acid, a *levo*-rotatory *iso*-propylsuccinic acid was obtained. Only slight racemisation had taken place. As the asymmetric carbon atom is not involved in the reactions, it is thereby surely established that the acids with the same configuration have opposite directions of rotation.

The result was not quite unexpected. Recently, one of us has found by another method that α -methylglutaric acid and methylsuccinic acid with opposite directions of rotation must be sterically related⁷. There was of course a certain probability that the same would be true for the *iso*-propyl derivatives. On the other hand, the new results afford additional support for the conclusions regarding the methyl-substituted acids.

As has been stated earlier, methylsuccinic acid and *iso*-propylsuccinic acid with the same mode of optical rotation must also be similar in configurative respect, both giving quasi-racemic compounds with ethylsuccinic acid

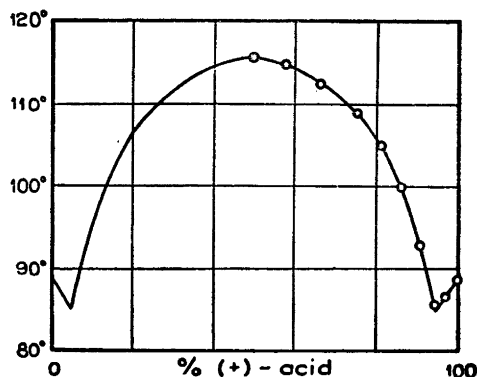


Fig. 3. (+)- and (—)-*iso*-Propylglutaric acid.

of opposite mode of rotation⁸. The question can, however, also be settled without the aid of the latter acid. (+)-Methylsuccinic acid and (—)-*iso*-propylsuccinic acid give a melting point curve clearly indicating the existence of a molecular compound 1 : 1, while the acids with the same mode of rotation give a diagram of the common eutectic type (figs. 1 and 2). The melting point curve for the two antipodes of *iso*-propylsuccinic acid (fig. 3) reveals a strong tendency to form a true racemic compound, and obviously the same tendency manifests itself not only against the next lower homologue, but also against the methylsuccinic acid.

In previous communications, the methylsuccinic acid could be sterically joined to the malic acid^{8, 9, 10}, and the α -*iso*-propylglutaric acid is thus sterically connected to the system of the glyceraldehyde. According to the convention of Fischer¹¹, the (+)-malic acid should be written (IV), and for the configuratively related forms of the other acids mentioned above we have the projection formulas (V—VII).

Some years ago, Hückel gave a survey of the steric relationships of the terpenes and related substances¹². He pointed out, that these compounds had not yet been connected sterically to the system of the glucose and the glyceraldehyde. For the terpenoid compounds, he therefore proposed an independent sterical system, referring to the (+)-camphor as standard substance. According to his convention, the part of the molecule acting as the bridge of a bicyclic system is always imagined to lie in front of (above) the plane of the paper. The wellknown formula (VIII) is then considered as a stereof formula and arbitrarily ascribed to the (+)-camphor. The formulas of all compounds sterically related to the camphor can then be written in an unambiguous way; for (+)- α -pinene we have for instance the formula (IX) and for (+)-fenchone (X).

By stepwise degradation of (+)-fenchone, Wallach^{13, 14} obtained, among other products, *α*-*iso*-propylglutaric acid (XIII). The intermediate steps are illustrated by the formulas (XI—XII). One of the asymmetric carbon atoms of the fenchone is not involved in the reactions, and the acid obtained was levo-rotatory, having $[\alpha]_D = -15.82^\circ$. It is thus represented by projection formula (VII), and it is now possible to connect the hitherto independent sterical systems of Fischer and Hückel. If (VII) is interpreted in accordance with the Fischer convention, we find on comparing (X) and (XIII) that the bridge in (X) must be situated *behind* the plane of the paper. The same must then of course hold good for the formulas of (+)-camphor (VIII) and (+)-*α*-pinene (IX).

The two sterical systems are thus by accident not consistent with each other. In this case it seems natural to give precedence to the much older system of Fischer and to change the notation of Hückel. It must be remembered, however, that the original convention of Fischer is not always observed. Several modern textbooks interpret the common projection formulas in the opposite way. It would be very fortunate if unanimity could be reached on this point.

As pointed out by Hückel¹², the so-called (—)-*trans*-menthone (XIV) having two asymmetric carbon atoms is sterically related on one side to the (+)-camphor (same configuration at C₄) and on the other to (+)-pulegon (XV) (same configuration at C₁). In (XIV) the *iso*-propyl group must consequently be situated behind the plane of the paper. As has been stated earlier⁸, the methyl group of (+)-pulegon must be situated in front of (above) the plane of the paper. We have here an additional proof of the *trans*-configuration of the menthone.

EXPERIMENTAL

Racemic and dextrogyric iso-propylglutaric acid and the corresponding anhydrides were prepared in the manner earlier described by one of us¹.

Degradation of racemic acid. 6.9 g (0.044 moles) of racemic anhydride were dissolved in 150 ml of carefully dried benzene. The Grignard reagent, prepared from 19.1 g (0.135 moles) methyl iodide and 3.15 g magnesium in 40 ml ether, was gradually added. After standing for 20 hours, the solution was heated to the boiling point of the benzene for 15 minutes and then poured out into 500 ml of water, acidified with 10 ml conc. sulphuric acid. The reaction products were extracted with ether. The ether was evaporated and the residue refluxed for 1 hour with a solution of 6 g sodium hydroxide in 60 ml of water. Finally the benzene was driven off with steam.

The different products were separated according to Komppa and Rohrmann⁵. The alkaline solution was acidified with sulphuric acid and distilled with steam; from the remaining solution the keto acid was extracted with ether. The distillate contained the lactone and the unsaturated acid; they were taken up in ether from which the unsaturated acid was extracted with dilute sodium carbonate solution.

Following these directions 4.2 g of »keto acid», 1.7 g of »lactone», and 0.6 g of »unsaturated acid» were obtained. The products were not analysed or further purified. 2.6 g of the »keto acid» were dissolved in a mixture of 95 ml water, 7.7 g conc. sulphuric acid and 4.15 g chromic acid. The mixture was heated on a water bath for 5 hours and refluxed for another 5 hours. About 2/3 of the chromic acid were reduced. After filtration, the solution was extracted with ether and the ether evaporated. The residue, which had a strong odour of acetic acid, was dissolved in water and heated on a steam bath in order to remove volatile acids. The remaining viscous liquid (1.5 g) solidified after standing for some days in a dessicator. It was dried on a porous plate and recrystallised three times from a little water. The remaining product (0.1 g) had m. p. 115.7—116.8° and was identified as racemic *iso*-propylsuccinic acid. An authentic specimen of this acid had m. p. 115.5—116.7°, a mixed sample 115.5—116.8°.

0.0708 g acid: 6.93 ml 0.1263 *N* NaOH.
 $C_7H_{12}O_4$ Equiv. wt. calc. 80.1, found 80.9.

Isolation of the acid through the sparingly soluble calcium salt might probably have given a better yield.

Oxidation experiments with the »unsaturated acid» met with no success.

Degradation of (+)-iso-propylglutaric acid. 7.0 g of the corresponding anhydride¹ were treated with methyl magnesium iodide in the manner described above; the yield of »keto acid» amounted to 3.4 g. It was dissolved in a mixture of 125 ml water, 5.4 g of chromic acid and 10 g conc. sulphuric acid, heated on a water bath for 9 hours and then refluxed for 7 hours. The reaction mixture was worked up as described above, yielding 1.45 g of a viscous liquid which partly crystallised on standing. The crystals were separated and recrystallised twice from benzene. As the acid was still rather impure, it was dissolved in a little water and neutralised with ammonia. On addition of calcium chloride solution, the calcium salt was gradually deposited as a crystalline precipitate which was collected after two days. Yield 0.40 g (fraction 1).

The uncrystallisable part of the reaction product and the acid contained

in the benzene mother liquors were combined and converted to calcium salt in the same manner. This salt was purified by reprecipitation. Yield 0.28 g (fraction 2).

The salt fractions were treated with hydrochloric acid, the organic acid was extracted with ether, and recrystallised from a little benzene. It was identified as levogyric *iso*-propylsuccinic acid.

Fraction 1 yielded 0.28 g acid, m. p. 85—97°.

0.0989 g acid: 9.70 ml 0.1263 *N* NaOH.

$C_7H_{12}O_4$ Equiv. wt. calc. 80.1 found 80.7

0.1016 g acid dissolved in water to 4.87 ml: $\alpha_D = -0.37^\circ$; $[\alpha]_D = -17.7^\circ$.

The activity indicates an *iso*-propylsuccinic acid containing 89 % of (—)-form and 11 % of (+)-form. The melting point found fits well in the diagram fig. 3. 0.0162 g of the acid was mixed with 0.0127 g of an authentic specimen of (+)-*iso*-propylsuccinic acid (m. p. 88—89°). The mixture, which ought to contain 50 % of each antipode, had m. p. 115.8—116.8° and gave no depression with an authentic specimen of racemic *iso*-propylsuccinic acid.

Fraction 2 of the calcium salt yielded 0.18 g of an acid with m. p. 84—87°.

0.1055 g acid dissolved in water to 4.87 ml: $\alpha_D = -0.465^\circ$; $[\alpha]_D = -21.5^\circ$.

The activity indicates an acid containing 96 % of the (—)-form and 4 % of the (+)-form. On mixing with a calculated amount of (+)-acid, racemic *iso*-propylsuccinic acid was obtained (no melting point depression with an authentic specimen).

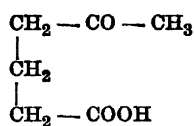
The *melting point diagrams* were determined by Rheinboldt's method¹⁵. In the figures 1—3 the composition is given in mole-%.

SUMMARY

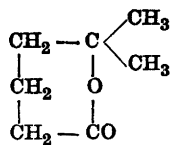
Dextro-rotatory *a*-*iso*-propylglutaric acid was by oxidative degradation converted to levo-rotatory *iso*-propylsuccinic acid. The steric relationships of these acids are thus established.

As (—)-*iso*-propylglutaric acid can be obtained on degradation of (+)-fenchone, a number of terpenoid compounds are in this way sterically connected to the system of glyceraldehyde.

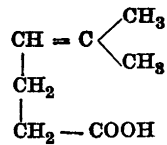
If the projection formula of (+)-glyceraldehyde is interpreted in accordance with the original Fischer convention¹¹, the bridge in the formulas of (+)-camphor, (+)-*a*-pinene and (+)-fenchone (VIII—X) must be imagined to lie behind the plane of the paper.



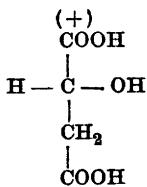
(I)



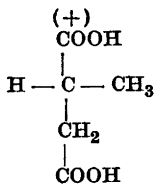
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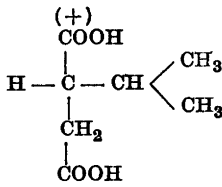
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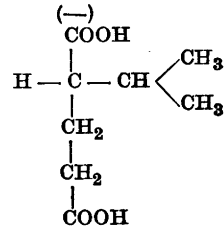
(IV)



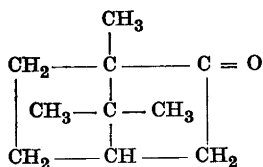
(V)



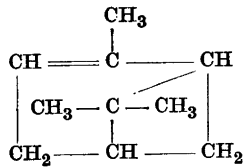
(VI)



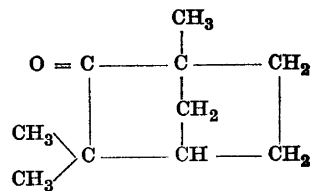
(VII)



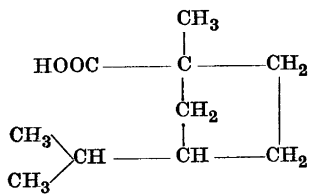
(VIII)



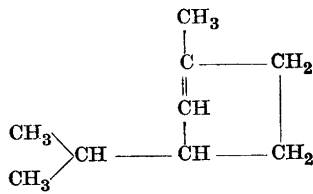
(IX)



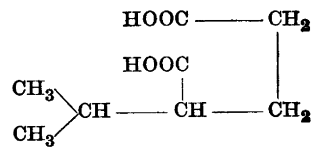
(X)



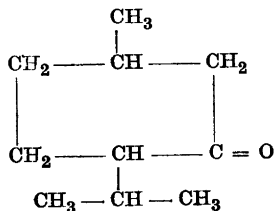
(XI)



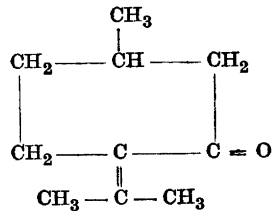
(XII)



(XIII)



(XIV)



(XV)

REFERENCES

1. Fredga, A. *Arkiv Kemi, Mineral. Geol.* **23B** (1946) no. 2.
2. Barbier, Ph. and Lœcquin, R. *Compt. rend.* **156** (1913) 1443.
3. Wieland, H., Schlichting, O. and Jacobi, R. *Z. physiol. Chem.* **161** (1926) 80.
4. Bouvet, M. *Bull.* [4] **17** (1915) 202.
5. Komppa, G., and Rohrmann, W., *Ann.* **509** (1934) 259.
6. » » » » *Ann.* **521** (1936) 227.
7. Fredga, A. *Arkiv Kemi, Mineral. Geol.* **24A** (1947) no. 32.
8. Fredga, A., and Leskinen, E. *Arkiv Kemi, Mineral. Geol.* **19B** (1944) no 1.
9. Fredga, A. *Arkiv Kemi, Mineral. Geol.* **14B** (1941) no 27.
10. » » *Arkiv Kemi, Mineral. Geol.* **15B** (1942) no 23.
11. Fischer, E. *Ber.* **24** (1891) 2683; see also Hudson, *J. Chem. Education* **18** (1941) 353.
12. Hückel, W. *J. prakt. Chem.* **157** (1941) 225.
13. Wallach, O. *Ann.* **369** (1909) 63.
14. » » *Ann.* **379** (1911) 182.
15. Reinboldt H. *J. prakt. Chem.* **111** (1925) 242.

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