LXXIV.—*The Chemistry of the Glutaconic Acids. Part XXII. Optically Active αγ-Dimethylglutaconic Acid.*

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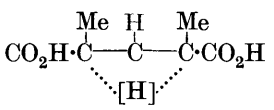
IN the glutaconic acids geometrical isomerism co-exists with three-carbon tautomeric mobility, and in Part XIX (Packer and Thorpe, J., 1926, 1199) a theoretical discussion of the consequences of this mobility is given. It is there pointed out that a number of the "peculiarities" of the glutaconic system which were formerly explained by assuming a "normal" structure for the stable forms of the acids can equally well be explained as a consequence of mobility and the resultant interconversion of the unsaturated *cis*- and *trans*-isomerides.

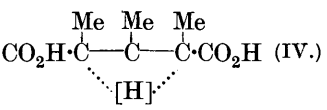
Since then there has gradually accumulated in these laboratories evidence that the "normal" structure formerly postulated has no independent existence as such, although it may possibly represent an intermediate (but non-isolable) phase in the interconversion of the isolable forms, which are thus regarded as possessing the ordinary unsaturated *cis*- and *trans*-structures.

Glutaconic acid and the symmetrically substituted glutaconic acids thus appear to be capable of existing in two (inactive) forms only, the labile form having the *cis*- and the stable ("normal") form the *trans*-configuration. In such cases as αγ-dimethylglutaconic acid (I) and αβγ-trimethylglutaconic acid (II), both *cis*- and *trans*-forms should be capable of resolution into optically active

(I.) $CO_2H{\cdot}CHMe{\cdot}CH{:}CMe{\cdot}CO_2H$. $CO_2H{\cdot}CHMe{\cdot}CMe{:}CMe{\cdot}CO_2H$ (II.)

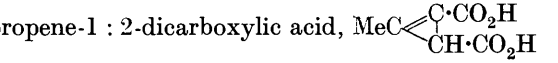
forms, since they each contain an asymmetric carbon atom, whereas the formerly postulated "normal" forms should be non-resolvable, since they were represented essentially by the symmetrical ("normal") structures (III) and (IV).

(III.)




(IV.)

An experimental investigation of these acids with the object of determining molecular asymmetry by optical resolution was therefore undertaken. The following attempts to resolve open-chain glutaconic acids have previously been made, with negative results :— Glutaconic acid (Thorpe and Wood, J., 1913, **103**, 277), "normal" (*trans*-) and labile (*cis*-) β-methylglutaconic acids (Howard, Imperial

College laboratories, work unpublished), normal" (*trans-*) β-methyl-α-ethylglutaconic acid and *trans-* (m. p. 155°) and *cis-* (m. p. 151°) β-phenyl-α-methylglutaconic acids (Feist, *Annalen*, 1922, **428**, 34) by the fractional crystallisation of the alkaloid salts. Feist (*ibid.*, p. 70) also commenced experiments on the resolution of αβ-dimethylglutaconic acid, but abandoned them on account of the unworkable nature of the alkaloid salts obtained. The cyclic "glutaconic" acid, 3-methyl*cyclo*propene-1 : 2-dicarboxylic acid, 
has, however, been resolved by Feist (*Annalen*, 1924, **436**, 135) and the asymmetry of its molecule therefore established.

trans- ("normal") αγ-Dimethylglutaconic acid (m. p. 147°) has now been very readily resolved by means of the acid strychnine salt, the fact being utilised that the salt of the *d*-acid is freely soluble in acetone or alcohol whereas that of the *l*-acid is only sparingly soluble in these solvents. By the addition of one equivalent of strychnine in chloroform solution to a cold solution of four equivalents of the inactive acid in acetone, impure *strychnine hydrogen* l-trans-*αγ-dimethylglutaconate* is precipitated in small crystals, the *d*-acid remaining in solution. The *l*-acid salt thus precipitated carries out of solution with it some *d*-acid salt, from which it cannot be freed by recrystallisation owing to the occurrence of racemisation under the conditions of recrystallisation; by isolating the impure *l*-acid by decomposition of the strychnine salt with cold dilute aqueous ammonia and repeating the process of cold precipitation as the strychnine salt, however, the *l*-acid is readily obtained pure. Pure l-trans-*αγ-dimethylglutaconic acid* melts at 132·5—133° and gives $[M]_D^{20° \text{ or } 25°} = -100°$ ($c = 1$ g. per 100 c.c.).

On account of racemisation in hot solutions of the strychnine salt, the dextro-form of the acid could not be obtained free from the racemic form and attempts to isolate the *d*-acid by means of other alkaloids and *d*-α-phenylethylamine failed owing to the nature of the salts they yielded, but a preparation of the *d*-acid, giving $[M]_D^{20°} = +75°$ and therefore containing about 25% of the racemic form, was readily obtained.

That these are the active forms of the *trans-* ("normal") and not of the *cis-* (labile) acid is proved by the fact that when mixed, either dry or in ethereal solution, in the theoretical quantities for optical neutralisation, they yielded the pure inactive *trans-* ("normal") acid, m. p. 147°, as the sole product.

These active forms do not show mutarotation at 25° in water or dilute aqueous ammonia, sodium hydroxide, and hydrochloric acid solutions. Racemisation, however, occurs in these solutions at their boiling points and also very slowly in boiling acetone. Strych-

nine also causes racemisation of the acid in hot solvents and since its action is of special interest it is dealt with separately below.

The rate at which racemisation of the *l*-acid takes place in water and in aqueous hydrochloric acid and sodium hydroxide solutions at or near their boiling points has been measured by following the change polarimetrically and it has been found to be unimolecular (see experimental part). Table I summarises the results. The unimolecular velocity coefficient k is calculated from the equation $k = 1/t \,.\, \log_e a/(a - x)$, where a = initial rotation and x = change in rotation in time t (expressed in hours). No correction has been made for the fact that the rotation is not exactly proportional to the concentration of the acid, but the error so introduced is within the limits of accuracy of the method. In 4 the volume of sodium hydroxide solution taken was approximately four times that required to neutralise the acid.

TABLE I.

Racemisation of *l-trans*-$\alpha\gamma$-dimethylglutaconic acid.

	Solvent.	Temp.	k (hr.$^{-1}$).	Half-change period.
1	Water	100°	0·0388	17·8 hrs.
2	*N*-HCl	101·5	0·0325	21·3 hrs.
3	5*N*-HCl	101	0·128	5·4 hrs.
4	*N*-NaOH	101·5	1·70	24·5 mins.
5	Acetone	56·5	*ca.* 0·0088	*ca.* 80 hrs.

It is immediately seen that racemisation is slightly slower in *N*-hydrochloric acid than in water, but from three to four times as fast in 5*N*-hydrochloric acid. There thus appears to be a minimum in the velocity of racemisation of *l-trans*-$\alpha\gamma$-dimethylglutaconic acid corresponding to a certain concentration of mineral acid, so the influence of the latter on the change is apparently not a simple one. It is intended to investigate this action further. Table I also shows that racemisation is very much faster in the presence of *N*-alkali than of water or of an equivalent concentration of mineral acid. Since this is also the usual order of the catalytic effect of these reagents on the three-carbon tautomeric change, these results are in agreement with the views put forward in Part XIX, *viz.*, that the tautomeric mobility will result in an equilibrium between the active forms thus :

$$\begin{array}{ccc} \textit{l-trans} & \rightleftharpoons & \textit{d-trans} \\ \Updownarrow & & \Updownarrow \\ \textit{l-cis} & \rightleftharpoons & \textit{d-cis} \end{array}$$

and that, owing to the tendency of like groups to take up positions as far apart as possible in the molecule, the active *trans*-forms

will tend to pass into one another (*i.e.*, undergo racemisation) rather than pass into the active *cis*-forms. That the equilibrium between the *cis*- and *trans*-forms is much in favour of the *trans*-form is also shown by the fact that no isolable quantity of the *cis*-acid can be obtained by the action of acids and alkalis (even hot 60% potassium hydroxide solution) on the *trans*-form. It appears likely, therefore, that the values of k recorded in Table I are actually measures of the mobility of the three-carbon system in *trans*-$\alpha\gamma$-dimethylglutaconic acid under the conditions of these experiments.

Mutarotation or racemisation of active $\alpha\gamma$-dimethylglutaconic acid also takes place more rapidly in hot solvents in the presence of strychnine than in its absence and even occurs very slowly in its presence in the cold. Owing to the much greater solubility of the strychnine *d*-acid salt than of the *l*-acid salt, this action of strychnine can be demonstrated in an interesting and unusual manner. If a solution of the racemic acid (two equivalents) in acetone is digested with strychnine (one equivalent) for several hours and the solvent allowed to escape gradually, and if then the whole of the residual strychnine salts is decomposed in the cold so as to yield the free acid, the acid so recovered (in almost the original quantity) is found to show a strong lævorotation and in one such experiment gave $[M]_D^{25^\circ} = -86^\circ$. This conversion of racemic and therefore of *d*-acid into *l*-acid, which was utilised as the first step in the preparation of the pure *l*-acid when the *d*-form was not required, is due (*a*) chiefly to the racemisation (under the catalytic influence of the strychnine) of the *d*-form of the acid, present in the solution as the readily soluble strychnine hydrogen salt, followed by precipitation of the sparingly soluble *l*-acid salt so formed, and (*b*) to a much smaller extent to the asymmetric influence of strychnine in organic solvents in displacing the equilibrium *l*-acid $\rightleftharpoons$ *d*-acid, which normally is established when equimolecular quantities of the two forms are present, in favour of the *l*-acid. This asymmetric influence was readily demonstrated by heating strychnine (one equivalent) and the *dl*-acid (two equivalents) in sufficient acetone to keep the whole of the salt in solution and then recovering the whole of the acid: the recovered acid gave $[M]_D^{25^\circ} = -0{\cdot}9^\circ$. Brucine in acetone causes a similar but somewhat greater displacement of the equilibrium; in this case the recovered acid gave $[M]_D^{25^\circ} = -2{\cdot}0^\circ$. When water is used as the solvent, no such displacement of the equilibrium is found, the recovered acid being quite inactive. Similar observations on the influence of an asymmetric agent have been recorded by Read and McMath (J., 1925, **127**, 1572) for chlorobromomethanesulphonic acid, by Mills and

Bain (J., 1910, **97**, 1866) for 4-oximino*cyclo*hexanecarboxylic acid, and by Pope and Peachey (P., 1900, **16**, 42, 116) for methylethylpropyltin compounds. In every case the asymmetric agent caused a displacement of the equilibrium in favour of the active form having the same sign of rotation as the asymmetric agent, and in asymmetric syntheses generally the production of an excess of the antimeride with the same sign of rotation as the directing influence is the general rule. The influence of the asymmetric agent in displacing the equilibrium between the active forms is readily understood when the equilibrium is formulated as one between the salts and not between the free acids, thus,

$$l\text{-base-}l\text{-acid salt} \rightleftharpoons l\text{-base-}d\text{-acid salt},$$

for these salts are not optical enantiomorphs and the velocities of the forward and the back reaction are not necessarily equal.

The rate at which strychnine hydrogen *l*-$\alpha\gamma$-dimethylglutaconate passes into the equilibrium mixture has been measured in water and acetone solutions at the respective boiling points and compared directly with the rate of racemisation of sodium hydrogen *l*-$\alpha\gamma$-dimethylglutaconate in boiling water. The results are in Table II.

TABLE II.

	k (hr.$^{-1}$).	Half-change period (mins.).
Strychnine hydrogen salt in water	0·58	72
Sodium hydrogen salt in water	0·18	225
Strychnine hydrogen salt in acetone	0·45	92

Although these figures can be regarded as approximate only, especially in the case of the acetone solution, on account of the experimental difficulties encountered, they show that the strychnine acid salt " racemises " more rapidly than the sodium acid salt in water and further, when account is taken of the difference in boiling points of acetone (56·5°) and water (100°), that the strychnine acid salt " racemises " more rapidly in acetone than in water. It is also evident that the strychnine and sodium salts " racemise " much more rapidly than the free acid.

It was originally intended to prepare the *cis*-form of $\alpha\gamma$-dimethylglutaconic acid by hydration of the hydroxy-anhydride in the presence of concentrated caustic potash as described in Part VII (Thorpe and Wood, J., 1913, **103**, 279) and to resolve it into active forms in order further to test the views set out above, but all the methods tried for the preparation of the hydroxy-anhydride failed to give a sufficient yield to be of practical value for the preparation of the desired quantity of the *cis*-acid, which also could not be obtained by the action of concentrated potash on the *trans*-acid,

its ester or the sodio-derivative of its ester, so that this part of the programme could not be carried out. In one experiment on the preparation of the hydroxy-anhydride, in which $\alpha\gamma$-dimethylglutaconic acid was heated with acetyl chloride in a sealed tube at 100° for some time, the complex anhydride, $C_{14}H_{14}O_5$, formed by condensation of two molecules of the acid and first described by Feist (*Annalen*, 1909, **370**, 82), was obtained as the main product, together with a small yield (7% of the theoretical only) of the desired hydroxy-anhydride. This is of interest because in the earlier experiments of Thole and Thorpe none of this complex product was obtained, whereas Feist (*loc. cit.*) states that he was unable to obtain any hydroxy-anhydride in his experiments and got only the complex anhydride.

Ordinary *trans*-glutaconic acid (the labile *cis*-form has recently been described by Malachowski, *Ber.*, 1929, **62**, 1323) yields a *strychnine hydrogen glutaconate* which in appearance and solubility is very similar to strychnine hydrogen *l*-$\alpha\gamma$-dimethylglutaconate. As is to be expected, however, the glutaconic acid regenerated from this salt is quite inactive and no resolution of glutaconic acid could be obtained by those methods which proved effective in the case of $\alpha\gamma$-dimethylglutaconic acid.

EXPERIMENTAL.

trans- (*normal*) $\alpha\gamma$-*Dimethylglutaconic Acid.*—This acid was prepared by the method of Thole and Thorpe (J., 1911, **99**, 2187) by the following series of reactions: Malonic ester and chloroform —→ ethyl sodio-$\alpha\gamma$-dicarbethoxyglutaconate —→ ethyl α-methyldicarbethoxyglutaconate —→ ethyl $\alpha\gamma$-dimethylcarbethoxyglutaconate —→ ethyl $\alpha\gamma$-dimethylglutaconate —→ *trans*-$\alpha\gamma$-dimethylglutaconic acid. The acid was recrystallised twice from dilute hydrochloric acid; it then melted sharply at 147° (uncorr.). It was identical with a specimen of $\alpha\gamma$-dimethylglutaconic acid prepared by Thole and Thorpe and yielded the hydroxy-anhydride, m. p. 75°. The total yield of recrystallised acid was 16% of the theoretical, calculated on the malonic ester taken.

Resolution of trans-$\alpha\gamma$-*Dimethylglutaconic Acid.*—The pure lævo-form of the acid was readily obtained by the following procedure, but the dextro-form so isolated always contained some of the parent racemic acid.

Strychnine (1 equiv.), in just sufficient chloroform to dissolve it, was added to a well-stirred cold solution of the inactive acid (4 equivs.) in acetone or a mixture of acetone (3 parts) and ether (1 part). Strychnine hydrogen *l-trans*-$\alpha\gamma$-dimethylglutaconate (see below) rapidly crystallised and was removed by filtration after the

solution had been cooled in ice for ½ hour. This crystalline solid was washed with acetone and ether, dried in the air, and used for the preparation of the pure *l*-acid : the filtrate was utilised for the preparation of the *d*-acid.

l-trans-αγ-*Dimethylglutaconic Acid.*—The strychnine *l*-acid salt was decomposed by shaking with a slight excess of dilute ammonium hydroxide solution, and the liquid extracted four times with chloroform to remove the strychnine. The solution was then acidified with a slight excess of dilute hydrochloric acid, and extracted four times with ether. The ethereal extract was washed twice with a little water and dried over calcium chloride, and the ether removed under reduced pressure at the ordinary temperature. The solid active acid obtained (m. p. 125—130°), which contained *dl*-acid, was dissolved in acetone and again precipitated as the strychnine hydrogen salt by the addition of somewhat less than the theoretical quantity (90%) of strychnine in chloroform, and the above procedure repeated. After three such precipitations the melting point and molecular rotation of the acid remained constant. Pure l-trans-αγ-*dimethylglutaconic acid* so obtained melted at 132·5—133° (uncorr.) and gave $[M]_D^{20^\circ \text{ or } 25^\circ} = -100^\circ \pm 1^\circ$ in water ($c = 1{\cdot}0$ g./100 c.c.), $[M]_D^{25^\circ} = -106^\circ$ in water ($c = 4{\cdot}0$ g./100 c.c.), and $[M]_D^{20^\circ} = -136^\circ$ in ethyl alcohol ($c = 0{\cdot}46$ g./100 c.c.) (Found : H, 6·4; C, 52·95. $C_7H_{10}O_4$ requires H, 6·3; C, 53·2%). Admixture with small quantities of the *dl*-acid depressed the melting point considerably. The yield of this *l*-acid can be greatly increased at the expense of the *d*-acid (when this is not required) by carrying out the first precipitation of the acid strychnine salt from boiling acetone under the conditions described later, 1 equivalent of strychnine being used to 2 equivalents of acid.

Solutions of the *l*-acid in water and dilute (normal) hydrochloric acid, ammonium hydroxide and sodium hydroxide underwent no change in rotation when kept at 25° for 3 days, so racemisation did not occur under these conditions.

d-trans-αγ-*Dimethylglutaconic Acid.*—The filtrate from the first precipitation of the strychnine *l*-acid salt was kept at 0° for 12 hours, and the further small precipitate filtered off. It was then evaporated to dryness under reduced pressure at atmospheric temperature, and the residue of impure *d*-acid dissolved in a slight excess of cold dilute ammonium hydroxide solution and extracted four times with chloroform to remove traces of strychnine. The solution was then acidified with a slight excess of dilute hydrochloric acid and extracted four times with ether, and the ethereal extract was washed with water, dried, and evaporated to dryness with the aid of a pump at the ordinary temperature. The solid

d-$\alpha\gamma$-dimethylglutaconic acid obtained melted at 117—128° and gave $[M]_D^{20°} = +75°$ in water ($c = 0{\cdot}44$ g./100 c.c.). This preparation of the *d*-acid therefore contained approximately 25% of the *dl*-acid, from which it could not be separated by fractional crystallisation from an ether–light petroleum mixture. Systematic fractional crystallisation of the strychnine salts failed to yield the *d*-acid on account of racemisation in hot solvents in the presence of strychnine, the only crystalline salt separating being the more or less impure strychnine *l*-acid salt. Brucine, quinine, quinidine, cinchonine, and *d*-α-phenylethylamine gave salts which either would not crystallise or were otherwise unsuitable for the resolution of the acid.

Recombination of the Active Forms to give dl-trans-$\alpha\gamma$-*Dimethylglutaconic Acid.*—0·0312 G. of the pure *l*-acid ($[M] = -100°$) and 0·0420 g. (theoretical quantity for optical neutralisation) of the *d*-acid ($[M] = +75°$) were mixed together in dry ethereal solution, and the ether removed under reduced pressure. The residual acid melted at 146·5—147° and was identical with inactive *trans*-$\alpha\gamma$-dimethylglutaconic acid.

Strychnine hydrogen l-trans-$\alpha\gamma$-*dimethylglutaconate*, prepared as described under the resolution of $\alpha\gamma$-dimethylglutaconic acid above, was almost insoluble in ether, chloroform, and benzene, very sparingly soluble in cold water, acetone, and ethyl alcohol, and sparingly to moderately easily soluble in boiling water, acetone, and ethyl alcohol, from which it separated in well-defined colourless crystals on cooling. It melted at 208—209° with immediate rapid evolution of gas, passing into a solid which melted at 260—263° to a brown liquid which gradually evolved gas at a higher temperature [Found: C, 67·7; H, 6·5; N, 5·75. $C_{21}H_{22}O_2N_2,C_7H_{10}O_4$ requires C, 68·25; H, 6·55; N, 5·7%. 0·1290 G. required 9·90 c.c. of 0·0522 *N*-NaOH, phenolphthalein being used as indicator (strychnine has no action on this indicator): *M*, 499. $C_{12}H_{22}O_2N_2,C_7H_{10}O_4$ requires *M*, 492].

The Action of Strychnine on dl-trans-$\alpha\gamma$-*Dimethylglutaconic Acid in Insufficient Boiling Acetone to dissolve the Salts formed.*—One equivalent of strychnine (20·74 g.) in just sufficient chloroform to dissolve it was added to a solution of 2 equivalents of the inactive acid (10 g.) in sufficient acetone to dissolve the acid readily. Strychnine *l*-acid salt separated, but was not removed. The whole was gently refluxed for 2 hours. Part of the solvent was then allowed to escape by removing the condenser for a time, and the refluxing continued. After each ½ hour this procedure was repeated until the whole of the solvent had gone. The solid residue was decomposed with cold dilute ammonium hydroxide solution, and the acid

separated from the strychnine as described under the resolution of the acid above. The acid obtained (85% recovered) gave a rotation $[M]_D^{25°} = -86°$ in water.

The Action of Strychnine on dl-trans-αγ-*Dimethylglutaconic Acid in Sufficient Boiling Acetone to dissolve the Salts formed.*—One equivalent of powdered strychnine (1·2725 g.) was added to a solution of 2 equivalents of the *dl*-acid (0·6020 g.) in sufficient acetone (1800 c.c.) to keep the salts formed completely in solution, and the solution boiled under reflux for 2 hours. It was then cooled in running water, and a slight excess of concentrated ammonia solution added. The solution was filtered from the precipitated strychnine, a small excess of concentrated hydrochloric acid added, and the acetone removed by distillation under reduced pressure, the temperature being kept below 25°. The residue was made alkaline with cold dilute aqueous ammonia, and the filtered solution extracted with chloroform to remove traces of strychnine. A slight excess of hydrochloric acid was then added, and the solution extracted four times with ether. After drying, the ether was removed. The recovered αγ-dimethylglutaconic acid (95% recovery) gave in one experiment $[M]_D^{25°} = -0·87°$ and in another $[M]_D^{25°} = -0·94°$ in water.

The Action of Strychnine on dl-trans-αγ-*Dimethylglutaconic Acid in a Cold Acetone–Chloroform Mixture.*—One equivalent of strychnine (1·2725 g.) in cold chloroform (15 c.c.) was added to 2 equivalents of the *dl*-acid (0·6020 g.) in cold acetone (10 c.c.), and the mixture stirred until crystallisation took place and then left for 24 hours. The mixture was extracted three times with dilute ammonia solution, the ammonia extracts were mixed, extracted three times with chloroform, and acidified with hydrochloric acid, and the αγ-dimethylglutaconic acid was extracted with ether and isolated in the manner already described. The acid (95% recovery) gave $[M]_D^{25°} = -2·7°$ in water.

The Action of Strychnine on dl-trans-αγ-*Dimethylglutaconic Acid in Sufficient Boiling Water to dissolve the Salts formed.*—One equivalent of finely powdered strychnine (1·2725 g.) was added to a solution of 2 equivalents of the *dl*-acid (0·6020 g.) in 150 c.c. of water, and the solution boiled till the whole dissolved. The boiling solution was placed in a steam-jacketed polarimeter tube and no change in rotation could be detected in 2 hours. The solution was then cooled, decomposed with cold dilute ammonia solution, and the acid recovered by the method already described. The recovered acid showed no detectable rotation.

The Action of Brucine on dl-trans-αγ-*Dimethylglutaconic Acid in Sufficient Boiling Acetone to dissolve the Salts formed.*—One

equivalent of brucine (1·4 g.) was added to a solution of 2 equivalents of the *dl*-acid (0·5 g.) in sufficient boiling acetone to keep the whole in solution. The amount of acetone required was much less than when strychnine was used on account of the greater solubility of the brucine salt. The solution was boiled under reflux for 2 hours and cooled, a slight excess of concentrated hydrochloric acid added, the acetone distilled off under reduced pressure at as low a temperature as possible, the residue dissolved in water, excess of dilute aqueous ammonia added, and the solution extracted several times with chloroform. The solution was then acidified, and the $\alpha\gamma$-dimethylglutaconic acid isolated. It gave $[M]_D^{25^\circ} = -2{\cdot}0^\circ$ in water.

A similar experiment with quinine could not be carried out on account of the small solubility of the quinine salts in suitable solvents.

Racemisation of l-trans-$\alpha\gamma$-*Dimethylglutaconic Acid in Boiling Water.*—The rotation of a solution of *l*-$\alpha\gamma$-dimethylglutaconic acid (0·5 g.) in water (25 c.c.) was measured and the solution was then boiled under reflux for a known time, cooled in running water, and its rotation observed. The boiling was then continued for a further period and the rotation again observed, and this process repeated. The results are in Table III. The unimolecular velocity coefficient is calculated from the equation $k = 1/t \,.\, \log_e a/(a - x)$, where $a =$ initial molecular rotation and $x =$ change in molecular rotation in time t, so that $a - x =$ molecular rotation at time t.

TABLE III.

t (mins.).	$[M]_D$.	k (min.$^{-1}$) $\times 10^3$.	t (mins.).	$[M]_D$.	k (min.$^{-1}$) $\times 10^3$.
0	− 88·4°	—	810	− 51·7°	0·662
180	− 83·4	0·323	1440	− 34·3	0·657
360	− 71·4	0·593	1800	− 25·4	0·693
450	− 66·7	0·625	2100	− 20·4	0·698
540	− 65·4	0·557	2500	− 15·7	0·692

Mean value of k (omitting the value at $t = 180$) = 0·000647 min.$^{-1}$ = 0·0388 hr.$^{-1}$. Half-change period = 17·8 hrs.

The p_H of the solution = 2·6, determined with the quinhydrone electrode. The *l*-acid used in this and most of the following experiments contained some inactive acid, hence the low initial molecular rotation recorded.

Racemisation of l-trans-$\alpha\gamma$-*Dimethylglutaconic Acid in Boiling Acetone.*—The course of the change was not followed as in the experiment with water, but a solution of 0·5 g. of *l-trans*-$\alpha\gamma$-dimethylglutaconic acid ($[M]_D = -100^\circ$) in 40 c.c. of dry acetone was refluxed (b. p. 56·5°) for 7 hours, and the acetone removed under reduced pressure. The residual acid gave $[M]_D = -94^\circ$ in

water. This corresponds to a unimolecular velocity coefficient $k = 0{\cdot}0088$ (hr.$^{-1}$) and a half-change period of about 80 hours.

Racemisation of l-trans-$\alpha\gamma$-*Dimethylglutaconic Acid in Hot Hydrochloric Acid.—Normal acid.* A solution of the *l*-acid (0·5 g.) in *N*-hydrochloric acid (25 c.c.) was used, and the rate of racemisation measured as in the experiment with water as solvent. The solution boiled at 101·5°. The results are in Table IV.

TABLE IV.

t (mins.).	$[M]_D$.	k (min.$^{-1}$) $\times 10^3$.	t (mins.).	$[M]_D$.	k (min.$^{-1}$) $\times 10^3$.
0	− 91·1°	—	360	− 74·9°	0·544
90	− 87·4	0·461	450	− 69·5	0·602
180	− 83·9	0·458	540	− 67·0	0·569
270	− 78·1	0·570	810	− 56·4	0·592

Mean $k = 0{\cdot}000542$ min.$^{-1}$ = 0·0325 hr.$^{-1}$

Half-change period = 21·3 hrs.

5N-*Hydrochloric acid.* A solution of 0·5 g. of the *l*-acid in 25 c.c. of 5*N*-hydrochloric acid was used, and the change followed as for the *N*-acid except that the solution was heated in a boiling calcium chloride solution (temperature inside the flask, 101°) instead of boiled. In order to bring the solution rapidly to this temperature after each reading, it was heated directly over a flame until the temperature reached 100° and then immersed in the boiling calcium chloride solution. The results are in Table V.

TABLE V.

t (mins.)	0	20	90	330
$[M]_D$	− 107·4°	− 102·7°	− 88·5°	− 55·3°
k (min.$^{-1}$) $\times 10^2$	—	0·226	0·216	0·201

Mean $k = 0{\cdot}00214$ (min.$^{-1}$) = 0·128 (hr.$^{-1}$).

Half-change period = 5·4 hrs.

Racemisation of l-trans-$\alpha\gamma$-*Dimethylglutaconic Acid in Boiling* N-*Sodium Hydroxide Solution.*—A solution of the *l*-acid (0·5 g.) in *N*-sodium hydroxide (25 c.c.) was used, and the change followed at the b. p. (101·5°) as in the experiments with water and *N*-hydrochloric acid. This quantity of sodium hydroxide is about four times that required to convert the acid into its disodium salt, which has a molecular rotation of only a quarter of that of the free acid. The results are in Table VI.

TABLE VI.

t (mins.).	$[M]_D$.	k (min.$^{-1}$).	t (mins.).	$[M]_D$.	k (min.$^{-1}$).
0	− 22·6°	—	40	− 7·8°	0·0266
10	− 17·9	0·0233	50	− 5·1	0·0298
20	− 11·8	0·0325	60	− 3·7	0·0302
30	− 10·0	0·0272			

Mean $k = 0{\cdot}0283$ min.$^{-1}$ = 1·70 hr.$^{-1}$.

Half-change period = 24·5 mins.

Racemisation of Sodium Hydrogen l-trans-$\alpha\gamma$-*Dimethylglutaconate in Boiling Water.*—0·5 G. of *l*-$\alpha\gamma$-dimethylglutaconic acid was dissolved in water, slightly less than the theoretical quantity of $N/2$-sodium hydroxide required to form the acid salt added, and the solution made up to 25 c.c. with water. The experiment was then carried out as in the previous case. The results are in Table VII.

TABLE VII.

t (mins.).	$[M]_D$.	k (min.$^{-1}$) $\times 10^2$.	t (mins.).	$[M]_D$.	k (min.$^{-1}$) $\times 10^2$.
0	− 69·3°	—	60	− 56·4°	0·343
10	− 67·7	0·234	75	− 54·4	0·323
30	− 63·4	0·297	95	− 49·7	0·350
45	− 60·7	0·294			

Mean k = 0·00307 min.$^{-1}$ = 0·184 hr.$^{-1}$.
Half-change period = 225 mins.

The p_H of the solution = 4·4, determined by the quinhydrone electrode.

Mutarotation of Strychnine Hydrogen l-trans-$\alpha\gamma$-*Dimethylglutaconate in Boiling Water.*—On account of the small solubility of the strychnine salt in water, the mutarotation could not be followed directly, so the following procedure was adopted. The theoretical quantity of strychnine (2·545 g.) to form the acid salt was added to a boiling solution of the *l*-acid (1·204 g.) in water (350 c.c.). As soon as the strychnine had dissolved, 50 c.c. of the solution were removed, immediately cooled, and decomposed with dilute aqueous ammonia, and the $\alpha\gamma$-dimethylglutaconic acid was recovered in the usual way and its molecular rotation in water determined. The rest of the solution was boiled under reflux and 50 c.c. were removed at measured time intervals. These samples were treated like the first, and the molecular rotations of the recovered acid measured in water. These are in Table VIII under $[M]_D$.

TABLE VIII.

t (mins.)	0	10	20	45	75
$[M]$	− 78·3°	− 79·4°	− 73·0°	− 59·1°	− 43·7°
k (min.$^{-1}$) $\times 10^2$	—	1·063	0·952	0·892	0·938

Mean k = 0·00961 min.$^{-1}$ = 0·577 hr.$^{-1}$.
Half-change period = 72 mins.

The p_H of the solution at 50° = 4·7 (quinhydrone electrode).

Mutarotation of Strychnine Hydrogen l-trans-$\alpha\gamma$-*Dimethylglutaconate in Boiling Acetone.*—Direct observation was again impossible on account of low solubility and the same method was adopted as in the previous experiment. The acid was recovered from the samples removed as described under the action of strychnine on

the inactive acid in boiling acetone. The rotations recorded in Table IX are thus those of the isolated acid in water.

No account has been taken of the fact that at equilibrium the isolated acid has a small lævorotation ($[M]_D = -0{\cdot}9°$), as the error introduced is negligible.

TABLE IX.

t (mins.)	0	20	30	75
$[M]_D$	− 89·9°	− 77·3°	− 71·7°	− 51·4°
k (min.$^{-1}$) × 10^2	—	0·755	0·754	0·746

Mean k = 0·00752 min.$^{-1}$ = 0·451 hr.$^{-1}$.

Half-change period = 92 mins.

The Action of Acetyl Chloride on trans-*αγ-Dimethylglutaconic Acid at* 100°.—5 G. of the acid were heated with 4·5 c.c. (2 mols.) of acetyl chloride in a sealed glass tube at 100° for 6 hours. On cooling, the complex anhydride of Feist (*Annalen*, 1909, **370**, 80) immediately separated as a colourless crystalline solid. The excess of acetyl chloride was removed by heating in an open dish at 100°, and the product taken up with ether. The crystalline complex anhydride remained insoluble in ether and was separated (yield, about 30%). The ethereal solution on standing deposited very small quantities of two crystalline solids, m. p. 192° and 243° respectively, which could not be further investigated. The ether was removed by evaporation, and a viscous oil, which would not crystallise, remained. When this was distilled, the first half passed over at 178°/20 mm. and solidified to an oily colourless crystalline solid, which was the desired hydroxy-anhydride, was readily soluble in benzene, and after recrystallisation from benzene–petrol melted at 73—75°. Yield, 0·3 g. (7% of the theoretical). The rest of the distillate passed over at a higher temperature and would not crystallise.

The complex anhydride after recrystallisation from glacial acetic acid melted sharply at 210° (Found: C, 63·9; H, 5·4. Calc. for $C_{14}H_{14}O_5$: C, 64·1; H, 5·4%). It dissolved slowly in hot dilute aqueous sodium hydroxide and this solution on acidification deposited the hydrated parent acid of this anhydride as long fine needles, m. p. 196—197°, readily soluble in alcohol (Found: C, 56·05; H, 6·0. Calc. for $C_{14}H_{18}O_7$: C, 56·4; H, 6·1%).

Strychnine Hydrogen Glutaconate. The Non-resolution of Glutaconic Acid.—The glutaconic acid used was prepared by the hydrolysis of ethyl sodio-αγ-dicarbethoxyglutaconate; after three crystallisations from benzene–ether it melted at 135—135·5°. Strychnine (1 equiv.), dissolved in chloroform, was added to a well-stirred cold solution of glutaconic acid (4 equivs.) in acetone. *Strychnine hydrogen glutaconate* rapidly separated from the solution as fine crystals

and was filtered off, washed with acetone, and air-dried. The acetone solution was evaporated to dryness. Both the strychnine salt and the residue from the acetone solution were treated with cold ammonium hydroxide solution, extracted with chloroform, etc., as described under the resolution of $\alpha\gamma$-dimethylglutaconic acid. The glutaconic acid recovered from both parts showed no rotation in aqueous solution. Digestion of glutaconic acid with strychnine in boiling acetone similarly yielded negative results.

Strychnine hydrogen glutaconate, prepared as just described, was very similar in appearance to strychnine hydrogen *l-trans*-$\alpha\gamma$-dimethylglutaconate but was more soluble in most solvents, being readily soluble in cold chloroform and water. It melted at 195° with decomposition and resolidification (Found: C, 66·6; H, 6·1; N, 6·15. $C_{21}H_{22}O_2N_2,C_5H_6O_4$ requires C, 67·2; H, 6·1; N, 6·0%. 0·0159 G. required 10·3 c.c. of 0·0522*N*-NaOH for neutralisation, with phenolphthalein as indicator: *M*, 469. $C_{21}H_{22}O_2N_2,C_5H_6O_4$ requires *M*, 464).

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