Novel Synthesis of Chrysanthemumdicarboxylic Acids

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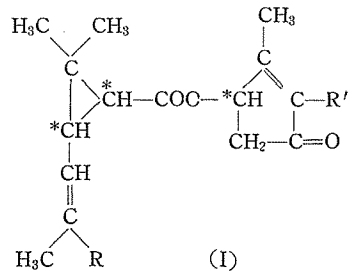
I. INTRODUCTION

It has been well known that the insecticidal constituent of pyrethrum flower, *Chrysanthemum cinerariifolium*, is a mixture of cyclic keto-esters, referred to as "pyrethrins". The insecticidal activity of "pyrethrins" is so specific in respects of its quick knockdown effect, of the nontoxicity against mammals inspite of the incomparably high insecticidal effect and of producing no resistance in insects. With these advantages it has been practically used as one of the most important insecticides.

The first and comprehensive study on "pyrethrins" was developed by Staudinger and Ruzicka. In 1924 they published their excellent studies[1] on the separation of the active constituents in Dalmatian pyrethrum flowers and the assignment to their structures. Since then, all the expansion in this field, has been based on these works. Although they pioneered the synthetic and structural study on naturally occurring pyrethrins, a quarter century after, their



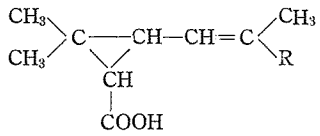
(I)

Pyrethrin-I	(I)	R=—CH_3	R′=—CH_2—CH=CH—CH=CH_2 (*cis*)
Pyrethrin-II	(I)	R=—$COOCH_3$	R′=—CH_2—CH=CH—CH=CH_2 (*cis*)
Cinerin-I	(I)	R=—CH_3	R′=—CH_2—CH=CH—CH_3 (*cis*)
Cinerin-II	(I)	R=—$COOCH_3$	R′=—CH_2—CH=CH—CH_3 (*cis*)

*大 野 稔, 井 上 雄 三, 杉 田 利 夫

conclusions were partly suffered very important corrections, of course, not that the conclusions were denied wholly. After the Second World War, LaForge and Harper brought a great advance in the structural and synthetic problems of pyrethrins. In consequence, it was established that the naturally occurring pyrethrins consist of a mixture of four substances, *i.e.* pyrethrin-I, pyrethrin-II, cinerin-I and cinerin-II. It is currently recognized and the structures of these constituents were determined as the foregoing structures.

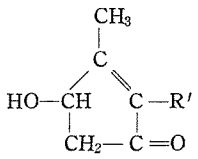
These four sturctures have some common features, that is, all of them are esters, their acid fragmants are the monoterpenic acids with cyclopropane nucleus, chrysanthemummonocarboxylic acid (chrysanthemic acid, II) and chrysanthemumdicarboxylic acid monomethylester (pyrethric acid, III′), and their alcohol moieties are cyclopentenolone derivatives, pyrethrolone (IV) and cinerolone (V). These fragments except one had already been synthesized and their geometrical configurations had also been confirmed. The remaining fragment, chrysanthemumdicarboxylic acid, was recentry synthesized by Inouye[2] and also by Harper[3].



(II) R= —CH_3 (*trans* about the cyclopropane ring)

(III) R= —COOH (〃 〃)

(III′) R= —$COOCH_3$ (〃 〃)



(IV) R′= —CH_2—CH=CH—CH=CH_2 (*cis*)

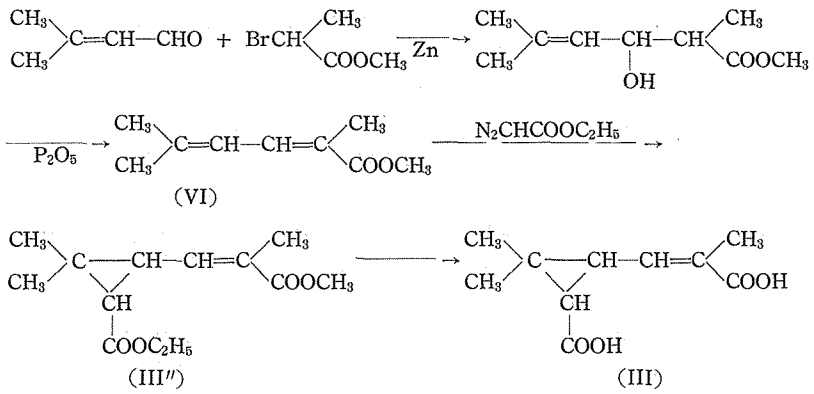
(V) R′= —CH_2—CH=CH—CH_3 (*cis*)

Chrysanthemumdicarboxylic acid (III) was at first isolated from Japanese pyrethrum flowers by Fujitani[4] as early as in 1909, and the melting point (164°) thereof was reported, but no further study was pursued. The structure of this crystalline dextrorotatory dicarboxylic acid was established by Staudinger and Ruzicka[1] as (+)-*trans*-3-(2′-carboxyprop-1′-enyl)-2 : 2-dimethylcyclopropane-1-carboxylic acid by ozonolysis to give (−)-*trans*-caronic acid and pyruvic acid. On cold sodium methylate fission of the crude semicarbazone of pyrethrins they isolated the half methyl ester of chrysanthemumdicarboxylic acid (pyrethric acid), from which methyl pyruvate was obtained as well as (−)-*trans*-caronic acid on ozonolysis. Therefore it was decided that the cyclopentenolone fragment was esterified with the carboxyl group directly attached to cyclopropane ring, namely the structure III′ was established for pyrethric acid.

Afterwards, Harper[3,5] and Inouye[6] established the absolute configuration of the naturally occurring (+)-*trans*-chrysanthemumdicarboxylic acid (III) on the configurative correlation for (+)-*trans*-chrysanthemic acid (II). But the stereochemistry of the side chain double bond was left unsettled.

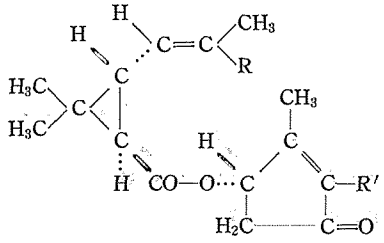
The total synthesis of chrysanthemumdicarboxylic acid was recently succeeded by Inouye[2] and Harper[3] almost concurrently but independently, pursuing

the following scheme. Afterwards, Matsui[7] also obtained the isomeric acids by the other process.



The authors[8,9] established the geometrical configuration of the side chain double bond to be *trans* by the synthetic procedures. The geometrical configuration of $\alpha\beta$-double bond of $\alpha\delta$-dimethylsorbic acid and its ester (VI) was decided to be *trans* by physico-chemical and chemical evidences. As well, this configuration was maintained to chrysanthemumdicarboxylic acid (III).

Also recentry Katsuda[10] decided the absolute configuration of pyrethrolone (IV) and cinerolone (V). Thus the final and complete structures of the naturally occurring pyrethrins were established as follows.



As the results of these developements, the chemical structures and cofigurations of the constituents of pyrethrum flowers have already been clarified and their total syntheses have further been accomplished. Although chrysanthemumdicarboxylic acid have four geometrical isomers theoretically, Inouye and Harper have obtained two of them, *i.e.* *trans, trans*- and *cis, trans*-isomers* which are the whole available from their synthetic procedures since the *trans*-isomer of $\alpha\delta$-dimethylsorbic acid alone has been obtainable as the starting material of the synthesis. Therefore, some other procedure has been required to obtain the remaining isomers. Beside this, the above-mentioned method is a complicated one, and there yet remains room for improvement in the yield.

The authors[11] succeeded in the synthesis of *trans, trans*- and *trans, cis*-

* Regarding the representation of configuratinons, refer to the footnote on page 26.

chrysanthemumdicarboxylic acids by a novel and stereospecific route of synthesis and established their geometrical configurations, which will be described in details in the following chapters. The latter isomer, *trans,cis*-chrysanthemumdicarboxylic acid could not be synthesized by Inouye's method. It is the further advantage of the novel route of synthesis that the each geometrical isomer of the acid is obtainable without contamination of the other isomers by more facile procedures.

II. RELATIVE REACTIVITY OF THE CONJUGATED DIENE CARBOXYL COMPOUNDS

The author will be concerned in this chapter with the reactivity of conjugated unsaturated systems, in particular the addition reactions to conjugated diene carboxylic acids. Reactions of the simple unsaturated systems have been kinetically studied, and also those of the simple conjugated diene compounds such as butadiene have been revealed to some extent. However, reactions of the conjugated diene carboxyl systems, especially those of substituted ones present a more complicated problem and have not completely been elucidated as yet.

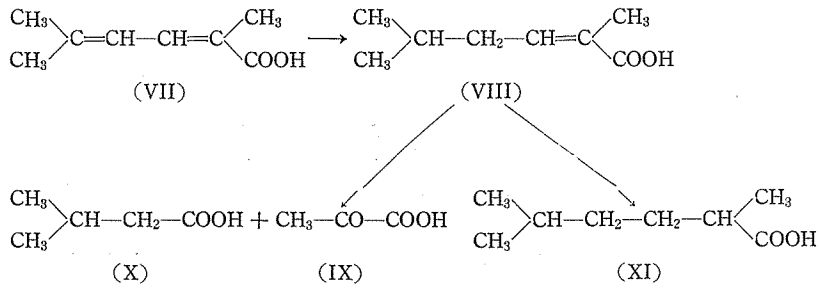
The addition reactions of symmetrical molecules, such as hydrogen which is considered as an electrophile, and of Diels-Alder type to conjugated dienes have been discussed already in many papers. Regarding the orientation of addition of these types, as is well known, 1,4-addition takes place more commonly. In nucleophilic additions to the conjugated polyene carbonyl systems, the orientation of addition takes place in somewhat different and complicated aspects. The orientation of reductions of conjugated dienoic acid by dissolving metals was more favourable in 1,4-addition. The mechanism of this reductions has been regarded as a nucleophilic one. On reduction with sodium amalgam, muconic acid, the simplest butadiene derivative having terminal carboxyl groups HOOC—CH=CH—CH=CH—COOH, gave predominantly the $\beta\gamma$-unsaturated dihydro-compund[12]. β-Vinylacrylic acid CH_2=CH—CH=CH—COOH also gave $\alpha\delta$-dihydro-derivative by the same reducing agent in alkali medium, however, its methyl derivatives gave $\alpha\beta$- as well as $\alpha\delta$-adducts on the reduction, and the proportion of $\alpha\beta$- to $\alpha\delta$-adducts varied with the position of the substituent[13]. On the other hand, additions of Michael type, for example, of a malonic or cyanoacetic ester to sorbic ester, are oriented to either the β- or the δ-position[14], since these positions are in principle positively polarisable, and are therefore potential positions of attachment of the anionic portion of the addendum.

As mentioned above, the relative reactivity of conjugated polyene system is very complicated and undergoes a change by the substituents. Therefore, the author had to deal with some reactions in relation to these problems.

§ Semihydrogenation of $\alpha\delta$-dimethylsorbic acid[8].

At first, the partial hydrogenation of $\alpha\delta$-dimethylsorbic acid (VII) to give

$\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid (VIII) is described. Farmer and Hughes[15] reported that sorbic acid, when submitted to 50% hydrogenation in the presence of palladium catalyst, gave a mixture of dihydro-acids in which the $\Delta\alpha$-dihydrosorbic acid predominated ranging from 85 to 90%, whilst with a platinum catalyst only a mixture of an almost equal amount of fully reduced and unchanged conjugated compounds was obtained, the production of small proportions (below 20%) of dihydro-compounds being recorded.



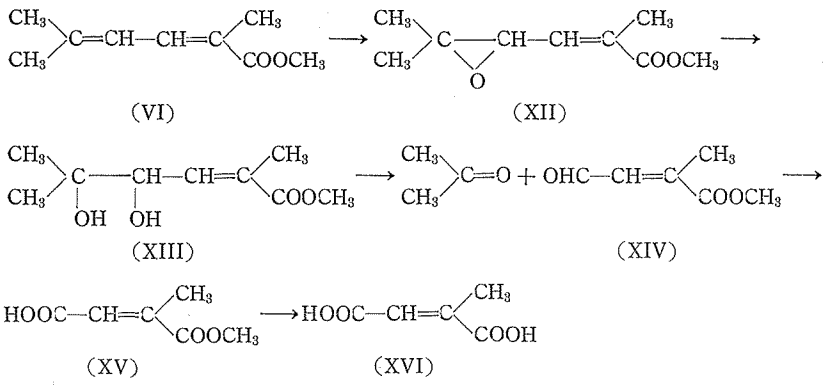
In the present authors' case, the semihydrogenation of $\alpha\delta$-dimethylsorbic acid (VII) over Pd-$BaSO_4$ catalyst predominantly afforded the $\Delta\alpha$-dihydro-compound, that is $\gamma\delta$-addition was favoured. $\alpha\delta$-Dimethyl-$\Delta\alpha$-hexenoic acid (VIII) was obtained in the yield of 73% after repeated purifications by means of partial esterification* and rectification. The product was characterized by ozonolysis to yield pyruvic acid (IX) and iso-valeric acid (X). In the UV-spectrum of the resulting $\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid, the occurrence of the single intense band (λmax. 218 mμ, ε 14,300), characteristic for the $\alpha\beta$-unsaturated carboxylic chromophore, together with the disappearance of the conjugated diene carboxylic band (λmax. 273 mμ) which was exhibited by the parent dimethylsorbic acid (VII), were consistent with the chemical evidence mentioned above. The fact that the extinction coefficient at this band did not alter on further purifications, excluded the contamination of the possible $\Delta\beta$-, $\Delta\gamma$-dihydro- or fully reduced compounds, which were spectrally inert in this region. This acid was quantitatively hydrogenated over a platinum catalyst and was shown to absorb one equivalent hydrogen, yielding the known $\alpha\delta$-dimethylcaproic acid (XI)[16].

The equivalent weight and the acid dissociation constant were also determined[8]. All criteria supported purity of this acid.

§ Selective oxidation of $\alpha\delta$-dimethylsorbic acid[9].

Heinänen[17] reporeted that the selective epoxidation occured at the $\gamma\delta$-double bond of methyl sorbate by the action of perbenzoic acid in the cold, giving methyl $\gamma\delta$-epoxy-$\Delta\alpha$-hexenoate.

* In the sense that $\Delta\beta$- and $\Delta\gamma$-dimethylhexenoic and dimethylcaproic acids become esterified, whilst $\Delta\alpha$-dimethylhexenoic acid remains unchanged. (Compare Ecott and Linstead's modification of Sudborough's method, *J. Chem. Soc.*, **1929**, 2153 ; **1932**, 125)



(VI) (XII)

(XIII) (XIV)

(XV) (XVI)

The epoxidation of our methyl $\alpha\delta$-dimethylsorbate (VI) by perbenzoic acid gave methyl $\gamma\delta$-epoxy-$\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoate (XII) as was expected, though this addition seems to proceed by a free-radical mechanism, one atom of oxygen being taken up at the $\gamma\delta$-double bond of the parent ester. The $\gamma\delta$-epoxy structure of the product can reasonably deduced from the subsequent degradations. Conversion of the epoxy-ester into the dihydroxy-compound was easily effected by the treatment with diluted sulphuric acid, yielding $\gamma\delta$-dihydroxy-$\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoate (XIII). Lead tetraacetate cleaved the glycolic carbon-carbon linkage of XIII and gave (α)-methyl mesaconaldehydate (XIV), which was characterized by 2,4-dinitrophenylhydrazone, mp. 204-4.5°. (α)-Methyl mesaconaldehydate was then oxidized with peracetic acid to (α)-methyl (β)-hydrogen mesaconate (XV), mp. 82-3°, which as well as the amide, mp. 117°, derived therefrom, were completely consistent with the literature[18]. Cold saponification of (α)-methyl (β)-hydrogen mesaconate gave mesaconic acid (XVI), mp. 202-3°, not depressed by mixed melting point comparison with an authentic specimen[19].

The direct peroxidation of $\alpha\delta$-dimethylsorbic acid (VII) by means of hydrogen peroxide, also gave mesaconic acid (XVI) but in an inferior yield. This result indicated that the selective oxidation took place at the same $\gamma\delta$-double bond as in its epoxidation.

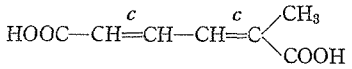
§ Addition of ethyl diazoacetate to $\alpha\delta$-dimethylsorbate[2a]

In the system of $\alpha\delta$-dimethylsorbic acid (VII), as mentioned above, the $\gamma\delta$-double bond is more reactive than is the $\alpha\beta$-double bond, and this result is supported also by the fact that ethyl diazoacetate adds exclusively to $\gamma\delta$-double bond of $\alpha\delta$-dimethylsorbate (VI), yielding chrysanthemumdicarboxylate (III''). Discussions on the mechanism of this reaction will be described in the next chapter.

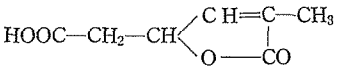
§ Lactonization of α-methylmuconic acid[20].

When α-methyl-*cis*, *cis*-muconic acid (XVII *c-c*) was treated with cold 80% sulphuric acid or boiled with water, an unsaturated lactonic acid, γ-carboxymethyl-α-methyl-$\Delta\alpha$-butenolide (XVIII) alone was obtained. Experiments and its structural arguments will be described in chapter III. Although two kinds of

lactonic acids are to be expected for this acid, namely the lactonic acid in which α-carboxyl group is concerned in the lactonization and the other in which δ-carboxyl group is concerned, only one of which has exclusively been obtained.

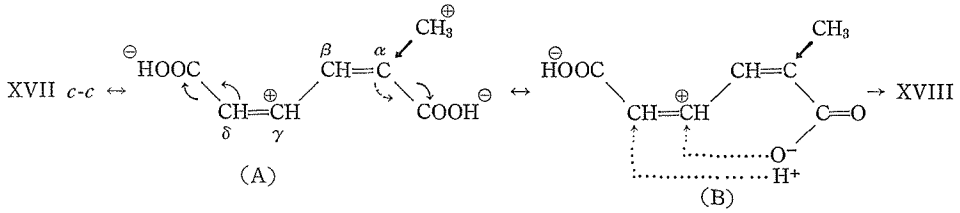


(XVII *c-c*)



(XVIII)

The uniformity of the lactonization of the *cis, cis*-acid can be interpleted as follows. In the starting acid (XVII *c-c*), the electrons are oriented as indicated in (A). The electron attractive effect of the carboxyl group, attached



(A) (B)

to the δ-carbon atom, induces the polarization of the adjascent double bond producing a positive charge on the γ-carbon atom. The same effect of the carboxyl group attached to the α-carbon atom, also produces a positive charge on the β-carbon atom, which is much more weakened by the electron releasing effect of the α-methyl substituent, and hence, the positive charge on the β-carbon atom is weaker than that on the γ-carbon atom. Consequently, the attack of the polarized α-carboxyl oxygen to the γ-carbon atom is preferred and then followed by the addition of proton to the δ-carbon atom, resulting in the formation of the only known lactonic acid (XVIII).

From the fact that the $\gamma\delta$-double bond was more reactive than the $\alpha\beta$-double bond in α-methylmuconic acid system as mentioned above, it was reasonably expected that the addition of dimethyldiazomethane to the $\gamma\delta$-double bond of α-methylmuconic acid should be favoured. Regarding this problem, the author will discuss in the next chapter in details. Indeed, this was the case with the addition reaction, thus verifying the proposed mechanism as well as the preferred reactivity of the $\gamma\delta$-ethylenic linkage in this system.

EXPERIMENTAL

Semihydrogenation of $\alpha\delta$-dimethylsorbic acid.

A 15.0 g quantity of $\alpha\delta$-dimethylsorbic acid (VII ; mp. 134-5°)[2a] dissolved in 150 ml of methanol was hydrogenated over Pd-$BaSO_4$ catalyst (1.2 g) in a shaking apparatus until 2564 ml (at 19°) of hydrogen (equivalent to one double bond) was absorbed. The reduction product thus obtained, was freed from the catalyst and solvent, and carefully distilled under reduced pressure. The di-

stillate was submitted to partial esterifications in order to eliminate the possible $\Delta\beta$- and $\Delta\gamma$-dihydro acids ; the distillate (14.3 g, 95%) was mixed with 0.2 *N*-ethanolic hydrogen chloride (70 ml) and kept at room temperature for 5.5 hrs. After the duration, the solution was diluted with four times its bulk of water, made faintly alkaline against lithmus paper by the addition of sodium carbonate. The neutral substance separated was collected with ether, then the aqueous layer was concentrated under a reduced pressure below 50° until free from alcohol. The neutral fraction was again completely removed with ether at this stage. Acidification of the aqueous residue and thorough extraction with ether, followed by drying and removal of the solvent, gave the fraction bp. 118-122°/10 mm (11.1 g, 73%). This crop was enough pure at this stage, but in order to obtain the sample of the highest purity for physico-chemical measurements which were needed for determination of the geometrical configuration of this acid*, this was again subjected to partial esterification exactly in the same manner as described above and in further rectifications, only a center cut of pure $\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid was collected, bp. 120.5-121.5°/10 mm (6.3 g), n_D^{25} 1.4597, equivalent weight : Found, 141.1, Calcd. for $C_7H_{13}COOH$, 142.2, λmax. 218 mμ, ε 14,300. It crystallized in a prism when chilled in dry-ice and melted at about 0°. p-*Phenylphenacylester*, mp. 54-6° (*Anal.* Found : C 75.55 , H 7.13. Calcd. for $C_{32}H_{24}O_3$: C 78.54, H 7.19). Distillation of the neutral ether extracts combined gave the fraction of ester, bp. 84-88°/22 mm, n_D^{25} 1.4313 (4.5 g). It decolourized the permanganate solution at room temperature and absorbed bromine instantly. However, this was not subjected to further investigation.

Ozonization : — One gram of the dihydro-acid in 50 ml of chloroform was treated with an excess of ozone at 0°. The solvent was removed *in vacuo*, and the remaining ozonide was decomposed with water on a water bath for 10-15 mins. To this aqueous solution, was then added the solution of 2,4-dinitrophenylhydrazine in dilute hydrochloric acid to precipitate any carbonyl compound present, and was kept overnight. The yellow precipitate was collected and recrystallized several times from ethanol to give 2,4-*dinitrophenylhydrazone* of *pyruvic acid*, mp. 218° (0.6 g). The melting point was not depressed by admixture with an authentic specimen. The filtrate from the hydrazone was thoroughly extracted with ether and the ether solution was dried over anhydrous sodium sulphate, and after removal of ether, the residue was distilled to give *isovaleric acid* (0.3 g), bp. 170-175°, n_D^{22} 1.4020. p-*Phenylphenacylester*, mp. 77-8° (*cf.* Drake[21] mp. 76°). The melting point was not depressed by admixture with an authentic specimen.

Quantitative hydrogenation : — A 0.233 g quantity of the acid (bp. 120.5-121.5°/10 mm) in 30 ml of ethanol was hydrogenated over a platinum oxide catalyst (11 mg) in a shaking hydrogenation apparatus, and absorbed 40.0 ml (at 27°) of hydrogen, equivalent to one double bond. The reduction product

* For physico-chemical determination of the geometry, which may be applicable to the conjugated diene carboxylic acid in general, see the detailed article by the same authors.[8]

was freed from both catalyst and solvent, and distilled to give the fully reduced *αδ-dimethylcaproic acid* (XI)[16] in a yield almost quantitative, bp. 115-116°/13 mm. n_D^{20} 1.4261. *Amide*, mp. 102-3° ; p-*Phenylphenacylester*, mp. 66°, identified by mixed melting point comparison with authentic specimens, respectively.

Selective oxidation of *αδ*-dimethylsorbic acid.

Methyl *γδ*-epoxy-*αδ*-dimethyl-*Δα*-hexenoate (XII). Four grams of methyl *αδ*-dimethylsorbate (VI ; 0.027 mole)[2a] were dissolved in 5 ml of dry chloroform and to this were added 147 ml of 3.5% perbenzoic acid in chloroform (0.038 mole). The mixture was kept at 0° and the consumption of the active oxygen was estimated by means of iodometry on a small portion drawn from the reaction mixture at intervals. After 5 days' standing, 0.03 atom of oxygen was taken up, then the excess of perbenzoic acid was decomposed with sodium sulphite, removed by washing with sodium carbonate and dried over anhydrous sodium sulphate. After removal of the solvent, the residue was distilled under a reduced pressure to give methyl *γδ*-epoxy-*αδ*-dimethyl-*Δα*-hexenoate, bp. 91-2°/6 mm, n_D^{20} 1.4672, yield 3.7 g (84%).

Methyl *γδ*-dihydroxy-*αδ*-dimethyl-*Δα*-hexenoate (XIII). To a 1.5 g quantity of epoxy-ester (XII), was added 0.5 ml of 5% sulphuric acid, kept at room temperature and after several hours it turned homogeneous. This was then extended in 100 ml of alcohol free ether and was completely dried over anhydrous sodium sulphate. Removal of ether gave methyl *γδ*-dihydroxy-*αδ*-dimethyl-*Δα*-hexenoate in quantitative yield, plates (from methanol and benzene), mp. 50-1°, *Anal.* Found : C 57.40, H 8.46. Calcd. for $C_9H_{16}O_4$: C 57.43 , H 8.57.

(*α*)-**Methyl mesaconaldehydate** (XIV). The dihydroxy-ester (XIII ; 1.48 g, 0.0079 mole) was dissolved in 100 ml of dry benzene and to this were added 3.9 g of freshly prepared lead tetraacetate (0.0087 mole) in three portions. The mixture was stirred at 50° for 2 hrs. and then at 60° for 2 hrs. After the duration, excess of lead tetraacetate was decomposed with water and lead oxide formed was removed by filtration. The filtrate was dried over anhydrous sodium sulphate and the solvent was distilled off. Distillation of the residue *in vacuo* gave (*α*)-methyl mesaconaldehydate, bp. 76-8°/12 mm, n_D^{20} 1.4680 (0.75 g, 75%). 2,4-*Dinitrophenylhydrazone*, orange needles (from methanol), mp. 204-4.5° (decomp.), (*Anal.* Found : C 46.73, H 3.92, N 18.21. Calcd. for $C_{12}H_{12}O_6N_4$: C 46.76, H 3.92, N 18.18).

(*α*)-**Methyl** (*β*)-**hydrogen mesaconate** (XV). The aldehyde-ester (XIV ; 0.3 g, 0.0024 mole) was dissolved in 2.7 ml of 13.3% peracetic acid (0.0047 mole) and the mixture was kept cold for 36 hrs. Then the mixture was diluted with water and dried up *in vacuo* to yield a crystalline mass. The residue was crystallized from petroleum ether (bp. 40-50°) to give (*α*)-methyl (*β*)-hydrogen mesaconate (0.31 g). needles, mp. 82-3°. *Anal.* Found : C 50.04, H 5.61. Calcd. for $C_6H_8O_4$: C 50.00, H 5.60. *Amide*, needles (from ether-petroleum ether), mp. 115.5-6.5° (*Anal.* Found : C 50.39, H 6.51, N 9.72. Calcd. for $C_6H_9O_3N$: C 50.34, H 6.34, N 9.79). These were perfectly consistent with the literature[19].

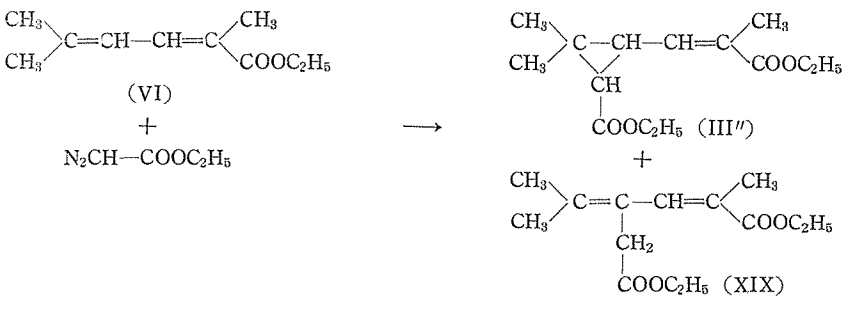
Mesaconic acid (XVI). (α)-Methyl (β)-hydrogen mesaconate (XV ; 0.1 g) was hydrolysed with cold 5% ethanolic potassium hydroxide, dried up *in vacuo* and acidified with dilute sulphuric acid. This was extended in ether, dried over anhydrous sodium sulphate and the removal of ether gave mesaconic acid, cubes (from water) mp, 202-3°. *Anal.* Found : C 46.07, H 4.60. Calcd. for $C_5H_6O_4$: C 46.16, H 4.65. The melting point was not depressed by the mixed melting point comparison with an authentic specimen prepared by the recorded method[19]. *Di*-p-*phenylphenacylester*, fine needles (from chloroform), mp. 204-5°. (*Anal.* Found : C 76.35, H 5.14. Calcd. For $C_{33}H_{26}O_6$: C 76.43, H 5.05).

Peroxidation of $\alpha\delta$-dimethylsorbic acid (VII) $\alpha\delta$-Dimethylsorbic acid (VII ; 0.5 g) was dissolved in 10 ml of dilute acetic acid, and to this were added 5 ml of 30% hydrogen peroxide. The mixture was warmed on a steam bath for ca 10 hrs. with additional peroxide at intervals. At the end of this time, the solution was dried up *in vacuo* and the solid residue was extracted with cold ether. To the remaining residue were added a drop of dilute sulphuric acid and 2 ml of water, and it was warmed on a water bath. Reduction of the volume gave mesaconic acid (19 mg), which melted at 201-3° after recrystalization from water. The melting point was not depressed by admixture with an authentic specimen. Further reduction of the filtrate gave a less pure product (ca 25 mg).

III. THEORY OF THE ADDITION OF ALIPHATIC DIAZOCOMPOUNDS TO DIENE SYSTEM

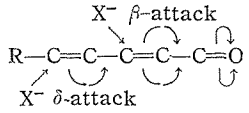
The mechanism of the addition of aliphatic diazo-compounds to olefins remains uncertain. It is currently interpreted by two ways, *i.e.* the participation of the free radicals and the path over pyrazoline intermediates, and the former seems to be used more widely for the interpretations at the present time.

Inouye[22] isolated a pyrazoline intermediate on the addition of diazoacetate to $\alpha\delta$-dimethylsorbate (VI), then he preferred the pyrazoline intermediate mechanism for that addition reaction. He also took the fact for the explanation that the addition of ethyl diazoacetate to ethyl $\alpha\delta$-dimethylsorbate (VI) produced an acyclic isomer (XIX) as well as the cyclopropane derivative, *i.e.* ethyl chrysanthemumdicarboxylate (III'').

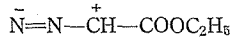


The formation of the acyclic isomer (XIX) could not be explained by means of the addition of the diradical $:CHCOOC_2H_5$. By assuming the pyrazoline intermediate (XX), the formation of all addition products could be satisfactorily explained.

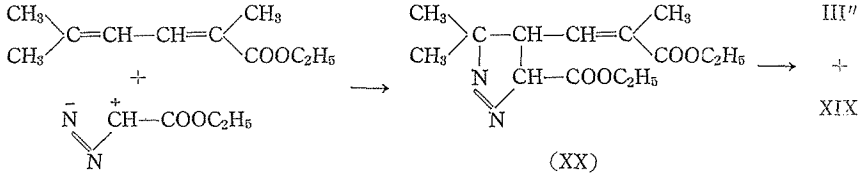
As mentioned in chapter II, Inouye[2a] obtained only the $\gamma\delta$-adduct in the addition of ethyl diazoacetate to ethyl $\alpha\delta$-dimethylsorbate. $\alpha\delta$-Dimethylsorbic acid (VII) also indicated the more reactivity at $\gamma\delta$-double bond in the catalytic hydrogenation and oxidations. Therefore, in order to explain the exclusive addition of diazo-compound to the $\gamma\delta$-double bond, the following mechanism seems appropriate. Either the β- or the δ-position in the conjugated compounds such as β-vinylacrylic acid and sorbic acid, is in principle positively polarisable, and is, therefore, a potential place of attachment of the anionic portion of the addendum, especially the δ-position is more potential in the substituted sorbic acid systems,



Whilst, diazoacetate takes part in the reaction under consideration as the resonance hybrid,



Thus, in due course, the anionic portion of diazoacetate enters the δ-position, and then the protonic part becomes bound at the γ-carbon atom. As the result of the addition of these two components, there forms the pyrazoline (XX), which is responsible for producing both ethyl chrysanthemumdicarboxylate (III'') and



its acyclic isomer (XIX). This mechanistic argument can apply to the reactions, such as the addition of ethyl diazoacetate to methyl $\alpha\beta\delta$-trimethylsorbate[23] and methyl sorbate[24] and of diphenyldiazomethane to menthyl sorbate[25]. All of these olefinic components had the same conjugated system as mentioned above, and each diazo-compound added exclusively to the $\gamma\delta$-double bond. Addition of ethyl diazoacetate also took place at $\gamma\delta$-ethylenic bond of 1-phenylbutadiene[26] which had an similar conjugated system as sorbic acid. In contrast, Guha and Sankaran[27] observed terminal addition of diazomethane to ethyl muconate. However, two ethylenic bonds of ethyl muconate are equally poralized and there is no difference of the reactivity in each double bond,

therefore the result seems to be reasonably expected. Should this theory be applied to the system of α-methylmuconate, in which the $\gamma\delta$-double bond is more reactive than $\alpha\beta$-double bond as mentioned in the preceding chapter, diazo-compound should add to the $\gamma\delta$-double bond of α-methylmuconate. Hence it must become possible to obtain chrysanthemumdicarboxylic acid by means of the addition of dimethyldiazomethane to α-methylmuconate. In the fact, the addition reaction did take place at the $\gamma\delta$-double bond, giving chrysanthemumdicarboxylic acid. The details of this reaction will be described in chapter V.

IV. SYNTHESIS AND STEREOCHEMISTRY OF α-METHYLMUCONIC ACID[20]

The theoretical consideration mentioned in the preceding chapters leads to a result that it is possible to synthesize isomeric chrysanthemumdicarboxylic acid by the addition of dimethyldiazomethane to α-methylmuconate. Hence, it became necessary to prepare a considerable amount of α-methylmuconic acid as a starting material, and to establish the geometrical configuration thereof for furthering this scheme. Kuhn and Michel[28] prepared an isomer of α-methylmuconic acid by the condensation of ethyl tiglate with ethyl oxalate, followed by acetylation and hydrolysis. The geometrical configuration of the acid, however, has not yet been confirmed, though it is assumed tentatively to be *trans,trans*.

α-Methylmuconic acid can exist theoretically in four geometrically isomeric forms *cis,cis*; *cis,trans*; *trans,cis* and *trans,trans*.* Of these, three isomers were obtained by the present author through a novel route of synthesis and their geometrical configurations were established. The isolation of the remaining one isomer, *trans,cis*, has failed in spite of any attempt.

The oxidation of *o*-cresol (XXI) with peracetic acid gave α-methyl-*cis,cis*-muconic acid (XVII *c-c*), mp. 189-90°, which was converted with diazomethane into the dimethylester (XXII *c-c*), mp. 35°.

The treatment of the *cis,cis*-acid (XVII *c-c*) with cold 80% sulphuric acid gave the unsaturated lactonic acid (XVIII), mp. 105-6°, the structure of which is evidenced by the subsequent chemical processes. The lactonization was also effected by boiling with water, yielding the same compound (XVIII). It was of interest that the lactonization of the acid (XVII *c-c*) under any reaction conditions employed, gave exclusively the lactonic acid (XVIII) alone. This seems very likely, from the theoretical consideration which was discussed in chapter II.

The lactonic acid (XVIII) afforded a liquid methyl ester (XXIII) with diazomethane. The unsaturated lactonic ester (XXIII) took up one mole

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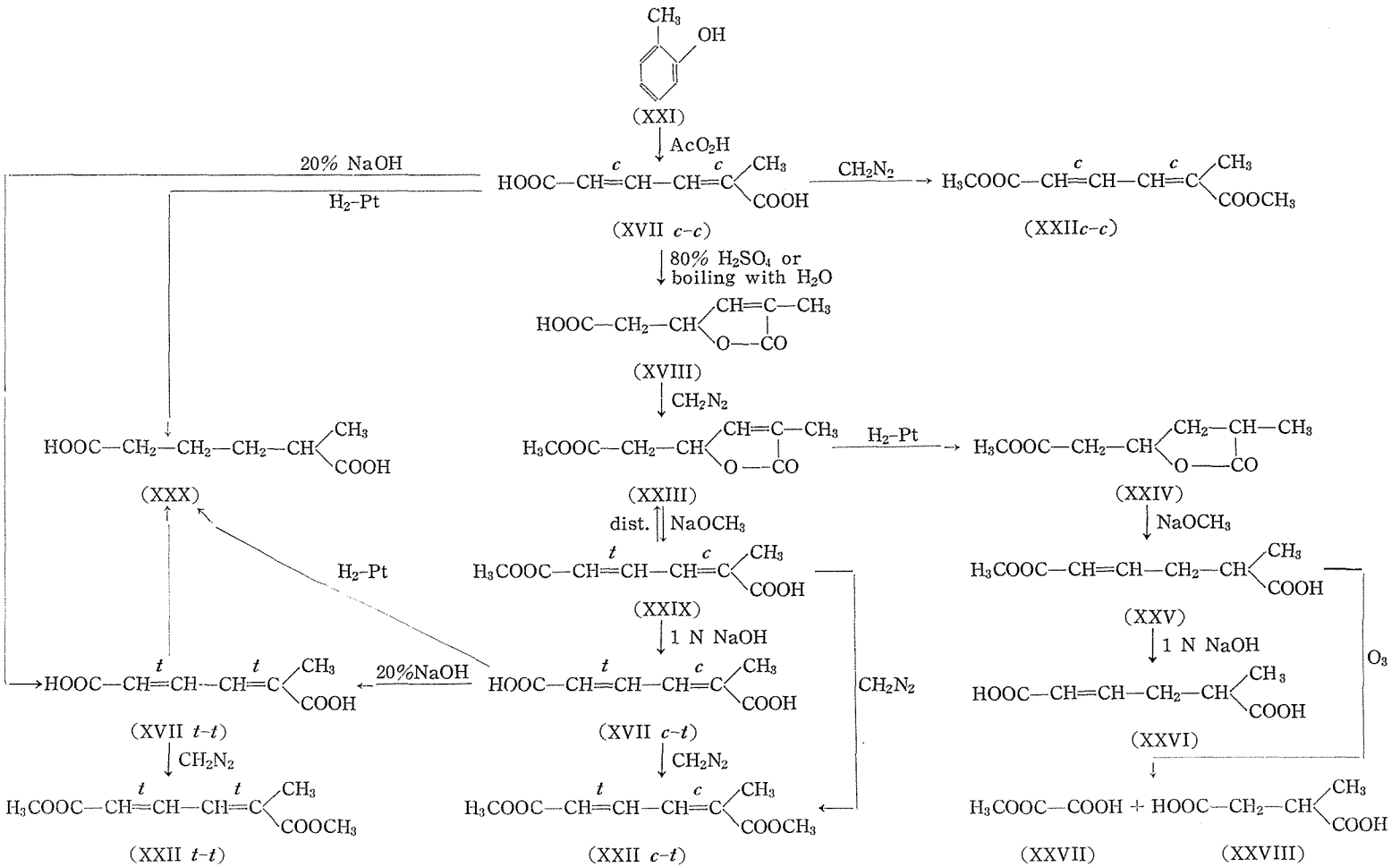
* The nomenclature of these compounds are based on α-methylmuconic acid, therefore, *e.g.* MeOOC—$\overset{trans}{CH}$=CH—$\overset{cis}{CH}$=CMe—COOH is named (δ)-methyl (α)-hydrogen α-methyl-*cis,trans*-muconate. The terms *cis* and *trans* are given in positional order, thence the first term indicated the configuration of the $\alpha\beta$-double bond.


(XXI)
AcO2H
20% NaOH
H2-Pt
HOOC—CH=CH—CH=C(CH3)COOH
(XVII c-c)
CH2N2
H3COOC—CH=CH—CH=C(CH3)COOCH3
(XXII c-c)
80% H2SO4 or boiling with H2O
(XVIII)
CH2N2
H3COOC—CH2—CH(CH=C—CH3)O—CO
(XXIII)
H2-Pt
H3COOC—CH2—CH(CH2—CH—CH3)O—CO
(XXIV)
dist. NaOCH3
NaOCH3
H3COOC—CH=CH—CH=C(CH3)COOH
(XXIX)
H3COOC—CH=CH—CH2—CH(CH3)COOH
(XXV)
1 N NaOH
HOOC—CH2—CH2—CH2—CH(CH3)COOH
(XXX)
H2-Pt
HOOC—CH=CH—CH=C(CH3)COOH
(XVII t-t)
20%NaOH
HOOC—CH=CH—CH=C(CH3)COOH
(XVII c-t)
1 N NaOH
HOOC—CH=CH—CH2—CH(CH3)COOH
(XXVI)
O3
CH2N2
CH2N2
H3COOC—CH=CH—CH=C(CH3)COOCH3
(XXII t-t)
H3COOC—CH=CH—CH=C(CH3)COOCH3
(XXII c-t)
H3COOC—COOH + HOOC—CH2—CH(CH3)COOH
(XXVII)
(XXVIII)

hydrogen on catalytic hydrogenation, giving the saturated lactonic ester (XXIV), mp. 45-6°. The treatment of the saturated lactonic ester (XXIV) with sodium methoxide in methanol gave an acyclic isomer (XXV), hydrolysis of which afforded α-methyl-$\Delta\gamma$-dihydromuconic acid (XXVI), mp. 121-2°. The half ester (XXV) was characterized by ozonolysis to yield methyl hydrogen oxalate (XXVII) and methylsuccinic acid (XXVIII). Therefore, the structures of the unsaturated lactonic acid and of the compounds derived therefrom, were confirmed as XVIII~XXVI.

The treatment of the unsaturated lactonic ester (XXIII) with sodium methoxide in methanol gave the expected (δ)-methyl (α)-hydrogen α-methyl-*cis*, *trans*-muconate (XXIX), mp. 121°, which was readily reconverted into the parent unsaturated lactonic ester (XXIII) by distillation under reduced pressure. On hydrolysis with dilute sodium hydroxide, the half-ester (XXIX) produced α-methyl-*cis*,*trans*-muconic acid (XVII *c-t*), mp. 172°. Esterification of either the acid (XVII *c-t*) or the half-ester (XXIX) with diazomethane yielded the same dimethyl ester (XXII *c-t*), mp. 60°.

When the *cis*,*cis*- (XVII *c-c*) and the *cis*,*trans*-acids (XVII *c-t*) were heated with 20% sodium hydroxide, these were equally isomerized into the *trans*,*trans*-form (XVII *t-t*), mp. 273°, which might be identical with that obtained by Kuhn and Michel,[28] mp. 276°, though direct comparison by mixed melting point is lacking. The acid (XVII *t-t*) was converted with diazomethane into the dimethyl ester (XXII *t-t*), mp. 55.5°, which also might correspond to the ester recorded by Harris and Binns,[29] mp. 46-7°.

On catalytic hydrogenation over platinum catalyst, each of the *trans*,*trans*-, *cis*,*trans*- and *cis*,*cis*-acids took up two moles hydrogen and gave the same α-methyladipic acid (XXX), mp. 58-9°, which was also characterized by its diamide, mp. 185-6°.

Configuration : — The configurations of the three acids, (XVII *c-c*), (XVII *c-t*) and (XVII *t-t*), followed unambiguously from the method of preparation and the spectral data. The high melting and the most stable isomer (XVII *t-t*) is expected to have all *trans*-configuration, because it is also obtained by the condensation of tiglate of the well-defined *trans*-configuration with oxalate, in which the *trans*-configuration is favoured in genaral. The failure of the isomer to be lactonized with 80% sulphuric acid into lactonic acid, is in good agreement with this deduction.

The acid (XVII *c-c*) obtained by the oxidative ring-fission of *o*-cresol is most likely to have *cis*,*cis*-configuration. It is, in fact, readily lactonized to XVIII. Moreover, it is isomerized to the high melting acid (XVII *t-t*) both directly and *via* the third acid (XVII *c-t*).

The half-ester of the third acid (XXIX) produced by ring opening reaction with alkoxide is expected to have *cis*,*trans*-configuration. The $\alpha\beta$-double bond must be undoubtedly *cis* in the lactone. The *cis*-configuration of the $\alpha\beta$-double bond should be retained as such during the ring opening reaction, since the resulting half-ester was capable of ready lactonization into the parent compound (XXIII). The $\gamma\delta$-double bond which is created by the ring opening

reaction, is considered to have *trans*-configuration by the analogies in similar reactions.

The third acid (XVII *c-t*) can also be isomerized to the *trans,trans*-acid (XVII *t-t*). It is evident, therefore, that the third acid (XVII *c-t*) has *cis,trans*-configuration.

The first acid (XVII *c-c*) produced by ring fission of *o*-cresol has at least one *cis*-double bond, since it is readily lactonizable. It can be isomerized to the *cis,trans*-isomer *via* the lactone, hence the *trans,cis*-configuration is excluded for it. Therefore, the first acid (XVII *c-c*) should reasonably be concluded to be *cis,cis*, also by the expectation that it is formed by the fission of an aromatic ring under a mild condition, then it will appear in a coiled phase with orientation of *cis,s-cis,cis* at the first step.

The conclusions on the configurations of each acid are in complete agreement with spectral data.

The UV-spectrum data of the isomeric α-methylmuconic acids and their esters are collected in Table 1, together with those of some isomeric homologues.

Table 1. Ultra-violet light absorption of isomeric α methylmuconic acids in comparison with some homologues.

	cis-cis		*cis-trans*		*trans-trans*	
	λmax. (mμ)	ε	λmax. (mμ)	ε	λmax. (mμ)	ε
α-Methylmuconic acid	269	20,700	269	25,700	273	29,700
methyl ester	270	24,800	272	27,600	275	31,100
Muconic acid[30]	258	17,000	259	25,600	259	29,100
methyl ester	259	26,400	260	29,800	259	36,700
$\alpha\alpha'$-Dimethylmuconic acid[31]	281	20,400	280	25,500	282	31,450
methyl ester	280	24,750	280	31,600	282	33,300
β-Methylmuconic acid[32]	—	—	265	19,000	265	22,400
methyl ester	—	—	265	22,100	266	28,400

Positions of the absorption maximum of each isomer are practically the same. There is no significant *cis*-shift, but the extinction coefficients show a significant difference in every case, the coefficient of *cis,cis*-isomer is the lowest and each *cis*→*trans* inversion increases the intensity. The validity of these criteria was also discussed in the series of α-methyl-$\alpha\beta$-unsaturated acids, reported in the previous paper of the authors[8].

The *cis,cis*-acid has a maximum extinction coefficient of 20,700 at 269 mμ, the *cis,trans*-acid, 25,700 at 269 mμ, and the *trans,trans*-acid, 29,700 at 273 mμ, The methyl esters have the values of 24,800 at 270 mμ, 27,600 at 272 mμ and 31,100 at 275 mμ, respectively. These values unequivocally agreed with the expected values for each configuration.

In Table 2 are summarized the characteristic bands in IR-spectra of the

isomers.

Table 2. Characteristic bands in the infra-red absorption spectra of the isomeric α-methylmuconic acids (cm^{-1}).

cis-cis	*cis-trans*	*trans-trans*
—	995	988
839	822	820
736	—	—

EXPERIMENTAL

α-Methyl-*cis,cis*-muconic acid (XVII *c-c*) A mixture of 73.5 g (0.68 mole) of *o*-cresol (XXI) and 790 ml of 13% peracetic acid solution (1.36 mole of peracetic acid) was cooled in ice for 24 hrs. and then kept cold for 1 or 2 weeks. After the duration, the crystalline precipitate was collected, washed with acetic acid and recrystallized from methanol by cooling with dry-ice, to give the pure α-methyl-*cis,cis*-muconic acid in prisms, mp. 189-90° (this mp. was taken from a bath at 160°, with the temperature rising 10° per minute, since it varied with the rate of heating), λmax. 269 mμ, ε 20,700. *Anal.* Found : C 53.73, H 5.26. Calcd. for $C_7H_8O_4$: C 53.84, H 5.16. yield 12.3 g (11.3%).

Quantitative hydrogenation :— A 0.103 g quantity of the acid (XVII *c-c*) in 60 ml of methanol was hydrogenated over a platinum oxide catalyst (10 mg) in a shaking apparatus and absorbed 36 ml (at 23°) of hydrogen, equivalent to two double bonds. The reduction product was freed from the catalyst and the solvent, and recrystallized from benzene to give *α-methyladipic acid* (XXX), mp. 58-9° (Mazza and DiMase[33] recorded mp. 61°). *Anal.* Found : C 52.57, H 7.45. Calcd. for $C_7H_{12}O_4$: C 52.49, H 7.55. Also characterized by *diamide*, mp. 185-6° (Bouveault and Locquin[34] recorded mp. 186.5°), (*Anal.* Found : C 53.06, H 8.91, N 17.79. Calcd. for $C_7H_{14}O_2N_2$: C 53.14, H 8.97, N 17.71).

Methyl α-methyl-*cis,cis*-muconate (XXII *c-c*) The *cis,cis*-acid (XVII *c-c*) was treated with ethereal diazomethane solution in the usual manner and the dimethyl ester was obtained in the yield almost quantitative. After recrystallization from light petroleum (bp. 40-50°) or methanol, it formed prisms, mp. 35°, λmax. 270 mμ, ε 24,800. *Anal.* Found : C 58.70, H 6.80. Calcd. for $C_9H_{12}O_4$: C 58.69, H, 6.57.

γ-Carboxymethyl-α-methyl-Δα-butenolide (XVIII) (a) A 3.62 g quantity of the *cis,cis*-acid (XVII *c-c*) was shaken with 36 ml of cold 80% sulphuric acid for 1 hr. After 24 hrs., the reaction mixture was poured onto ice and the bulk of the acid was neutralized with an aqueous ammonia (acid to Congo-red). The solution was thoroughly extracted with ether. After removal of ether, the product was recrystallized from chloroform to yield the lactonic acid (XVIII) in prisms, mp. 105-6°. *Anal.* Found : C 53.60, H 5.34. Calcd. for $C_7H_8O_4$: C 53.84, H 5.16. yield 3.08 g.

(b) A 0.75 g quantity of the *cis,cis*-acid (XVII *c-c*) was heated with water under reflux for 1 hr. The reaction mixture was dried up on a water bath and the residue was recrystallized from ethyl acetate to yield γ-carboxymethyl-α-methyl-$\Delta\alpha$-butenolide, mp. 105°. *Anal.* Found : C 53.88, H 5.03. Calcd. for $C_7H_8O_4$: C 53.84, H 5.16. The mixed mp. with the product in the procedure (a) was 105°, yield 0.60 g.

γ-Carbomethoxymethyl-α-methyl-$\Delta\alpha$-butenolide (XXIII) To the lactonic acid (XVIII ; 9.21 g, 0.059 mole) in ether was added an ethereal solution of diazomethane (0.065 mole) under cooling and well stirring, the product then distilled under reduced pressure to give the lactonic ester, bp. 150-1°/9 mm, n_D^{20} 1.4741. (9.28 g)

γ-Carbomethoxymethyl-α-methylbutanolide (XXIV) A 1.314g quantity (0.0077 mole) of the unsaturated lactonic ester (XXIII) in 50 ml of methanol was hydrogenated over platinum catalyst and it took up 218 ml (at 20°) of hydrogen, equivalent to 1.1 mole. The reduction product was freed from the catalyst and the solvent, and distilled to give the saturated lactonic ester, bp. 135-9°/5 mm ; it crystallized from ether-light petroleum in laths, mp. 45-6°. *Anal.* Found : C 55.73, H 6.98. Calcd. for $C_8H_{12}O_4$: C 55.80, H 7.03.

(δ)-Methyl (α)-hydrogen α-methyl-$\Delta\gamma$-dihydromuconate (XXV) To 0.74 g (0.0043 mole) of the saturated lactonic ester (XXIV) in 8 ml of methanol was added 1.64 ml of methanolic sodium methoxide (2.62 *N*; 0.0043 mole) at room temperature. After 15 min., the reaction mixture was evaporated under reduced pressure and then, were added 6 ml of water and it was acidified with dilute hydrochloric acid. An oily substance separated was extracted with ether. The solvent was removed and the residual product was completely dried over paraffin *in vacuo*, n_D^{23} 1.4642, yield 1.20 g.

Ozonization ; — A 1.7 g quantity of the half-ester in chloroform was treated with an excess of ozone at 0°. The solvent was removed *in vacuo*, and the remaining ozonide was decomposed with water on a water bath for 10-15 min. and extracted with ether. The ethereal solution was distilled under reduced pressure to give methyl hydrogen oxalate (XXVII), bp. 110-4°/8 mm. (Anschütz,[35] bp. 108-9°/12 mm), yield 0.75 g. This half-ester was readily hydrolyzed to oxalic acid, mp. 185°, not depressed by admixture with an authentic specimen. The residue of the distillation was recrystallized from ethyl acetate, to yield methylsuccinic acid (XXVIII), mp. 106°, not depressed by mixed melting point comparison with an authentic specimen,[36] yield 0.9 g. This acid was also characterized by *di*-p-*phenylphenacylester*, mp. 179° (*Anal.* Found : C 75.92, H 5.54. Calcd. for $C_{33}H_{28}O_6$: C 76.14, H 5.42).

α-Methyl-$\Delta\gamma$-dihydromuconic acid (XXVI). A 1.17 g quantity of the half-ester (XXV) was warmed on a steam bath with 12.5 ml of 1 *N* sodium hydroxide for 1 hr., then, the reaction mixture was acidified with dilute hydrochloric acid, and extracted with ether, the acid was recrystallized from benzene in needles, mp. 121-2°. *Anal.* Found : C 53.38, H 6.44. Calcd. for $C_7H_{10}O_4$: C 53.16, H 6.37. yield 0.64 g.

(δ)-Methyl (α)-hydrogen α-methyl-*cis,trans*-muconate (XXIX) To the un-

saturated lactonic ester (XXIII; 5.09 g, 0.0299 mole) in 50 ml of methanol, was added 12.5 ml of methanolic sodium methoxide (2.39 *N*). After 15 min., the solution was evaporated under reduced pressure. Water (50 ml) was added and the solution was acidified with hydrochloric acid, whereupon methyl hydrogen *α*-methyl-*cis,trans*-muconate separated, which crystallized from benzene in prismatic needles, mp. 121°, λmax. 275 mμ, ε 22,000. *Anal.* Found: C 56.53, H 5.98. Calcd. for $C_8H_{10}O_4$: C 56.46, H 5.92. yield 4.60 g.

Reconversion into the lactonic ester: — When the half-ester (0.27 g) was heated at 170-5° under reduced pressure, a liquid distillate was obtained. After redistillation it gave the unsaturated lactonic ester (XXIII), bp. 150-5°/11 mm, n_D^{25} 1.4820 (yield 0.18 g), which was identified by the IR-spectrum.

***α*-Methyl-*cis,trans*-muconic acid** (XVII *c-t*) A 1.50 g quantity of the preceding half-ester (XXIX) was warmed with 17.6 ml of 1 *N* sodium hydroxide on a steam bath for 1 hr. After the duration, the solution was acidified with hydrochloric acid, the separated crystal was recrystallized from methanol and from ethyl acetate to yield the *cis,trans*-acid in plates, mp. 172°, λmax. 269 mμ, ε 25,700. *Anal.* Found: C 53.87, H 5.23. Calcd. for $C_7H_8O_4$: C 53.84, H 5.16. yield 1.35 g.

Hydrogenation: — The hydrogenation of the *cis,trans*-acid (XVII *c-t*) over a platinum catalyst gave *α-methyladipic acid* (XXX), having mp. and mixed mp. 58-9°.

Methyl *α*-methyl-*cis,trans*-muconate (XXII *c-t*) Treatment of methyl hydrogen *α*-methyl-*cis,trans*-muconate (XXIX) with ethereal diazomethane, and evaporation of the solution afforded the dimethyl ester which, after recrystallization from methanol, formed prisms, mp, 60°, λmax. 272 mμ, ε 27,600. *Anal.* Found: C 53.84, H 6.70. Calcd. for $C_9H_{12}O_4$: C 58.69, H 6.57. The same dimethyl ester was also obtained by the same procedure from the *cis,trans*-acid (XVII *c-t*).

***α*-Methyl-*trans,trans*-muconic acid** (XVII *t-t*) (a) *α*-Methyl-*cis,cis*-muconic acid (XVII *c-c*; 0.51 g) was heated with 30 ml of 20% aqueous sodium hydroxide for 4 hrs. The solution was cooled and acidified with dilute sulphuric acid. The separated precipitate was recrystallized from methanol to yield the *trans, trans*-acid in prisms, mp. 273° (Kuhn and Michel[28] recorded mp. 270°), λmax. 273 mμ, ε 29,700. *Anal.* Found: C 54.00, H 5.29. Calcd. for $C_7H_8O_4$: C 53.84, H 5.16. yield 0.45 g.

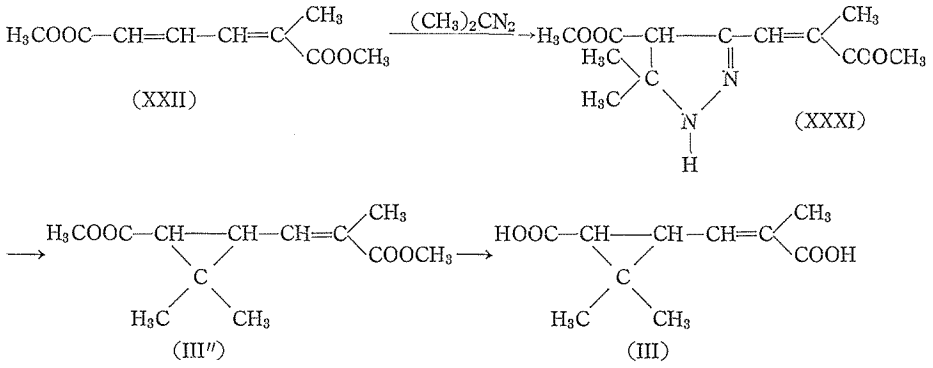
(b) *α*-Methyl-*cis,trans*-muconic acid (XVII *c-t*) gave the same acid exactly by the same procedures as mentioned above.

Hydrogenation of the *trans,trans*-acid gave *α-methyladipic acid* (XXX), as was the case with the *cis,cis*- and *cis,trans*-acids.

Methyl *α*-methyl-*trans,trans*-muconate (XXII *t-t*) The esterification of the *trans,trans*-acid (XVII *t-t*) with diazomethane gave the dimethyl ester in plates (from methanol), mp. 55.5°, λmax. 275 mμ, ε 31,100 (Harris and Binns[29] reported mp. 46-7°, λmax. 276 mμ, log ε 4.17), *Anal.* Found: C 58.51, H 6.87. Calcd. for $C_9H_{12}O_4$: C 58.69, H 6.57.

V. ADDITION OF DIMETHYLDIAZOMETHANE TO METHYL α-METHYLMUCONATE[11]

Dimethyldiazomethane was added to methyl α-methyl-*trans,trans*-muconate (XXII *t-t*) in chilled xylene solution yielding a crystalline *trans*-pyrazoline ester (XXXI *t*), mp. 144-5°. Since the IR-spectrum of the pyrazoline ester indicated well-defined N-H (3270 cm^{-1}), carboxyl C=O (1712 cm^{-1}) and C=N (1675 cm^{-1}) bands as well as the UV-spectrum thereof had maxima at 213 mμ (ε 13,200, end absorption) and 299 mμ (ε 9,600), the Δ^2-pyrazoline structure was established for the pyrazoline ester. The addition of dimethyldiazomethane occurred, as



was expected, selectively at the γδ-double bond of α-methylmuconate, this should reasonably be deduced from the subsequent processes. The thermal decomposition of *trans*-pyrazoline ester (XXXI *t*) in the presence of copper as catalyst took place under vigorous evolution of nitrogen, and subsequent distillation *in vacuo* of the residue gave methyl *trans,trans*-chrysanthemumdicarboxylate (III'' *t-t*)*, mp. 78-9°.

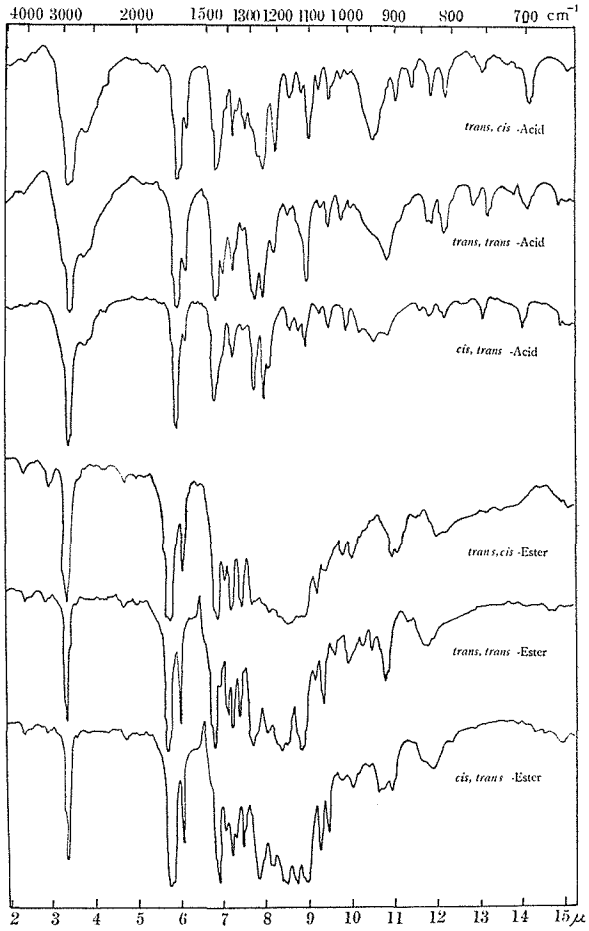
This crystalline ester as well as the corresponding free acid, mp. 206-8°, which was obtained by alkaline hydrolysis of the ester, were completely identical with the respective authentic specimens of methyl *trans,trans*-chrysanthemumdicarboxylate (III'' *t-t*) and its free acid (III *t-t*) previously obtained through a different route by Inouye[2]. It was shown by the mixed melting point comparison as well as by the complete identity of IR- and UV-spectra. The formation of *trans,trans*-chrysanthemumdicarboxylic acid (III *t-t*) from α-methyl-*trans,trans*-muconic acid (XVII *t-t*) by the addition of dimethyldiazomethane provides another evidence for the geometrical configuration of the side chain double bond of naturally occurring chrysanthemumdicarboxylic acid to be *trans* which has been concluded by the authors.[8,9]

The addition of dimethyldiazomethane to methyl α-methyl-*cis,trans*-muconate

* As to the representation of configurations of chrysanthemumdicarboxylic acids and their esters, the first prefix indicates the geometry of the cyclopropane ring and then the second that of the side chain double bond. Thence, the order of those terms in the parent α-methylmuconic acids are reversed.

(XXII *c-t*) gave *cis*-pyrazoline ester (XXXI *c*), mp. 99-103°. The $\gamma\delta$-Δ^2-pyrazoline structure of this pyrazoline ester was also deduced from its IR-spectrum and the following procedures. The same *cis*-pyrazoline ester (XXXI *c*) was obtained by the addition of dimethyldiazomethane to methyl α-methyl-*cis*,*cis*-muconate (XXII *c-c*). It is reasonable that the same pyrazoline ester should be given from the *cis*,*trans*- and *cis*,*cis*-isomers of the starting material, because the configuration of $\alpha\beta$-double bond of the starting materials are retained as such in the side chain double bond of the adducts and the specific geometry of the $\gamma\delta$-double bond is broken, since the pyrazoline had a planar Δ^2-pyrazoline structure.

On the thermal decomposition followed by hydrolysis, the *cis*-pyrazoline ester (XXXI *c*) converted into an acid of mp. 191°. By mixed melting point comparison with the authentic specimens of *trans*,*trans*- (III *t-t*) and *cis*,*trans*-chrysanthemumdicarboxylic acid (III *c-t*)[2] respectively, this acid showed marked depression of the melting point. Then it was established that this acid differed



Infra-red spectra of the isomeric chrysanthemumdicarboxylic acids in nujol mull and their methyl esters in carbontetrachloride solution.

from both *trans,trans*- and *cis,trans*-chrysanthemumdicarboxylic acids. Although the IR-spectra of this acid and its methyl ester differed from those of *trans,trans*- and *cis,trans*-chrysanthemumdicarboxylic acids and their methyl esters in fine features, these were similar in most respects each other sufficient to establish that this acid had an analogous structure to these acids. The UV-absorption maximum of this acid (λmax. 236 mμ) showed that this acid had the same chromophore as *trans,trans*- and *cis,trans*-chrysanthemumdicarboxylic acids, and its molecular extinction coefficient was consistent with the value expected by the *cis*-side chain structure. Therefore, this acid was established as *trans, cis*-chrysanthemumdicarboxylic acid (III *t-c*) having *trans*-structure about cyclopropane ring and *cis* form about side chain double bond.

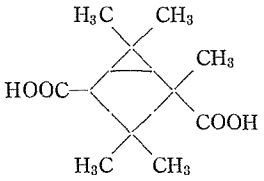
Acid	mp.	λmax.	ε	Dimethylester
trans,trans	206-8°	237 mμ	15,400	mp. 78-9°
cis,trans	208-9°	234	14,700	bp. 100.5-101.5°/0.5 mm, n_D^{20} 1.4882
trans,cis	191°	236	9,500	bp. 101-2°/1 mm, n_D^{20} 1.4748

Matsui[7] and his co-workers obtained an acid of mp. 175-7° as *trans,cis*-chrysanthemumdicarboxylic acid starting from *trans*-caronylpropionitrile, however there yet remains some doubts in their conclusion that the *trans,cis*-isomer alone can be obtained stereospecifically in their processes, and also the mixture of equal amount of pure *trans,trans*- (mp. 206-8°) and *trans,cis*-acids (mp. 191°) prepared by the present author showed a similar melting point (176-180°) to that of Matsui's acid. Therefore, the acid prepared by Matsui seems likely to contaminate the *trans,trans*-isomer. This was also convinced by Matsui and his co-workers, who described that they recognized their acid to be heterogeneous on X-ray diffractions and they tried to purify by means of recrystallization but in vain.

It was somewhat surprising that *trans,cis*-chrysanthemumdicarboxylic acid retained its *cis*-configuration of the side chain double bond after being boiled in caustic alkaline solution, contrary to that the starting material, α-methyl-*cis,trans*-muconic acid (XVII *c-t*), was easily isomerized under the same conditions. It seems likely to be related to the fact that chrysanthemumdicarboxylic acid is very difficult to add bromine as well as hydrogen.

We now return to the by-products in these processes. In the addition of dimethyldiazomethane to methyl α-methyl-*cis,cis*-muconate, a small amount of a pyrazoline ester of mp. 151° (XXXII) was obtained, the yield of which varied from 5.5 to 0% according to the portion of dimethyldiazomethane employed. Both the analytical and spectral data showed that this pyrazoline ester should have a bicyclic pyrazoline structure which resulted from 1,4-addition of one molecule of dimethyldiazomethane and subsequent addition of another molecule of dimethyldiazomethane to the double bond newly created by the rearrangement. This pyrazoline ester gave an acid, mp. 220°, by thermal decom-

position and subsequent hydrolysis, which is assumed to be 2,3,3,6,6,-pentamethylbicyclo [3,1,0] hexane-2,4-dicarboxylic acid (XXXIII) from the analytical data but further elucidation of the structure has not yet been completed.

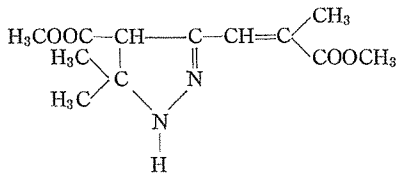


(XXXIII)

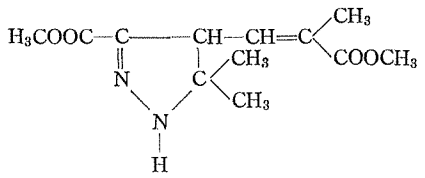
In the thermal decomposition of the pyrazoline esters, aliphatic by-products were obtained, and it was partially responsible for reducing the yield of the expected cyclopropane acids, chrysanthemumdicarboxylic acids.

From the *trans*-pyrazoline ester (XXXI *t*), a small quantity of an acid having mp. 121° was obtained as a by-product in the thermal decomposition and subsequent hydrolysis. This acid had a molecular formula $C_{10}H_{14}O_4$ identical with that of chrysanthemumdicarboxylic acid, and it showed λmax. at 218 mμ. The IR-spectrum of this acid resembled in most respects to that of the acid by-produced from *cis*-pyrazoline ester, described below, though there were some differences between them.

An acid of mp. 120-1° was obtained as a by-product in the thermal decomposition and subsequent hydrolysis of the *cis*-pyrazoline ester (XXXI *c*) in the yield of 16%. This acid had the same empirical formula $C_{10}H_{14}O_4$, as the *trans*-isomer mentioned above. The equivalent weight by titration of this acid was found as 191.8, which indicated that this acid had a formula $C_9H_{13}O_2COOH$; it was also supported by the analytical data of the amide derived therefrom. This acid absorbed 1 mole equivalent of hydrogen over a platinum catalyst giving an acid of mp. 132.5~133.5°, which had an empirical formula $C_{10}H_{16}O_4$. Therefore, it was expected that the acid of mp. 121° was an acyclic isomeric acid which formed on the way of thermal decomposition of the pyrazoline ring, and one of the two carboxylic groups became bound with one of the double bonds as to form a lactone ring. This expectation was supported by the fact that this acid consumed 2 mole of alkali after being refluxed with diluted alkaline solution and that the IR-spectra of this acid and of its amide showed an lactonic C=O band at 1718 cm^{-1} and 1678 cm^{-1} respectively. These lactonic C=O bands were located in longer wave length reagion than those of γ- or δ-lactones except $\alpha\beta$-unsaturated δ-lactone,[37] then this acid seems to have the $\alpha\beta$-unsaturted δ-lactone or less strained large lactone ring. The UV-spectrum of this acid showed an end absorption maximum at 220 mμ and did not show any other maximum, thereby indicating that this acid had not more-conjugated unsaturated systems than $\alpha\beta$-unsaturated carboxyl system. Regarding the structure of the parent substance (XXII), two structures are considerable to the pyrazoline ester in Δ^2-form, *i. e.* in one of them the terminal nitrogen atom of dimethyldiazomethane is bonded with the γ-carbon atom of α-methylmucon-

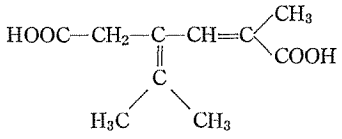


(XXXI)

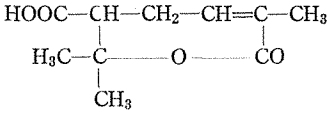


(XXXIV)

ate, as shown in formula XXXI, and in the other the nitrogen becomes bound at δ-carbon atom of α-methylmuconate, as shown in formula XXXIV. However, the latter form is excluded by the mechanistic argument of the addition of diazo-compound mentioned in chapter III, and also by the fact that the acyclic isomer (XXXV) expected from the pyrazoline structure (XXXIV) was already



(XXXV)



(XXXVI)

obtained by Inonye[2] which was too stable to lactonize under the conditions used. Therefore, the structure of this by-produced acid might be $\alpha\varepsilon\varepsilon$-trimethyl-$\delta$-carboxy-$\Delta\alpha$-hexenolide (XXXVI).

EXPERIMENTAL

Addition of dimethyldiazomethane to methyl α-methylmuconates.

(a) Addition to the *trans,trans*-ester. To the dimethyldiazomethane solution in xylene prepared from 5.3 g of acetone-hydrazone by Guha and Sankaran's method[38], were added 4.9 g of methyl α-methyl-*trans,trans*-muconate (XXII *t-t*) under vigorous stirring and cooling at -15 - $-20°$. The cooling and stirring were continued for ca 3 hrs., and then the solution was stood still overnight at room temterature. The reaction mixture was separated from a slaggy mercury and mercurous oxide by filtration. The filtrate was concentrated under reduced pressure. By cooling, the crystal of *trans*-pyrazoline ester (XXXI *t*) was obtained in lathes (from methanol or ethyl acetate), mp. 144-5° (decomp.), yield 3.7 g (56%). *Anal.* Found : C 56.59, H 7.01, Calcd. for $C_{12}H_{18}O_4N_2$: C 56.68, H 7.14.

IR-spectrum : N—H 3270, carboxyl C=O 1712, C=N 1675 cm^{-1}.

UV-spectrum : λmax. 213 mμ (end absorption) ε 13,200 ; 299 mμ, ε 9,600.

(b) Addition to the *cis,trans*-ester. To the dimethyldiazomethane solution prepared from 37 g of acetone-hydrazone, were added 31.4 g of methyl α-methyl-*cis,trans*-muconate (XXII *c-t*) in the same condition as the *trans,trans*-isomer. Xylene was removed from the reaction mixture and the crystal obtained by cooling of the residue was recrystallized from methanol yielding the *cis*-pyrazoline ester (XXXI *c*), mp. 99-100° (decomp.), plates, yield 21.4 g (49%).

Anal. Found : C 56.65, H 7.27. Calcd. for $C_{12}H_{18}O_4N_2$: C 56.68, H 7.14.
IR-spectrum : N—H 3230, carboxyl C=O 1715, C=N 1672 cm^{-1}.
UV-spectrum : λmax. 213 mμ (end absorption) ε 10,700 ; 299 mμ, ε 10,200.

(c) Addition to the *cis,cis*-ester. The addition of dimethyldiazomethane, prepared from 35.0g of acetone-hydrazone(3mole equivalent to the olefinic compound), to 30.0 g of methyl *α*-methyl-*cis,cis*-muconate (XXII *c-c*) was pursued in the same way as mentioned above. As well as the *cis*-pyrazoline ester (XXXI *c*), the other pyrazoline ester of mp. 151° (decomp.) (XXXII) was obtained in lathes. The yield of them were 17 g (41%) and 2.3 g (5.6%) respectively. In the case that the ratio of acetone-hydrazone used for preparing dimethyldiazomethane and methyl *α*-methyl-*cis,cis*-muconate was 1.5 to 1.0, the by-product of mp. 151° could not be obtained, though there is no distinct variation in the yield of the *cis*-pyrazoline ester (XXXI *c*). For the structure of the latter adduct, see the text. *Anal.* Found : C 55.65, H 7.74, N 17.09. Calcd. for $C_{15}H_{24}O_4N_4$: C 55.54, H 7.46, N 17.27.
UV-spectrum : λmax. 214 mμ (end absorption), ε 3,580.

Thermal decomposition of the pyrazoline esters.

(a) Decomposition of the *trans*-pyrazoline ester. One gram of the *trans*-pyrazoline ester (XXXI *t*) was mixed with 0.1 g of Gattermann's copper powder and heated at 160-170°, whereby the decomposition occurred with evolution of nitrogen. After nitrogen release was over, copper and resinous product insoluble in petroleum ether were removed, and the resulting oily substance was distilled under reduced pressure. Bp. 104-8°/1 mm, n_D^{20} 1.4855, yield 0.71g (79%). The distillate was partly crystallized after repeated rectifications, mp. 78-9°. The melting point was not depressed by the mixed melting point comparison with an authentic specimen of methyl *trans,trans*-chrysanthemumdicarboxylate (III'' *t-t*)[2].

(b) Decomposition of *cis*-pyrazoline ester. Five grams of *cis*-pyrazoline ester (XXXI *c*) was decomposed with 0.5 g of copper powder at 160-170°. The decomposition product was treated as above-mentioned, and an oily substance was obtained. Bp. 103-5°/1 mm, n_D^{20} 1.4758, yield 3.1 g (70%)

Hydrolysis of the esters (III'')

(a) A 0.58 g quantity of the ester of bp. 104-8°/1 mm was refluxed with 5.5 ml of 5% methanolic sodium hydroxide on a steam bath for 2 hrs. After removal of the solvent, the residue was dissolved in water, acidified with hydrochloric acid and extracted with ether. The ethereal extract was recrystallized from ethyl acetate to give the expected *trans,trans*-chrysanthemumdicarboxylic acid (III *t-t*), mp. 206-8° (mixed melting point with an authentic specimen[2] was 206-8°), yield 0.35 g (69%), as well as an by-produced acid of mp. 122°, yield 0.07g (14%). The characteristics of the latter acid, *Anal.* Found : C 60.90, H 7.40, Calcd. for $C_{10}H_{14}O_4$: C 60.59, H 7.12. UV-spectrum : λmax. 218 mμ, ε 14,200.

(b) In exactly the same way as mentioned above, 3.0 g of the ester of bp.

103-5°/1 mm was hydrolyzed. *trans,cis*-Chrysanthemumdicarboxylic acid (III *t-c*), mp. 191°, and an acid of mp. 120-1°, were obtained after fractional recrystallization from chloroform or methanol. The yield of them were 0.6 g (23%) and 0.4 g (16%) respectively. The characteristics of *trans,cis*-chrysanthemumdicarboxylic acid were as follows, prisms (from methanol), mixed melting points with *trans,trans*-chrysanthemumdicarboxylic acid (mp. 206-8°) and the *cis, trans*-isomer (mp. 208-9°) were 176-80° and 167-72° respectively. *Anal.* Found : C 60.68, H 7.38. Calcd. for $C_{10}H_{14}O_4$: C 60.59, H 7.12.

IR-spectrum : in the text.

UV-spectrum : λmax. 236 mμ, ε 9,500.

This acid was recovered unchanged after being refluxed with aquious 20% sodium hydroxide for 4 hrs., mp. 191° (recrystallized from ethyl acetate).

This acid was esterified with diazomethane to yield quantitatively its methylester (III'' *t-c*), bp. 101-2°/1 mm, n_D^{20} 1.4748.

The data of the by-produced acid of mp. 120-1° (XXXVI) were mentioned below. Prisms (from methanol). *Anal.* Found : C 60.78, H 7.24. Calcd. for $C_{10}H_{14}O_4$: C 60.59, H 7.12. Eq. wt. Found : 191.8, Calcd. for $C_9H_{13}O_2COOH$: 198.21

UV-spectrum : λmax. 220 mμ (end absorption), ε 6,700.

Hydrogenation : — A 0.998 g quantity of the acid of mp. 120-1° (XXXVI) in 80 ml of methanol was hydrogenated over a platinum catalyst (PtO_2 30 mg) in a shaking apparatus and absorbed 125 ml (at 19°) of hydrogen, equivalent to one double bond in $C_{10}H_{14}O_4$. The reduction product was freed from catalyst and the solvent, and recrystallized from benzene to give an acid mp. 132.5-133.5°, long needles, *Anal.* Found : C 60.10, H 8.15. Calcd. for $C_{10}H_{16}O_4$: C 59.98, H 8.05. Eq. wt. Found : 201.2, Calcd. for $C_9H_{15}O_2COOH$: 200.23 ; eq. wt. after the acid was refluxed with 1 *N* sodium hydroxide solution on a steam bath for 1 hr., Found : 104.2, Calcd. for $C_8H_{16}O(COOH)_2$: 109.12. *Amide*, mp. 152.5-3°, needles (from chloroform and light petroleum), *Anal.* Found : C 60.91, H 7.66, N 7.40. Calcd. for $C_{10}H_{15}O_3N$: C 60.89, H 7.67, N 7.10.

Thermal decomposition and subsequent hydrolysis of the pyrazoline ester (XXXII). A 2.41 g quantity of the pyrazoline ester (XXXII), mp. 151°, was decomposed with 0.15 g of copper powder, to give an oily substance, bp. 111-3°/0.5 mm, n_D^{20} 1.4688, yield 1.48 g. This ester (1.48 g) was hydrolysed and the product was recrystallized from ethyl acetate or benzene yielding an acid (XXXIII) of mp. 218-20°. *Anal.* Found : C 65.66, H 8.51. Calcd. for $C_{13}H_{20}O_4$: C 64.98, H 8.39.

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