Synthesis and Stereochemistry of Chrysanthemum-Dicarboxylic Acid

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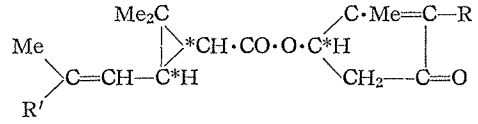
I. INTRODUCTION

The insecticidal constituents of the flower-heads of pyrethrum, *Chrysanthemum cinerariifolium*, which is grown commercially in Japan, Kenya and Latin America, are now known to be a mixture of cyclic keto-esters, collectively referred to as the "pyrethrins". The insecticidal activity of the "pyrethrins" is so specific and is advantageous over other types of insecticides in that the pyrethroids are non-toxic against the mammalia in spite of the incomparably high insecticidal effect and allow no resistance of insects. Especially, "pyrethrin IIs", i.e. esters of chrysanthemum-dicarboxylic acid, are far superior to "Is", esters of chrysanthemic acid, in knockdown effect and this is one of the reasons that the synthesis of chrysanthemum-dicarboxylic acid attracted the author's attention. Structures of four naturally occurring pyrethrins are recognised as follows.



(I)

Pyrethrin I.... (I), R= *cis*$CH_2CH{=}CH{\cdot}CH{=}CH_2$, R′=Me
Pyrethrin II... (I), R= *cis*$CH_2CH{=}CH{\cdot}CH{=}CH_2$, R′=$CO_2$Me
Cinerin I..... (I), R= *cis*$CH_2CH{=}CH{\cdot}$Me, R′=Me
Cinerin II..... (I), R= *cis*$CH_2CH{=}CH{\cdot}$Me, R′=CO_2Me

These structures have some features in common, i.e. they are all keto-esters,

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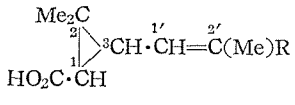
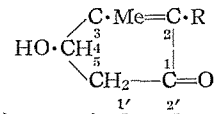
each giving on hydrolysis an acid with a cyclopropane nucleus and a keto-alcoholic derivative of cyclopentene. Pyrethrin I and cinerin I can each exist in 16 stereoisomeric forms, as each has two centres of optical activity together with the possibility of geometrical isomerism about the plane of the cyclopropane ring and the side chain double bond of the cyclopentenolone fragment. Pyrethrin II and cinerin II must also have either a *cis*- and *trans*- arrangement about the double bond in the cyclopropane portion and 32 stereoisomeric forms are possible.

The hydrolysis products are chrysanthemum-monocarboxylic acid (chrysanthemic acid) (II) and monomethyl ester of chrysanthemum-dicarboxylic acid (pyrethric acid) (IIa) as acid moiety, and cinerolone (III) and pyrethrolone (IIIa) as alcohol moiety.



(II), R=Me

(IIa), R=CO_2Me



(III), R=*cis* $CH_2\cdot CH=CH\cdot Me$

(IIIa), R=*cis* $CH_2\cdot CH=CH\cdot CH=CH_2$

Staudinger and Ruzicka[1], published a first and comprehensive study on structural problems in research as well as on the total synthesis of pyrethrins, but achieved partial success. Synthetic and structural problems of the naturally occurring pyrethrins were not taken up again until World War II, but have been vividly prosecuted by LaForge and his school in the United States and by Harper and his students in Great Britain since 1945 onwards with great success, completing the total synthesis of chrysanthemic acid, cinerolone and pyrethrolone. Thus it follows that the total synthesis of cinerin I and pyrethrin I is achieved.

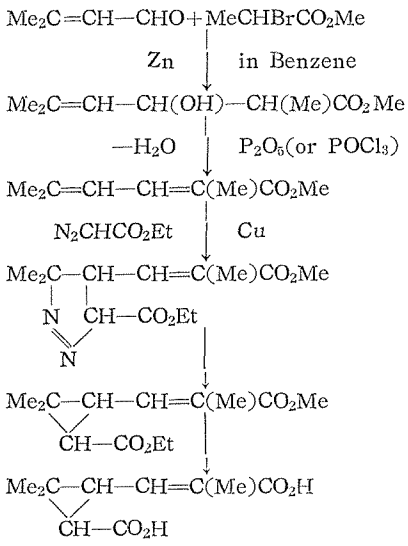
Chrysanthemum-dicarboxylic acid had been obtained by Fujitani[2] as early as 1909, from Japanese pyrethrum flowers and the melting point (164°) thereof had been reported, but no further study was prosecuted. Afterwards, this crystalline dextrorotatory dicarboxylic acid, accompanied by its monomethyl- (i.e. pyrethric acid) and dimethyl esters, was isolated by Staudinger and Ruzicka from cold natrium methylate fission of the mixed semicarbazones of the pyrethrins. At the present time it is easily separated by steam distillation from the hydrolysis products of pyrethrum extracts, the dicarboxylic acid being non-volatile. Chrysanthemum-dicarboxylic acid absorbs bromine but very slowly and resists catalytic hydrogenation, and loses one molecule of carbon dioxide on slow distillation to yield monocarboxylic acid with propenyl side chain instead of 2'-carboxypropenyl in the parent dicarboxylic acid.

The structure of chrysanthemum-dicarboxylic acid was demonstrated by ozonolysis to (−)-*trans*-caronic acid and pyruvic acid, whilst pyrethric acid was degradated on ozonization to (−)-*trans* caronic acid and methyl pyruvate, thus necessitating the structures (IIa). Mild hydrolysis of pyrethrin II and cinerin II yields pyrethric acid, showing that it is the carboxylic grouping directly attached to the cyclopropane ring corresponding to that of chrysanthemic acid, which is esterified with the ketol fragment.

Both the total synthesis of chrysanthemum-dicarboxylic acid and the elucida-

tion of stereochemistry of the side chain double bond thereof were not taken up until 1954 when the present author's report on these subjects at first appeared in *Botyu-Kagaku*.

The author succeeded in the total synthesis of chrysanthemum-dicarboxylic acid by the synthetic scheme which will be described in details in the following chapters and established the geometrical configuration of the side chain double bond to be *trans* by the synthetic evidence.



Some preliminary studies have been made by British school[3] and the half aldehyde of *trans*-caronic ester, which was claimed to be an useful intermediate, has been reported but no further investigation of synthesis from this aldehyde has been developed. Afterwards, Harper and his colleagues[4] obtained the geometrical isomers of chrysanthemum-dicarboxylic acid by the same route as the author's. Recently Matsui and his co-workers[5] have also obtained isomeric acids by other schemes. However, no experimental evidence has, so far, been available as to the configuration of the side chain double bond of the acids synthesized by these two groups of workers.

The author is indebted to Prof. S. Takei for his advice in carrying out these experiments. Appreciation is also expressed to Prof. M. Ohno and to Ass. Prof. M. Nakajima. Thanks are due to the help of co-workers in our laboratory.

II. SYNTHESIS OF β-METHYLCROTONALDEHYDE[6]

In the course of our synthesis of chrysanthemum-dicarboxylic acid, a considerable amount of β-methylcrotonaldehyde was needed as a starting material.

Fischer's method of synthesis for this αβ-unsaturated aldehyde was the only one hitherto reported[7]. On practical performance of this scheme, however, it was proved that the reaction velocity of bromination of *iso*valeraldehyde was

very much retarded by the application of lower temperature below -25° even under a strong irradiation of osrum lamp, and therefore very time-consuming. Furthermore, the contamination of α-methylcrotonaldehyde and α-ethylacrolein in the resulting crop, probably derived from the active amylalcohol as a source of *iso*valeraldehyde or heat isomerisation during the process of alkali-fusion at a higher temperature, showed the method unsatisfactory together with the poor over-all yield of the aldehyde desired by this route.

$$Me_2CH\cdot CH_2\cdot CH_2OH$$
$$\downarrow\ -H_2,\ \text{Ag-asbestos}$$
$$Me_2CH\cdot CH_2\cdot CHO$$
$$\downarrow\ Br_2,\ -25°$$
$$Me_2CH\cdot CHBr\cdot CHO$$
$$\downarrow\ EtOH$$
$$Me_2CH\cdot CHBr\cdot CH(OEt)_2$$
$$\downarrow\ -HBr,\ KOH\ (170°)$$
$$Me_2C{=}CH\cdot CH(OEt)_2$$
$$\downarrow\ \text{tartaric acid}$$
$$Me_2C{=}CH\cdot CHO$$

Modification of Rupe's synthesis in which *tert.* yn-carbinol was inverted into αβ-unsaturated aldehyde by boiling with concentrated formic acid, was not successful in such a case that the ethyn-carbinol derived from lower homologue of aliphatic ketone such as acetone was dealt.

$$Me_2C{=}O$$
$$\downarrow\ CH{\equiv}CH$$
$$Me_2C(OH){-}C{\equiv}CH$$
$$\downarrow\ HCO_2H$$
$$Me_2C{=}CH\cdot CHO$$

The partial reduction of nitrile by the action of lithium aluminum hydride gave an intermediate metal-imide compound which yielded a corresponding aldehyde on acid hydrolysis[9].

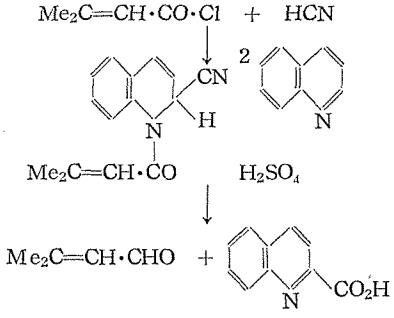
$$Me_2C{=}CH\cdot CN$$
$$\downarrow\ 1/4\ LiAlH_4$$
$$Me_2C{=}CH\cdot CH{=}N{-}M\ (M{=}1/4\ LiAl)$$
$$\downarrow\ H_2SO_4$$
$$Me_2C{=}CH\cdot CHO$$

ββ-Dimethylacrylonitrile was reduced by lithium aluminum hydride to give β-methylcrotonaldehyde in a yield of 30-35 %, but the majority of the nitrile was fully reduced to amine.

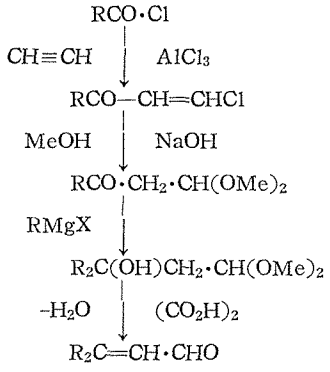
Stephen's modification[10] was also tried on this nitrile by employing stannous

chloride, but only a trace of carbonyl compound was characterized by semicarbazone formation.

Reissert[11] has prepared quinaldinic acids through benzoyl dihydroquinaldonitrile, followed by acid hydrolysis, whence benzaldehyde as a by-product distilled with steam in a considerable amount. Modification of Reissert's synthesis for the purpose of obtaining aldehyde, gave a somewhat satisfactory result when applied to dimethylacrylyl chloride, yielding the aldehyde desired in about 30 % of the theoretical amount.



Recently Price[12] described a new preparative scheme for $\alpha\beta$-unsaturated aldehyde outlined below.



Following this scheme, acetyl chloride was converted to methyl β-chlorovinyl ketone and then to methyl β-ketoaldehyde dimethyl acetal and grignardized with methyl magnesium bromide to the corresponding β-hydroxyacetal, followed by dehydration and simultaneous hydrolysis with anhydrous oxalic acid to yield β-methylcrotonaldehyde in an over-all yield of 10 % or so.

EXPERIMENTAL

α-Bromo-*iso*valeraldehyde. *iso*Valeraldehyde used was obtained by catalytic dehydrogenation of *iso*amylalcohol over silver asbestos in a Bouveault apparatus. bp. 90–2°, n_D^{20} 1.3922. Eighty six grams of *iso*valeraldehyde in 70 ml. of chloroform were placed in a three-necked round-bottomed flask equipped with a stirrer, thermometer and a dropping funnel and to this were added 52 ml. of bromine in 35 ml. of chloroform under an effective stirring and chilling in dry-ice acetone bath and a strong irradiation of osrum lamp.

The temperature was maintained at -25° during the addition of bromine and additional 15 hrs. until the reddish brown colour disappeared. After the duration, 650 ml. of absolute ethanol were added to the reaction mixture at -20° and stood still with 100 g. of anhydrous calcium chloride for 50 hrs. The resulting solution was poured into 2 l. of 10 % sodium acetate solution and the organic layer was separated. The chloroform solution was repeatedly fractionated over ignited potassium carbonate through an effective column to give the aldehyde, bp. 89°/13 mm. n_D^{20} 1.4632 (160-194 g. 67-81 %).

β-Methylcrotonaldehyde-diethylacetal. Sixty grams of bromoacetal were stirred with 120 g. of potassium hydroxide at 160-170° in a nitrogen atmosphere. After six hours' stirring at this temperature, the supernatant liquid was separated and this was again treated with the same amount of potassium hydroxide.

This procedures were repeated three times. The organic layer thus obtained, combined with ether extracts from the solid, was distilled with a small amount of potassium hydroxide in a vacuum and gave a bromine-free fraction, bp. 163-5°, n_D^{20} 1.4233 (24 g., 60 %).

β-Methylcrotonaldehyde. Seventy five grams of diethylacetal (0.45 mole) were stirred with 15 ml. of cold saturated tartaric acid solution in a nitrogen atmosphere and after 10 minutes, 250 ml. of ice-cold saturated calcium chloride solution were added.

The aldehyde separated was taken up in ether and the combined ether extract was washed with calcium chloride solution and dried over anhydrous calcium chloride. After removal of the solvent, the residue was fractionated under reduced pressure to give a fraction, bp. 62-3°/60 mm., n_D^{20} 1.4552 (22 g., 58 %). By standard method the *semicarbazone* mp. 221-2° (methanol) (*Anal.* Found : N, 29.71. Calcd. for $C_6H_{11}ON_3$: N, 29.83) and 2,4-*dinitrophenylhydrazone* mp. 183-4° (*Anal.* Found : C, 49.81 ; H, 4.50. Calcd. for $C_{11}H_{12}O_4N_4$: C, 50.09 ; H, 4.54) were prepared.

Attempted Rupe's Rearrangement of Dimethylethynylcarbinol. Dimethylethynylcarbinol, bp. 103-7°, n_D^{20} 1.4188 prepared following the procedure of Org. Synth[13], was boiled with 80 % formic acid and the reaction product was distilled under reduced pressure. Only a trace of the corresponding fraction was obtained and was characterized as semicarbazone (mp. 210-215°). The yield was not improved by varying the reaction conditions employed.

β-Methylcrotonitrile. Three grams of cyanoacetic acid (mp. 70°, 0.5 mole) dissolved in 35 g. of acetone (0.6 mole) were cooled in an ice-salt bath and to this were added 70 g. of piperidine. Condensation occurred instantly. The resulting *isopropylidencyanoacetic acid* had mp. 130-1° (*Anal.* Found : C, 57.19 ; H, 5.77. Calcd. for $C_6H_7O_2N$: C, 57.59 ; H, 5.64). The piperidine solution was then refluxed at 100-110° for 3 hrs. After completion of decarboxylation, piperidine was removed by washing with dilute sulphuric acid and the residue, dried over calcium chloride, was distilled to yield the nitrile, bp. 140-2°, n_D^{20} 1.4330. (33 g., 80 %).

Lithium Aluminum Hydride Reduction of β-Methylcrotonitrile. Twenty

grams of the nitrile (0.25 mole) in 100 ml. of absolute ether was chilled at -60° in dry-ice acetone bath and to this, 2.7 g. of lithium aluminum hydride (0.07 mole) in 90 ml. of absolute ether were added dropwise under effective stirring. The temperature was raised gradually to the room temperature and was stirred for additional 2 hrs. The reaction mixture was decomposed by the addition of ice-cold 10 % sulphuric acid at a lower temperature. Fractionation of the combined ether extracts gave β-methylcrotonaldehyde (6 g., 30 %).

1-Dimethylacrylyl-1,2-dihydroquinaldonitrile. To 70 g. of freshly distilled quinoline (0.54 mole) chilled at -10°, were added 10 g. of liquid hydrogen cyanide (0.4 mole) and then 25 g. of dimethylacrylyl chloride (bp. 84-5°/90 mm., n_D^{20} 1.4695, 0.21 mole) were added under effective stirring and cooling.

After 24 hours' standing, quinoline hydrochloride separated was removed and washed with 600 ml. of ether and the combined ether solution was washed with water, dilute sulphuric acid, and again with water. Ether-free residue was transferred into a steam distillation flask together with 1 l. of 10-*N* sulphuric acid and was distilled with steam in a rapid stream of nitrogen. The distillate was saturated with calcium chloride and repeatedly extracted with ether. Fractional distillation of the combined extract gave the aldehyde desired in a yield of about 30 % (5.4-7.2 g.).

Methyl β-Chlorovinyl Ketone. A stream of dry acetylene gas was bubbled into acetyl chloride (78 g., 1.0 mole) in 300 ml. of carbon tetrachloride with vigorous stirring and ice cooling, and concurrently aluminum chloride (147 g., 1.1 mole) was added in small portions over about 1 hr., the reaction mixture was protected from moisture and maintained at 0-5°. The introduction of acetylene gas (total *ca.* 75 l., 3.4 mole) was stopped after 6-7 hrs. The reaction mixture was poured onto a mixture of ice and salt. The organic layer was separated and the aqueous layer was extracted several times with ether, the combined extract was dried. After removal of ether, the residue was distilled under reduced pressure to give methyl β-chlorovinyl ketone, bp. 58-60°/40 mm., 42-3°/20 mm., (yield, 55-60 %).

β-Ketobutyraldehyde Dimethylacetal. Methyl β-chlorovinyl ketone (104 g., 1.0 mole) in 150 ml. of absolute methanol was treated with sodium hydroxide (42 g., 1.05 mole) in 350 ml. of absolute methanol under effective stirring, the temperature being kept at -15°. The reaction mixture was then poured into *ca.* 600 ml. of cold saturated salt solution and extracted with ether.

The combined ethereal solution was dried and fractionated under reduced pressure. The acetal had bp. 70-72°/20 mm., n_D^{25} 1.4136, and the yield was 65-70 %.

β-Methyl-β-hydroxy-butyraldehyde Dimethylacetal. Methyl magnesium bromide (*ca.* 1.1 mole) was prepared in absolute ether and to this was added keto-acetal (100 g., 0.76 mole) with stirring under moderate refluxing. After hydrolysis with cold aqueous ammonium acetate, the product was completely extracted with ether. The ethereal extract was dried and distilled under reduced pressure with a small amount of potassium carbonate. The acetal, bp. 77-9°/18 mm., n_D^{25} 1.4230, was obtained in 80-84 % yield.

β-Methylcrotonaldehyde. One hundred and forty eight grams of the hydroxy-

acetal (1.0 mole) were added dropwise to a Claisen flask containing 20 g. of anhydrous oxalic acid and 2 g. of hydroquinone, preheated at 120–30° in an oil bath and the system was maintained under *ca.* 150 mm. pressure. The distillate was dissolved in ether, and washed with cold saturated calcium chloride solution and dried over anhydrous calcium chloride and then distilled. The aldehyde had bp. 60–2°/60 mm., n_D^{25} 1.4552. The yield amounted to 15–20 % (maximum yield recorded 34 %). The operations were carried out in nitrogen atmosphere. *Semicarbazone* mp. 214–5°.

III. SYNTHESIS OF $\alpha\delta$-DIMETHYLSORBIC ACID ESTERS[14)15)16)]

The similarity in structure between chrysanthemum mono- and dicarboxylic acids suggested that the method developed by Harper[17)] with success for the synthesis of the former, might serve a possible route to the latter. Thus, our attention was directed to $\alpha\delta$-dimethylsorbic acid ester as the olefinic component required for the addition of diazoacetate, because of the resemblance to dimethylhexadiene in the case of chrysanthemic acid.

The Reformatski condensation of β-methylcrotonaldehyde (I), prepared by the method described in the preceding chapter, with methyl or ethyl α-bromopropionate in the presence of activated zinc gave the corresponding β-hydroxy ester (II) and this was dehydrated with phosphorus pentoxide or phosphoric oxychloride in dry benzene to yield an unsaturated ester (III). Hydrolysis of this ester with ethanolic potassium hydroxide gave the corresponding acid (IV), $C_8H_{12}O_2$, which melted at 133–5°. Both the ester and acid were readily hydrogenated over platinum oxide catalyst, two molecules of hydrogen being taken up to give $\alpha\delta$-dimethylcaproate (V) and the corresponding acid respectively. This was characterized by amide and *p*-phenylphenacyl ester. Ultra-violet absorption ($\lambda_{max.}$ 273 mμ, ε 22,300) as well as the catalytic hydrogenation, showed the unsaturated acid obtaind to be the required $\alpha\delta$-dimethylsorbic acid. This was the only product obtained by dehydration of the parent Reformatski ester (II). Reconversion of $\alpha\delta$-dimethylsorbic acid into methyl ester by means of dizomethane gave an ester completely identical with that obtained by the dehydration of the Reformatski ester (II). This excludes the stereomutation during hydrolysis of ester and provides certification for the homogeneity of the ester which resulted from the dehydration.

$Me_2C{=}CH{\cdot}CHO$ (I)

Zn | $MeCH(Br)CO_2Me$(or Et)

$Me_2C{=}CH{\cdot}CH(OH){\cdot}CH(Me)CO_2Me$(or Et) (II)

$-H_2O$ | P_2O_5(or $POCl_3$)

$Me_2C{=}CH{-}CH{=}C(Me)CO_2Me$(or Et) (III)

KOH |

$Me_2C{=}CH{\cdot}CH{=}C(Me)CO_2H$ (IV)

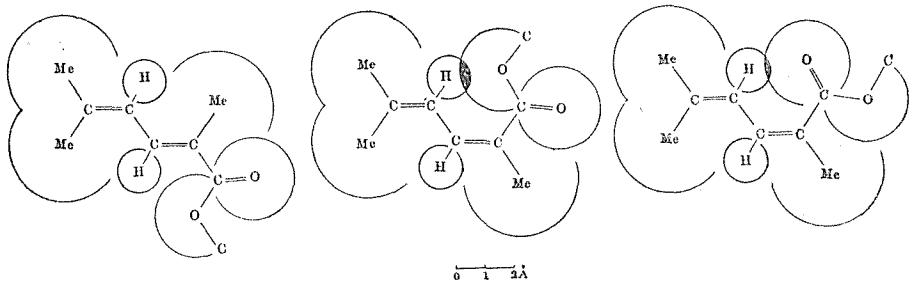
H_2—Pt |

$Me_2CH{\cdot}CH_2{\cdot}CH{\cdot}CH(Me)CO_2H$ (V)

When hydroxy compounds, such as derived from the Reformatski and the Grignard reactions, are dehydrated with chemical reagents at a comparatively lower temperature, the mixture of geometrical isomers is to be expected, even if the dehydration is stereospecific. Sometimes, however, only a *trans* isomer has been isolated[18], as is the case with the author's. This may be due to stereomutation or to experimental difficulties.

Stereochemical consideration on the atomic model of this acid and/or its ester shows that there is a considerable steric hindrance in *cis*-form, in which steric overlap is indicated between C_4-hydrogen atom and carbonyl oxygen atom, be the C_1–C_2 bond single-*cis* or single-*trans*. On the contrary, such steric hindrance is not indicated at all in that of the *trans*-form. Therefore, the configuration of the only known form of *αδ*-dimethylsorbic acid is considered to be *trans* on the stereochemical basis.

The absence of *cis*-form may be due to stereomutation during the process of dehydration.



trans *cis*(C_1—C_2 *s-trans*) *cis*(C_1—C_2 *s-cis*)

Fig. 1. Planar projection diagrams of *cis*- and *trans*-*αδ*-dimethylsorbic esters. Employing the following values for bond lengths: C=C 1.35, C—C 1.54, C—H 1.09, C=O 1.24, C—O 1.44 Å and bond angles: C—C=C 124°, C—C=O 121°, O=C—O 124°, C=C—H 120°, van der Waals radii for oxygen as 1.40, for hydrogen as 0.75, for CH_3 as 2.0 Å.[19]

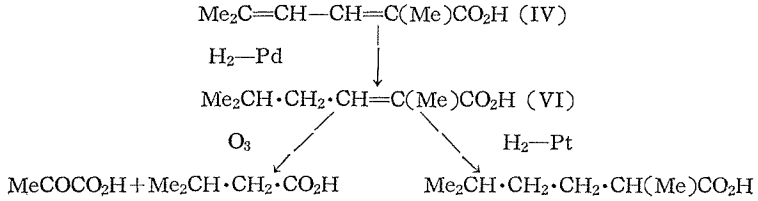
The experimental assignment of this configuration of the hitherto undescribed *αδ*-dimethylsorbic acid is of great importance, because this configuration is retained as such during the addition of ethyl diazoacetate to produce the synthetic chrysanthemum-dicarboxylic acids.

Linstead and his co-workers[20] have recently summarized evidence to establish the geometrical configurations of the isomeric sorbic acids, showing that partial inversion to *cis-trans* markedly affects the ultra-violet light absorption. The ultra-violet light absorption of *αδ*-dimethylsorbic acid in question shows the single intense band (λ_{max}. 273 mμ, ε 22,300) that would surmise the *trans*-configuration. However, even if the bathochromic shift produced by two additional methyl substituents in *α*- and *δ*-positions of sorbic acid is allowed, it seems subject to uncertainty to decide the configuration of *αβ*-double bond to be *trans* by applying Linstead's spectral data to the author's acid, because of the absence of geometrical isomerism with reference to *γδ*-double bond in contrast to the isomeric sorbic acids in which geometrical isomerism exists in both double bonds.

So far, no reliable method for assigning geometrical configuration to the α-alkyl substituted sorbic acids has been developed. Farmer and Hughes[21] reported that sorbic acid, when submitted to 50 % hydrogenation in the presence of a palladium catalyst, yielded a mixture of dihydro-compounds 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 dihydro-compounds of smaller proportions (below 20 %) being recorded.

The semi-hydrogenation of $\alpha\delta$-dimethylsorbic acid (IV) over a palladised barium sulphate predominantly afforded the $\Delta\alpha$-dihydro-compound as was expected, and repeated purification by rectifications and partial esterifications (in the sense that $\Delta\beta$- and $\Delta\gamma$-dimethylhexenoic acids, and dimethylcaproic acid become esterified, whilst $\Delta\alpha$-dimethylhexenoic acid remains unchanged; *cf.* Ecott and Linstead's modification of Sudborough's method[22]) gave the pure $\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid (VI), which was characterized by ozonolysis to yield pyruvic acid (as 2, 4-dinitrophenylhydrazone, mp. 218°) and *iso*valeric acid (as itself and as a *p*-phenylphenacyl ester mp. 77°). In the ultra-violet light absorption spectrum of the resulting $\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid, the occurrence of the single intense band ($\lambda_{max.}$ 218 mμ, ε 14,300) characteristic of the $\alpha\beta$-unsaturated carboxylic chromophore, together with the disappearance of the conjugated diene carboxylic band ($\lambda_{max.}$ 273 mμ, ε 22,300) which was exhibited by the parent $\alpha\delta$-dimethylsorbic acid, were in good agreement with the chemical evidence mentioned above. The fact that the extinction at this band did not alter by further purifications, excluded the contamination of the possible $\Delta\beta\gamma$-, $\Delta\gamma\delta$-dihydro or fully hydrogenated compounds which are spectrally inert in this region. This acid was quantitatively hydrogenated over a platinum catalyst and was shown to absorb one epuivalent hydrogen, yielding $\alpha\delta$-dimethylcaproic acid. The equivalent weight and the acid dissociation constant were also determined. All criteria supported purity of this acid.

The stereomutation during the semi-hydrogenation over a palladium catalyst has not been observed so far as is known, and the configuration of the $\alpha\beta$-double bond in the parent conjugated diene acid is believed to be retained during the semi-hydrogenation. For example, ordinary *trans-trans*-sorbic acid, when it undergoes the same reduction sequence, affords solid $\Delta\alpha$-dihydrosorbic acid[21] mp. 34°, which is completely identical with the *trans*- acid obtained from the Doebner condensation of malonic acid with butyraldehyde in pyridine[23,24], in contrast to another liquid isomeric acid[25] (bp. 201°), obtained from the semi-hydrogenation of pentin-1-carboxylic acid over colloidal palladium, that the *cis*-configuration is favoured in general from this reduction scheme.



Furthermore, the stereomutation during any of the procedures employed throughout the purification could be excluded, for this acid was not submitted to the thermal conditions likely to invert the configuration. Reference has been made to the thermodynamic stability of angelic acid[26], and to the thermal equilibration data[27] on isomeric 2-methyl-2-hexenoic acids. At this molecular weight, approximately the same order of magnitude as that of (VI), the isomeric acids proved to be sufficiently stable to heat (temperature involved being the range as high as 220–270°) to allow purification by fractional distillation under reduced pressure.

Naturally, it is desirable to examine both geometrical isomers in comparison, if possible, before making the assignment, but the only one known form is available in the present case.

Fortunately, spectral data[27] of some homologous geometrical isomers of well-established configuration are available for reference. In Fig. 2 are shown the ultra-violet light absorption spectra of $\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid, together with those of the homologous C_5—C_7 α-methyl-$\alpha\beta$-unsaturated acids given by Cason.

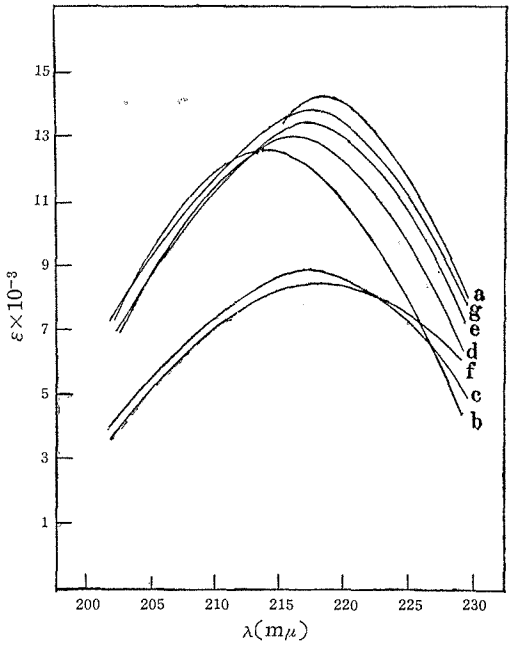


Fig. 2. Ultra-violet absorption spectra of 2-methyl-2-alkenoic acids.
a) $\alpha\delta$-Dimethyl-$\Delta\alpha$-hexenoic acid. b) Tiglic acid. c) Angelic acid.
d) *trans*-2-Methyl-2-pentenoic acid. e) *trans*-2-Methyl-2-hexenoic acid.
f) *cis*-2-Methyl-2-hexenoic acid. g) *trans*-2-Methyl-2-heptenoic acid.
(b–g by Cason[27])

It was somewhat surprising that the ultra-violet light absorption maxima of both isomers were at essentially the same wavelength (217–8 mμ), unlikely to serve as a decisive criterion, but the extinction coefficients showed a significant difference, those of *cis*-isomers being much lower in every case.

$\alpha\delta$-Dimethyl-$\Delta\alpha$-hexenoic acid has an extinction coefficient of 14,300 and $\lambda_{max.}$ at 218 mμ. Since steric interaction between carboxyl and terminal alkyl may be regarded as the cause of the less intense absorption of the *cis*-form, the small decrease in absorption accompanying change from terminal methyl to a larger group may be interpreted as indicating only small steric interferrence (*cf.* thermal equilibration data[27] and spectral data of the higher homologues[28]) of the substituent beyond the γ-position. Thus, steric influence of the branched chain substituent beyond γ-position of $\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid could be neglected in the case of comparison with the straight chain homologues (Fig. 2. b-g), and it is, therefore, concluded from the spectral properties given above that this is of the *trans* acid series.

In Fig. 3 are assembled the infra-red spectra of $\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid together with those of several homologous isomeric acids prepared by Cason.

At a glance, the differences in these curves are not so characteristic as to distinguish the two isomeric acids, but elaborate inspection of the fine structures indicates the regions of clean-cut distinction. For simplicity, the wave lenghths

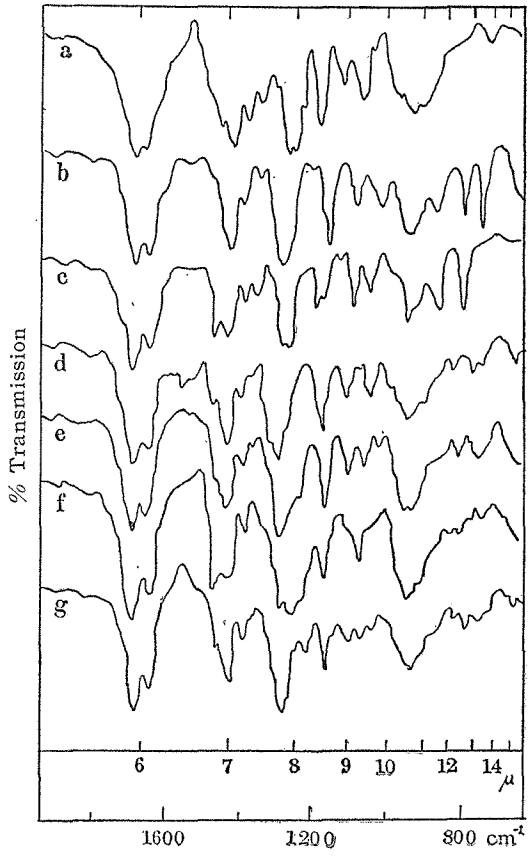


Fig. 3. Infra-red absorption spectra of 2-methyl-2-alkenoic acids.
a) $\alpha\delta$-Dimethyl-$\Delta\alpha$-hexenoic acid. b) Tiglic acid. c) Angelic acid. d) *trans*-2-Methyl-2-pentenoic acid. e) *trans*-2-Methyl-2-hexenoic acid. f) *cis*-2-Methyl-2-hexenoic acid. g) *trans*-2-Methyl-2-heptenoic acid (b-g by Cason[27]).

of the bands of $\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid in comparison with those of isomeric 2-methyl-2-hexenoic acids, most useful for distinction, are tabulated in Table 1.

Table 1. Infra-red absorption spectra of 2-methyl-2-alkenoic acids. Bands most suitable for differentiation of isomers (in micron).

$\alpha\delta$-Dimethyl-$\Delta\alpha$-hexenoic acid	*trans*-2-Methyl-2-hexenoic acid[27]	*cis*-2-Methyl-2-hexenoic acid[27]
6.10 VS	6.09 VS	6.11 VS
6.85 S	6.85 W	6.84 VS
7.08 VS	7.03 VS	7.04 VS
7.80 VS	7.76 VS	7.78 VS
7.95 Sh	7.95 Sh	8.00 VS
8.18 M	8.15 M	8.12 Sh
8.63 S	8.60 S	8.54 S
9.03 M	9.08 M	9.08 Sh
—	—	9.33 S
9.45 M	9.44 M	—
—	—	9.55 Sh
9.64 W	9.70 W	—
10.7 S	10.7 S	10.55 VS
10.9 Sh	10.9 S	—

Legend to band intensity abbreviations: VS, very strong; S, strong; M, medium; W, weak; Sh, shoulder.

According to Cason, the 9–10 μ region is quite useful for differentiation between the *cis* and *trans* isomers.

Freeman[29] has also pointed out the relatively complex structures of this region in his spectra of the *trans* acids. The *cis* isomer shows a single well-defined band at 9.33 μ, in contrast to the complexity in this region of the *trans* isomers. Of the double band at 6.85, 7.03 μ which is present in all *trans* acids, the former band is always much weaker and sometimes is only a shoulder, whereas, in the *cis* isomers, the shorter wave-length band proves to be the stronger of the two. As another difference between the two isomers, the overlapping carboxyl bands at 7.8 and 8.0 μ are indicated. Freeman[29] indicates that in saturated acids the latter is always the weaker unless in the presence of an α-alkyl (methyl) substituent, in this case the second being the stronger.

The 8.0 μ band is weaker in *trans* isomers as is seen from Fig. 3 and Table 1, whilst in the *cis* isomers, the second band is the stronger. Therefore, the relative intensities of the two pairs of bands are reversed in the *cis* and *trans* isomers. The longer wave-length unsaturation bands beyond 11 μ have not been considered for this distinction between *cis* and *trans* isomers, because it has been observed by Freeman that these bands are markedly influenced by the molecular environments such as the substituents on or near a double bond. Recently, Buchta[30] pointed out the 12.3μ band to be characteristic for "all *trans*"-2, 7-dimethyl-octadiene-2, 6-diacid-1, 8 but this seems unsuitable for this distinction. As is apparent from the Table and comparison discussed above, $\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid is concluded to be the *trans* acid.

In addition, the best criterion of identifying the *trans* configuration of this acid is the acid dissociation constant. Steric effects on the acidity of $\alpha\beta$-unsaturated acids have been frequently discussed in the earlier literatures.

It has been well known that the *cis* isomers of $\alpha\beta$-unsaturated acids are usually stronger than their *trans* isomers. It seems probable that the acid-strengthening effect is due to the twisting of the carboxyl groups away from the plane of the rest of the unsaturated systems, as suggested by Ingold[31].

The *p*K value of $\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid in comparison with those of the isomeric 2-methyl-2-hexenoic acids and of tiglic and angelic acids, are tabulated below.

Table 2. *p*K values at 25°.

$\alpha\delta$-Dimethyl-$\Delta\alpha$-hexenoic acid	5.15
Tiglic acid[32]	5.05
Angelic acid[32]	4.30
trans-2-Methyl-2-hexenoic acid[27]	5.13
cis-2-Methyl-2-hexenoic acid[27]	4.44

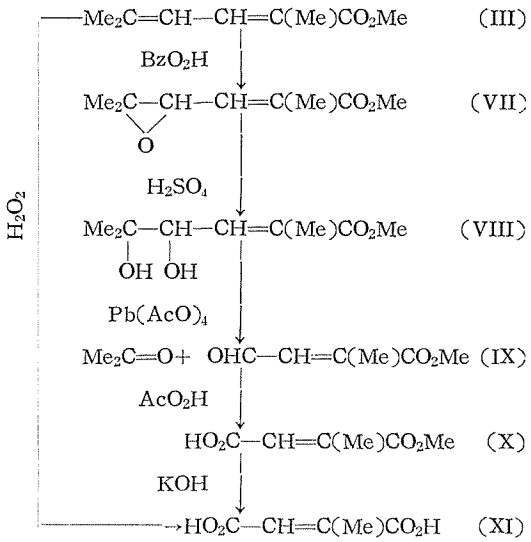
The ratio of these constants could hardly be influenced significantly by substitution of a larger group for methyl, and thus *p*K value (5.15) of $\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid unambiguously shows the *trans* configuration.

Therefore, the independent evidence mentioned above leads to the same conclusion and it follows that the parent $\alpha\delta$-dimethylsorbic acid has the *trans* configuration with respect to the $\alpha\beta$-double bond.

In addition to the physico-chemical evidence, another cogent chemical evidence for the *trans* configuration was also provided.

Heinänen[33] reported that the selective epoxydation occurred 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.

Epoxydation of methyl $\alpha\delta$-dimethylsorbate (III) by perbenzoic acid gave



methyl $\gamma\delta$-epoxy-$\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoate (VII) as was expected, one atom of oxygen being taken up.

The $\gamma\delta$-epoxy structure of VII can reasonably be deduced from the subsequent processes. Conversion of the epoxy-ester into the dihydroxy-compound was easily effected by treatment with dilute sulphuric acid, yielding $\gamma\delta$-dihydroxy-$\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoate (VIII).

Lead tetraacetate cleaved the glycolic carbon-carbon linkage of (VIII) and gave β-monomethyl masconaldehydate (IX), which was characterized by 2, 4-dinitrophenylhydrazone, mp. 204-4.5°.

β-Monomethyl mesaconaldehydate (IX) was then oxidized with peracetic acid to β-monomethyl mesaconate (X), mp. 82-3°, which as well as its amide, mp. 117°, derived therefrom, was completely consistent with the literature[34].

Cold saponification of β-monomethyl mesaconate gave mesaconic acid (XI), mp. 202-3°, not depressed by the mixed melting point comparison with an authentic specimen.

Since the oxidation sequence involves no process likely to invert the geometrical configuration of the double bond, the retention of the configuration in the parent compound can reasonably be concluded. Thus, the final formation of mesaconic acid of the well-established *trans*-configuration unambiguously shows the *trans*-configuration of the $\alpha\beta$-double bond of the parent methyl $\alpha\delta$-dimethylsorbate.

Direct peroxydation of $\alpha\delta$-dimethylsorbic acid also gave mesaconic acid in an inferior yield.

The chemical evidence is in good agreement with the physicochemical conclusion.

These methods of assignment may, in general, be applicable to the α-alkyl substituted conjugated diene carboxylic acids.

EXPERIMENTAL

Methyl and Ethyl β-Hydroxy-$\alpha\delta$-dimethyl-$\Delta\gamma$-hexenoate. About 50 ml. of a mixture of β-methylcrotonaldehyde (42 g. 0.5 mole) prepared by the method described in the preceding chapter, ethyl α-bromopropionate (91 g. 0.5 mole) and 90 ml. of dry benzene were added on 33 g. (0.5 atom) of activated zinc and it was warmed with effective stirring until reaction set in. Addition of a trace of mercuric chloride initiates the reaction smoothly. The remaining mixture was then run in at such a rate that the refluxing benzene was under control. It was then warmed for an additional half an hour on a water bath, cooled and poured into an ice-cold solution of dilute sulphuric acid. After removal of the unchanged zinc, the organic layer was washed with small portions of water and dried over anhydrous magnesium sulphate. The benzene was removed through a column, and the residue fractionated under reduced pressure to give the ethyl ester (52 g.), bp. 84-5°/4 mm., n_D^{15} 1.4580. *Methylester* bp. 90-2°/7 mm.

This Reformatski ester gave on hydrolysis a viscous liquid acid. p-*Phenylphenacylester* mp. 82-3° (*Anal.* Found: C, 74. 53; H, 6.84. Calcd. for $C_{22}H_{24}O_4$:

C, 74.97; H, 6.86) and p-*iodophenacylester* mp. 107-8° (*Anal.* Found: C, 47.70; H, 4.72. Calcd. for $C_{16}H_{19}O_4I$: C, 47.77; H, 4.76) were prepared by standard method.

$\alpha\delta$-Dimethylsorbic Acid. Fifty six grams (0.3 mole) of the Reformatski ester was diluted with three volumes of dry benzene and boiled under reflux for 1.5 hrs. with slight excess of phosphorus pentoxide (45 g.) or phosphoric oxychloride. Water was then added, and the ester isolated in usual way. The ethyl ester had bp. 85-6°/6 mm., n_D^{20} 1.5015 (yield 32 g.) *Methylester* had bp. 85-6°/7 mm., n_D^{19} 1.5242. Hydrolysis of the ester with 10% ethanolic potassium hydroxide gave the acid, mp. 133-5°, $\lambda_{max.}$ 273 mμ, ε 22,300 (*Anal.* Found: C, 68.44, H, 8.69. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63). p-*Phenylphenacyl ester* melted at 102-3° (*Anal.* Found: C, 79.13; H, 6.64. Calcd. for $C_{22}H_{22}O_3$: C, 79.01; H, 6.63).

On hydrogenation over a platinum oxide catalyst this acid absorbed 1.79 mole hydrogen yielding $\alpha\delta$-dimethylcaproic acid, bp. 115-6°/13 mm., n_D^{20} 1.4261, *Amide* mp. 102-3° (*Anal.* Found: C, 67.18; H, 12.01, Calcd. for $C_8H_{17}ON$: C, 67.09; H, 11.96) and p-*phenylphenacyl ester* mp. 66° (*Anal.* Found: C, 78.31; H 7.91. Calcd. for $C_{22}H_{26}O_3$: C, 78.09; H, 7.74) were prepared by standard method. A 4.5 g. quantity of $\alpha\delta$-dimethylsorbic acid was treated with 1.3 g. of diazomethane in ether and the ester was isolated in the usual way to give methyl $\alpha\delta$-dimethylsorbate in 85% yield. This was completely identical in every respect with that obtained by the dehydration of the corresponding Reformatski ester.

$\alpha\delta$-Dimethyl-$\Delta\alpha$-hexenoic Acid. A 15.0 g quantity of $\alpha\delta$-dimethylsorbic acid dissolved in 150 ml. of methanol was hydrogenated over Pd-$BaSO_4$ catalyst (1.2 g.) in a shaking apparatus until 2564 ml. of hydrogen (at 19°, 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 distillate 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 of 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 again concentrated under reduced pressure below 50° until free from ethanol.

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 sufficiently pure at this stage, but in order to obtain the sample of the highest purity for physico-chemical measurements, this was again subjected to partial esterification exactly in the same manner as described above, and afforded $\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid (9.5 g.) bp. 119-122°/10 mm. In further rectifications, only a centre cut of pure $\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid, boiling at 120.5-121.5°/10 mm., and having n_D^{25} 1.4597 was collected (6.3 g.), *equivalent* by titration 141.1 (Calcd. for $C_7H_{13}CO_2H$: 142.2), $\lambda_{max.}$ 218 mμ, ε 14,300 (in *n*-hexane; Beckman Model-DU quartz spectrophotometre). For infra-red sepectrum, see

Fig. 3-a in the text (one-molar solution in carbon tetrachloride on Perkin Elmer Model-21 double beam recording spectrophotometre). It crystallizes in prisms when chilled in dry-ice and melts at about 0°. p-*Phenylphenacylester* melted at 54-6° (*Anal.* Found: C, 78.55; H, 7.13. Calcd. for $C_{22}H_{24}O_3$: 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 decolourizes the permanganate solution at room temperature and absorbs 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 minutes. 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 (0.6 g.) mp. 218°; 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 the removal of solvent, the residue was distilled to give *iso*valeric acid (0.3 g.) bp. 170-75° n_D^{22} 1.4020. p-*Phenylphenacylester*, mp. 77-8° (*cf.* Drake[35] mp. 76°), not depressed by admixture with an authentic specimen.

Quantitative hydrogention:- A 0.233 g. quantity of the acid (bp. 120.5°/10 mm.) in 30 ml. of ethanol was hydrogenated over a platinum oxide catalyst (11 mg.) in a shaking hydrogenation apparatus and absorbed 40 ml. (at 27°) of hydrogen, equivalent to one double bond. The reduction product was freed from both catalyst and solvent, and distilled to give the fully hydrogenated $\alpha\delta$-dimethylcaproic acid, bp. 115-116°/13 mm., n_D^{20} 1.4261, in a yield almost quantitative. *Amide* mp. 102-3° and p-*phenylphenacylester* mp. 66° were identified by mixed melting point comparison with authentic specimens respectively.

Determination of *p*K value:- The *p*K value was determined from the value of the *p*H at the half neutralisation point in a graph of *p*H *vs.* volume of sodium hydroxide solution. A sample of the acid (0.2 g.) was dissolved in 30 ml. of 50 vol. % methanol-water, then titrated with carbonate-free sodium hydroxide (0.1 *N*) at a constant temperature (25°). The *p*H determination was with a Yanagimoto Model-40A *p*H metre, using glass electrodes; frequent standardizations were run against standard buffer solutions. At least twenty readings were taken after successive addition of sodium hydroxide and after determinations were carried out in triplicate, the values were confirmed to be reliable and reproducible, and corrected for hydrolysis, solvation and repression of the acid[36].

Methyl $\gamma\delta$-Epoxy-$\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoate. Four grams of methyl $\alpha\delta$-dimethylsorbate (0.027 mole) 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 reduced pressure to give methyl $\gamma\delta$-epoxy-$\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoate, bp. 91-2°/6 mm., n_D^{20} 1.4672 (3.7 g., 84%).

Methyl $\gamma\delta$-Dihydroxy-$\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoate. To a 1.5 g. quantity of epoxy-ester was added 0.5 ml. of 5% sulphuric acid, kept at room temperature and after several hrs, it turned homogeneous. This was then extended in 100 ml. of ethanol-free ether and was completely dried over anhydrous sodium sulphate.

Removal of ether gave methyl $\gamma\delta$-dihydroxy-$\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoate in a quantitatitative yield. It crystallized from methanol and benzene in plates, mp. 50-1° (*Anal.* Found: C, 57.40; H, 8.46. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57).

β-Monomethyl Mesaconaldehydate. The dihydroxy-ester (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 β-monomethyl mesaconaldehydate, bp. 76-8°/12 mm., n_D^{20} 1.4680 (0.75 g. 75%). 2,4-*Dinitrophenylhydrazone* crystallized in orange needles from methanol and melted at 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).

β-Monomethyl Mesaconate. The aldehyde-ester (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 evaporated *in vacuo* to dryness and the residue was recrystallized from petroleum ether (bp. 40-50°) to give β-monomethyl mesaconate (0.31 g.), in 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* crystallized in needles from ether-petroleum ether and melted at 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 completely consistent with the literature.

Mesaconic Acid. β-Monomethyl mesaconate (0.1 g.) was hydrolyzed with cold 5% ethanolic potassium hydroxide. The mixture was evaporated *in vacuo* and the residue was acidified with dilute sulphuric acid. This was taken up in ether, dried over anhydrous sodium sulphate and removal of ether gave mesaconic acid. Recrystallization from water afforded the pure acid in cubes melting at 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 recorded method[37]. *Di*-p-*phenylphenacylester* formed fine needles from chloroform and melted at 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. $\alpha\delta$-Dimethylsorbic acid (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 then warmed on a water bath for about 10 hrs. with additional peroxide at intervals. At the end of this time, the solu-

tion was evaporated *in vacuo* and the solid residue was extracted with 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 recrystallisation 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.).

IV. ADDITION OF ETHYL DIAZOACETATE TO ETHYL β-HYDROXY-αδ-DIMETHYL-Δγ-HEXENOATE[14] AND METHYL αβδ-TRIMETHYLSORBATE[38]

In the first attempt, ethyl β-hydroxy-αδ-dimethyl-Δγ-hexenoate, prepared by the Reformatski condensation of β-methylcrotonaldehyde with ethyl α-bromopropionate, was used as an olefinic component for the addition of ethyl diazoacetate.

At first sight, it seemed likely that the addition of ethyl diazoacetate could

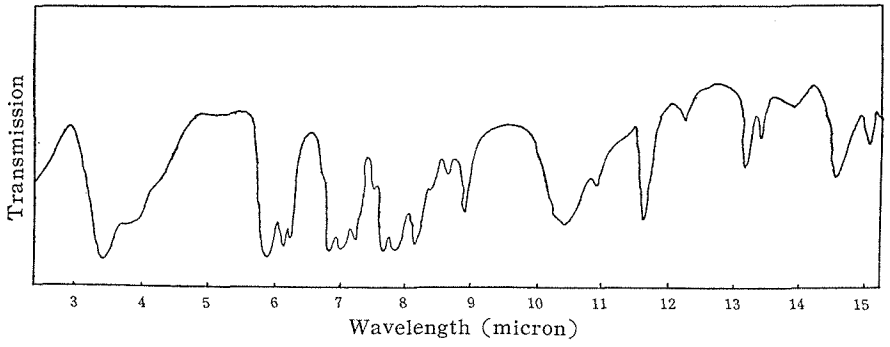
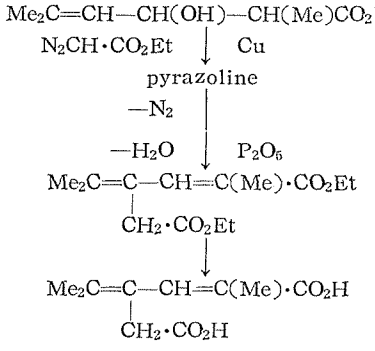


Fig. 4. αδ-Dimethyl-γ-carboxymethylsorbic acid (Nujol)

only take place at the γδ-ethylenic bond in the Reformatski ester, giving cyclopropane derivative, followed by dehydration to produce chrysanthemum-dicarboxylic acid desired. Experiment showed that the addition really occurred at the γδ-ethlyenic bond as was expected, but the possible intermediate pyrazoline ester decomposed in a way to yield an acyclic isomeric acid, $C_{10}H_{14}O_4$, mp. 185-6°. Determination of the equivalent by titration showed that this compound was a dicarboxylic acid but the infra-red spectrum (Fig. 4) had no absorption in the region 9.8-10μ in which alkyl substituted cyclopropane derivatives show a strong band[39].

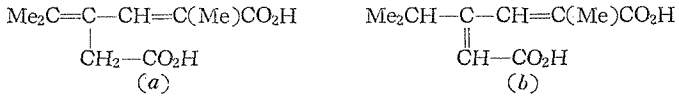


The ultra-violet light absorption spectrum (λ_{max}. 273-4 mμ, ε 31,700) indicates

the alkyl substituted conjugated diene carboxylic chromophore in this molecule as in $\alpha\delta$-dimethylsorbic acid. In fact, this acid absorbs two molecules of hydro- on catalytic hydrogenation over a platinum oxide catalyst, yielding α-methyl-γ-*iso*propyladipic acid.

This conjugated diene carboxylic acid was also obtained by the addition of ethyl diazoacetate to $\alpha\delta$-dimethylsorbic acid esters under rather drastic reaction conditions, as will be detailed in the next chapter.

This excludes the combination of diazoacetate residue to δ-carbon atom and thus, the structure (*a*) and (*b*) are possible for this acyclic acid.



(*a*) (*b*)

Of the two, only (*a*) can give rise to acetone on ozonolysis, which was isolated as 2,4-dinitrophenylhydrazone, together with pyruvic acid and an acid suggesting oxalacetic acid.

Stereochemical consideration on the atomic model of *cis*-form which exhibits considerable steric hindrance in contrast to the sterically unhindered *trans*-form, favours the *trans*-configuration of the $\alpha\beta$-double bond in this molecule.

The identity of the ultra-violet light absorption of this dicarboxylic acid with that of $\alpha\delta$-dimethylsorbic acid (see Part III) unambiguously shows the *trans*-configuration.

Attempts to obtain cyclopropane derivatives through this synthetic course by employing any suitable reaction condition ended in failure.

Thus, the author's attention was directed to ethyl $\alpha\delta$-dimethylsorbate as an olefinic component required, in place of the Reformatski ester.

In the addition of ethyl diazoacetate to $\alpha\delta$-dimethylsorbate, however, the sorbate has two ethylenic bonds in the molecule and lacks symmetry, and successful synthesis of chrysanthemum-dicarboxylic acid would postulate the addition of diazoacetate to the $\gamma\delta$-ethylenic bond.

Available experimental data concerning the addition of aliphatic diazoacetate to unsymmetrical diene systems substituted by polar groups, are not sufficient to make a confident prediction on this point.

Heide[40] reported that, with 1-phenylbutadiene, ethyl diazoacetate adds to the $\gamma\delta$-ethylenic bond. Selective semi-hydrogenation over a palladium catalyst of sorbic acid gives $\Delta\alpha$-hexenoic acid[21] and with $\alpha\delta$-dimethylsorbic acid, $\alpha\delta$-dimethyl-$\Delta\alpha$-hexenoic acid as was shown by the present author in the preceding chapter.

Epoxydation of methyl sorbate by perbenzoic acid gives $\gamma\delta$-addition, as does peroxydation[33]. This is also the case with $\alpha\delta$-dimethylsorbate as was detailed in the foregoing chapter.

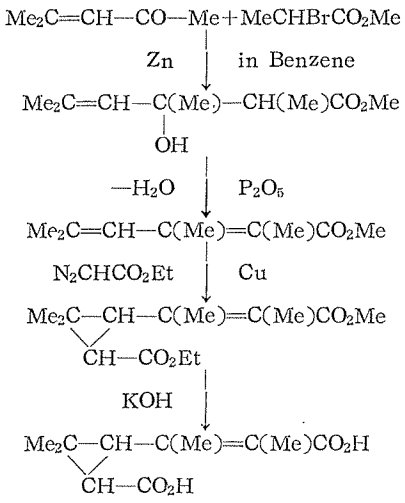
It is well known that ethylenic bond, when substituted by electro-negative groups, behaves less unsaturated as compared with simple olefinic bond. Therefore, it looked probable that addition of ethyl diazoacetate would take place predominantly at $\gamma\delta$ rather than at $\alpha\beta$-double bond in $\alpha\delta$-dimethylsorbic esters.

Thus, in order to gain information on this point a preliminary experiment was made of methyl $\alpha\beta\delta$-trimethylsorbate.

Methyl $\alpha\beta\delta$-trimethylsorbate has a close structure to $\alpha\delta$-dimethylsorbate and though hitherto undescribed, is prepared from the Reformatski condensation of readily accessible mesityloxide with methyl α-bromopropionate. Furthermore, with this model compound, the $\gamma\delta$-addition of diazoacetate could easily be indicated by the isolation of well-known caronic acids from the oxidation products of the adducts, and the absence of geometrical isomerism with respect to the $\gamma\delta$-ethylenic bond in this molecule would facilitate stereochemical consideration of the products.

Ethyl diazoacetate was added to methyl $\alpha\beta\delta$-trimethylsorbate in boiling ligroin in the presence of copper powder, following D'yakonov's procedure[41].

Hydrolysis of the adduct gave a viscous acid which partially crystallized after a long standing in the cold.



Recrystallization of the solid gave a dicarboxylic acid $C_{11}H_{16}O_4$, mp. 164-5°, which was also characterized by di-*p*-phenylphenacylester.

Ultra-violet light absorption ($\lambda_{max.}$ 238 mμ, ε 19,700) indicated the presence of the same chromophore system in this adduct acid as that in chrysanthemum-dicarboxylic acid (*cf.* Part V). The infra-red absorption spectrum (Fig. 5) was very

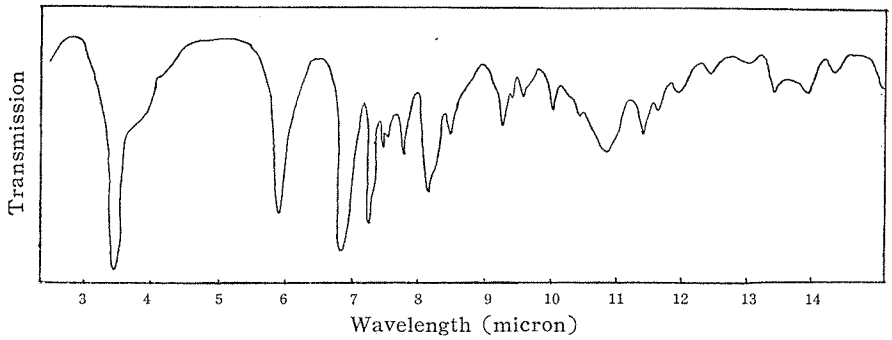


Fig. 5. (±)-*cis*-3-(1'-Methyl-2'-carboxypropenyl)-2,2-dimethylcyclopane-1-carboxylic acid (Nujol).

similar to that of chrysanthemum-dicarboxylic acid (*cf.* Part V), the occurrence

of the characteristic band at 10μ indicating the presence of cyclopropane ring. In addition to these evidence, the isolation of *cis*-caronic acid from ozonolysis and subsequent hypobromite oxidation of the diacid, revealed the structure to be (±)-*cis*-3-(1′-methyl-2′-carboxypropenyl)-2,2-dimethylcyclopropane-1-carboxylic acid, arising from the $\gamma\delta$-addition of diazoacetate to the parent methyl $\alpha\beta\delta$-trimethylsorbate.

The residual part of the hydrolyzate, from which no more crystallization occurred, was treated with ozone, followed by hypobromite oxidation by the same procedure as above, so as to give a mixture of both *cis*- and *trans*-caronic acids, also indicating the $\gamma\delta$-addition. The addition in the present case is considered to proceed through the corresponding pyrazoline intermediate in a way as will be discussed in the next chapter. The geometrical configuration of $\alpha\beta$-ethylenic bond of methyl $\alpha\beta\delta$-trimethylsorbate used is unknown and there has not yet been developed an experimental methed for assigning geometrical configuration to the tetra-substituted ethylenic linkage.

EXPERIMENTAL

Addition of Ethyl Diazoacetate to β-Hydroxy-αδ-dimethyl-Δγ-hexenoate. Addition of ethyl diazoacetate (0.06 mole) to the Reformatski ester was performed in the presence of copper powder (0.2 g.) at 130–140° in a nitrogen atmosphere. The resulting adduct was treated with phosphorus pentoxide (slight excess) in dry benzene. The ester formed, bp. 91–2°/0.05 mm., n_D^{15} 1.4725, was isolated in the usual way. (yield 2.1 g.). The ester was hydrolyzed with 10 % ethanolic potassium hydroxide to give $\alpha\delta$-dimethyl-γ-carboxymethylsorbic acid, mp. 185–6° (*Anal.* Found: C, 60.69; H, 7.06. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12). $\lambda_{max.}$ 273–4 mμ, ε 31.700. For infra-red absorption spectrum, see Fig. 4 in the text. p-*Phenylphenacyl ester* melted at 150–151° (*Anal.* Found: C, 77.94; H, 5.86. Calcd. for $C_{38}H_{34}O_6$: C, 77.79; H, 5.84).

Ozonization :- The acid (mp. 185–6°) in chloform was treated with 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 minutes. The solution was distilled at first at an atmospheric pressure and then under reduced pressure.

From the first distillate, acetone was isolated as a 2,4-*dinitrophenylhydrazone*, mp. 127–8° (*Anal.* Found: C, 45.67; H, 4.24. Calcd. for $C_9H_{10}O_4N_4$: C, 45.38; H, 4.23) and from the second distillate, pyruvic acid as a 2,4-*dinitrophenylhydrazone* mp. 216° (*Anal.* Found: C, 40.36; H, 3.06. Calcd. for $C_9H_8O_6N_4$: C, 40.30; H, 3.01), not depressed by each authentic specimen of the same mp. The residue, when derived to *p*-phenylphenacyl ester, gave a crystall, mp. 119–120° (*Anal.* Found: C, 72.80; H, 5.11. Calcd. for di-*p*-phenylphenacylester of oxalacetic acid $C_{32}H_{24}O_7$: C, 73.84; H, 4.65).

Hydrogenation :- The acid (0.4 g.) in 10 ml. of ethanol was hydrogenated over Adams' platinum oxide catalyst in a shaking hydrogenation apparatus, and absorbed 95 ml. (at 20°) of hydrogen, giving α-methyl-γ-*iso*propyladipic acid, mp. 104–5° (*Anal.* Found: C, 59.16; H, 8.68. Calcd. for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97). *Di*-p-

phenylphenacylester, prepared by standard method, formed fine needles from methanol, mp. 92-3° (*Anal.* Found: C, 77.18; H, 6.69. Calcd. for $C_{38}H_{38}O_6$: C, 77.26; H, 6.48).

Methyl β-Hydroxy-αβδ-trimethyl-Δγ-hexenoate. About 50 ml. of a mixture of methyl α-bromopropionate (bp. 48°/12 mm., 50 g. 0.3 mole) and mesityloxide (33 g. 0.3 mole) in 50 ml. of dry benzene, were added on 22 g. (0.3 atom) of activated zinc, then it was warmed with effective stirring until a vigorous reaction set in. Addition of a bit of copper powder and/or mercuric chloride initiated the reaction smoothly. The remaining mixture was then run in at such a rate that the steady reflux of benzene was under control.

It was then warmed under reflux for an additional half an hour, cooled, poured into an ice-cold solution of dilute sulphuric acid. After removal of the unchanged zinc, the organic layer which separated, was washed with several portions of water and dried over anhydrous magnesium sulphate. Replacement of zinc by magnesium and a prolonged refluxing time increased the high boiling polymer and reduced the yield of the β-hydroxyester desired. The solvent was removed through a column and the residue was fractionated under reduced pressure to give the *methyl ester*, bp. 66-7°/2.5 mm., n_D^{20} 1.4540, $R_{D(obs.)}$ 51.61, $R_{D(calcd.)}$ 51.12 (yield 34-39 g.). When ethyl α-bromopropionate was used, the corresponding *ethyl ester* (36-41 g.) bp. 77-8°/2.5 mm., n_D^{20} 1.4493 $R_{D(obs.)}$ 56.31 $R_{D(calcd.)}$ 55.76, was obtained.

Methyl αβδ-Trimethylsorbate. The Reformatski ester was dehydrated by refluxing with a slight excess of phosphorus pentoxide in dry benzene for an hour. *Methyl ester* had bp. 68-9°/7 mm., n_D^{20} 1.4650, $R_{D(obs.)}$ 49.52 $R_{D(calcd.)}$ 49.11 (yield, 55-58 %). *Ethyl ester* had bp. 70-71°/5 mm, n_D^{20} 1.4610, $R_{D(obs.)}$ 54.43 $R_{D(calcd.)}$ 53.76 (yield, 55 %).

Hydrolysis of the ester with ethanolic potassium hydroxide gave the free acid, bp. 97/4 mm., n_D^{20} 1.4809. p-*Iodophenacylester* melted at 41-2° (*Anal.* Found: C, 51.10; H, 4.94. Calcd. for $C_{17}H_{19}O_3I$: C, 51.27; H, 4.81).

On catalytic hydrogenation over a platinum catalyst, the acid (1 g.) absorbed 292 ml. (at 21°) of hydrogen (equivalent to 1.88 double bond), yielding αβδ-trimethylcaproic acid bp. 127-8°/16 mm., n_D^{20} 1.4365. *Amide* mp. 126-7° (*Anal.* Found: C, 68.81; H, 12.15. Calcd. for $C_9H_{19}ON$: C, 68.79; H, 12.18) was prepared by standard method. *Methyl ester* had bp. 76-8°/15 mm., n_D^{20} 1.4240.

Additation of Ethyl Diazoacetate to Methyl αβδ-Trimethylsorbate. About 1 g. of ethyl diazoacetate was added to a solution of methyl αβδ-trimethylsorbate (50 g., 0.3 mole) in an equal volume of ligroin containing 1 g. of copper powder, the mixture was heated until reaction set in with the evolution of nitrogen. The remaining diazoacetate (16 g. in total, 0.15 mole) was then added at such a rate that the steady reflux and the smooth evolution of nitrogen maintained without external heating.

After removal of the solvent and unreacted sorbate under reduced pressure, the residual adduct was fractionated to give four fractions within the range of bp. 95-115°/1.5 mm., main fraction distilling at 103-4°/1.5 mm., $R_{D(obs.)}$ 68.56 $R_{D(calcd.)}$ 68.27, n_D^{20} 1.4660, yield (13 g.).

These fractions were separately hydrolyzed with ethanolic potassium hydroxide, and the isolated viscous acids were kept cold for a week or so. Partial crystallization occured, and the separate crystallisation gave the acid, mp. 164–5°, (*Anal.* Found: C, 62.26; H, 7.88. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60), *equivalent weight* by titration 106.8 (Calcd. for $C_9H_{14}(CO_2H)_2$, 106.1), $\lambda_{max.}$ 238 mμ, ε 19,700. For infra-red absorption spectrum, see Fig. 5 in the text. *Di*-p-*phenylphenacylester* mp. 115° (*Anal.* Found: C, 77.76; H, 6.01. Calcd. for $C_{39}H_{36}O_6$: C, 77.98; H, 6.04) was prepared by standard method.

Ozonization :- The acid (mp. 164–5°, 1 g.) in chloroform was treated with an excess of ozonized air for several hours at 0°

The solvent was removed under reduced pressure, and the ozonide decomposed with addition of water by warming on a water bath for ten minutes. The aqueous solution was concentrated on a water bath, but no crystallization occurred. This was then taken up with alkali, poured into a cold solution of sodium hypobromite (2.3 g. bromine in 40 ml. of 5% sodium hydroxide solution). After an hour's stirring, the excess of hypobromite was decomposed by addition of hyposulphite, acidified with dilute sulphuric acid and thoroughly extracted with ether. After removal of the solvent, the residue was crystallized several times from water to yield *cis*-caronic acid (150 mg.), mp. 171–2°.

Two grams of the mother liquor, from which the partially crystallized acid was removed, was treated with ozone and then with sodium hypobromite in exactly the same way as mentioned above. The ether extract, on evaporating, deposited a crystalline mass (*ca.* 800 mg.) and to this, 9 ml. of 20% aqueous ammonia was added and evaporated to dryness. The ammonium salt was ground up with cold absolute ethanol. The insoluble salt was dissolved in a small amount of water, acidified with dilute sulphuric acid and repeatedly extracted with ether. The ether extract, on evaporating, gave *trans*-caronic acid(230 mg.) which melted at 212° after several crystallizations from water.

The ethanol-soluble fraction of the ammonium salt was evaporated, acidified with dilute sulphuric acid and repeatedly extracted with ether. After removal of ether, the residue was recrystallized from water so as to give *cis*-caronic acid (200 mg.), mp. 170–3°.

V. SYNTHESIS OF (±)-*trans*-, AND (±)-*cis*-3-(*trans*-2′-CARBOXYPROPENYL)-2,2-DIMETHYLCYCLOPROPANE-1-CARBOXYLIC ACIDS[14)42)43)44)]

Preliminary experiments showed that ethyl diazoacetate added predominantly to the $\gamma\delta$-ethylenic bond of substituted sorbic esters (see Part IV). Hence, the addition of ethyl diazoacetate to ethyl $\alpha\delta$-dimethylsorbate was performed with success under the reaction condition employed in the preliminary experiment.

Ethyl diazoacetate was added to ethyl $\alpha\delta$-dimethylsorbate in large excess or in boiling ligroin in the presence of copper powder. Vigorous evolution of nitrogen occurred and subsequent distillation gave the adduct in 30–40% yield.

The adduct was hydrolyzed with ethanolic potassium hydroxide to give a mixture of isomeric acids. Fractional crystallization of the solid mixture from

ethyl acetate, methanol-water, gave three acids, mp. 185-6°, mp. 206-8°, and mp. 208-9. The acid, mp. 185-6°, was identical with that obtained from the addition of ethyl diazoacetate to the Reformatski ester, the structure of which has already demonstrated in the preceding chapter (see Part IV). These acids were isomeric, dibasic and of the expected formula $C_{10}H_{14}O_4$. On fractional crystallization the ultra-violet absorption technique was very useful. The fractions of $\lambda_{max.}$ 273-5 mμ, indicative of the presence of conjugated diene carboxylic chromophere, were of the unchanged sorbic acid and the acyclic adduct acid (mp. 185-6°).

On the contrary, the fractions with absorption maxima at 230-240 mμ were of the cyclopropane adducts. Both cyclopropane derivatives melted at essentially the same melting point but they are entirely different. Mixed melting point comparison showed a remarkable depression.

Ultra-violet light absorption of the acid, mp. 206-8°, ($\lambda_{max.}$ 237 mμ, ε 15,400) indicated the same chromophoric system in this compound as in the naturally derived chrysanthemum-dicarboxylic acid ($\lambda_{max.}$ 238 mμ, ε 15,300).

Ozonization gave (±)-*trans*-caronic acid, mp. 212°, as well as pyruvic acid (as a 2,4-dinitrophenylhydrazone, mp. 218°) and the comparison with authentic specimens resulted no depression of the melting points respectively. Infra-red absorption spectrum (Fig. 6) was very similar to that of the naturally derived acid. The complete identity of the infra-red spectrum of dimethyl ester (mp. 78-9°) with that of dimethyl ester of the naturally derived chrysanthemum-dicarboxylic acid (Fig. 7, in carbon tetrachloride) shows that the acid, mp. 206-8°, is the racemic form of the naturally derived chrysanthemum-dicarboxylic acid.

The latter isomeric acid, mp. 208-9°, showed depression of melting point when mixed with the former and further difference is in that both dimethyl and

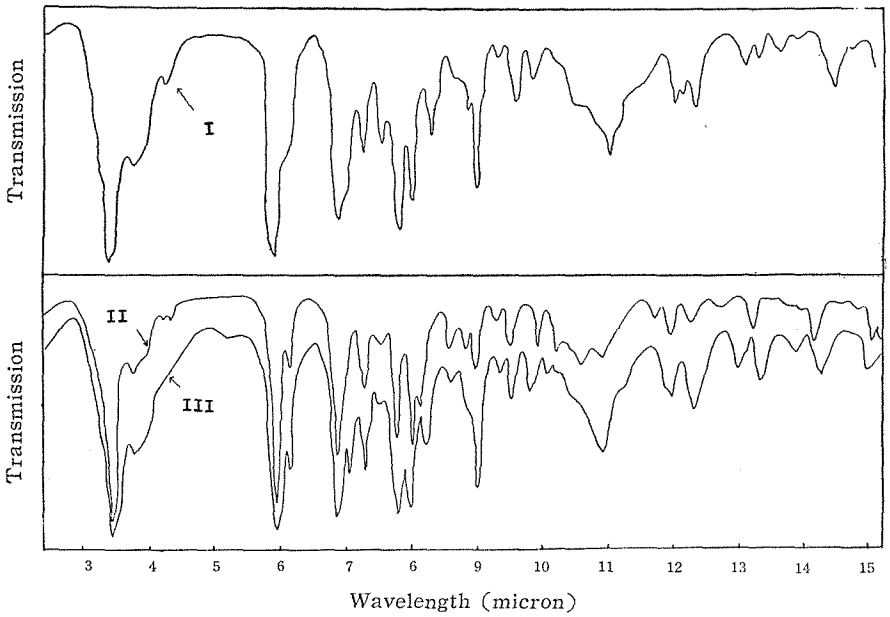


Fig. 6. I- Natural chrysanthemum-dicarboxylic acid, II- (±)-*trans*-, and III- (±)-*cis*-3-(*trans*-2′-carboxypropenyl)-2,2-dimethylcyclopropane-1-carboxylic acid (Nujol).

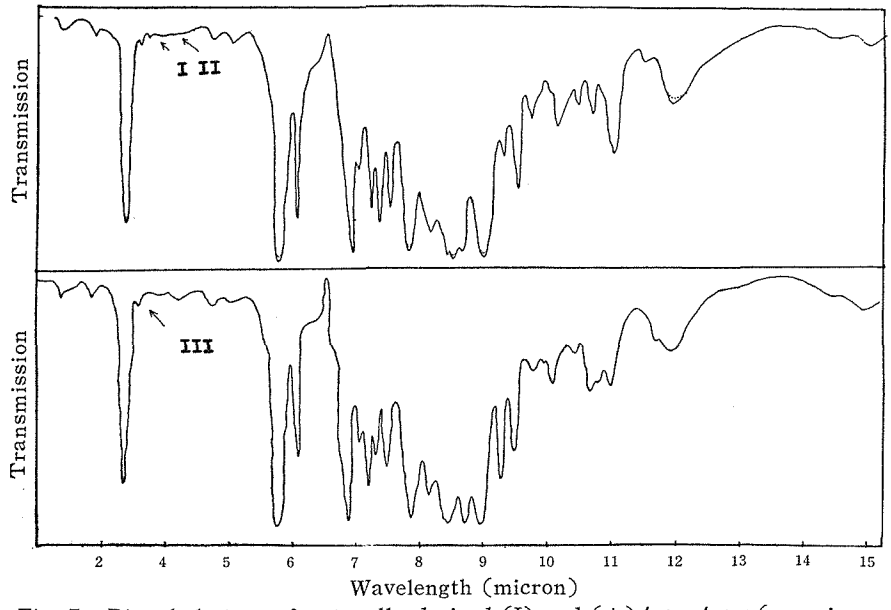


Fig. 7. Dimethylesters of naturally derived (I) and (±)-*trans-trans*-(superimposed II) and (±)-*cis-trans*-chrysanthemum-dicarboxylic acid (III) (solution in carbon tetrachloride).

di-*p*-phenylphenacyl esters are liquid in contrast to the solid esters of the former.

Ozonolysis of the acid, mp. 208-9°, to give (±)-*cis*-caronic acid together with pyruvic acid (as a 2,4-dinitrophenylhydrazone) shows that the acid, mp. 208-9° is the geometrical isomer of the former, mp. 206-8°, with respect to the cyclopropane ring.

Infra-red absorptions of the acid and its dimethyl ester were similar to those of the former isomer, but the ultra-violet absorption (λ_{max}. 234 mμ, ε 14,700) was not identical.

In an addition without any diluent and under a drastic condition, the main adduct was the acyclic structural isomer, mp. 185-6°. In another experiment, ethyl diazoacetate was added to $\alpha\delta$-dimethylsorbate in large excess at lower temperature without copper catalyst, and the careful removal of the unchanged sorbate under reduced pressure gave an intermediate pyrazoline ester, which, though neither isolated pure nor derived to acetyl compound, was characterised by qualitative tests[45] and by the thermal decomposition with or without copper powder to give a mixture of the acids, mp. 185-6°, mp. 206-8°, and mp. 208-9°.

At any rate, the addition product was always the mixture of these three isomeric acids and the addition proceeds through the pyrazoline intermediate. Thus, the formation of the acid, mp. 185-6° with *trans*-$\alpha\beta$-configuration by the addition of ethyl diazoacetate to ethyl $\alpha\delta$-dimethylsorbate of the demonstrated *trans*-configuration, unambiguously shows the retention of the *trans*-configuration during the addition reaction. Therefore, it is reasonably concluded that the 2'-carboxypropenyl group of the resulting isomeric acids has the *trans*-configuration.

Thus, the acid, mp. 206-8°, is (±)-*trans*-3-(*trans*-2'-carboxypropenyl)-2,2-di-

methylcyclopropane-1-carboxylic acid and the isomeric acid, mp. 208-9°, is (±)-*cis*-3-(*trans*-2'-carboxypropenyl)-2,2-dimethylcyclopropane-1-carboxylic acid.

The mechanism of the addition of aliphatic diazo-compounds to olefins remains uncertain, but the participation of free radicals is rather favoured at present.

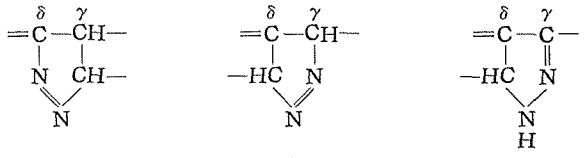
However, the formation of the acyclic structural isomer in the author's experiment and the formation of the pyrazoline intermediate during the addition of diazoacetate favours the pyrazoline intermediate mechanism rather than free radical mechanism.

It seems probable that the addition of diazoacetate would not proceed by a simultaneous addition of the alkoxycarbonylmethylene radical at both ends of the ethylenic bond, but proceed by stepwise process.

In order to explain the formation of these products by the free radical mechanism, either cyclopropane intermediate or diradical should be postulated. Cyclopropane derivative i.e. chrysanthemum-dicarboxylic acid in this case, is too rigid, as is well known, to be regarded as an intermediate which decomposes to give the acyclic compound by ring fission and to give rise to inversion by intramolecular rearrangement. The assumption of successive occurrence of diradicals are thermodynamically unreasonable.

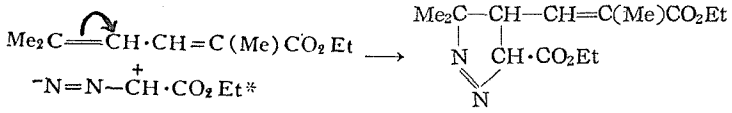
The author prefers the pyrazoline intermediate mechanism which could explain satisfactorily the formation of all these addition products.

Although the structure of the pyrazoline formed in the addition was not established, three following structures are theoretically possible.



a *b* *c*

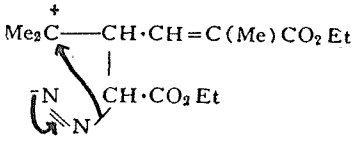
Among these, Δ^2-structure *c* and Δ^1-structure *b* are excluded, because these structures can not give rise to the acyclic isomer, in which the diazoacetate residue attaches to the γ-carbon atom of the sorbate. By exclusion, Δ^1-structure *a* is considered to be that of the existing pyrazoline and this is also supported by the following scheme of formation:



This structure agrees with the fact that the pyrazoline gives no acetyl derivative.

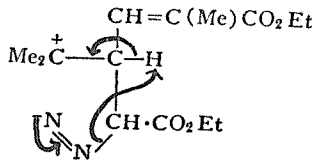
The intermediate pyrazoline ester thus formed is postulated to decompose with expulsion of nitrogen to give the cyclopropane derivative.

Scheme A



For the formation of acyclic isomer, the pyrazoline is postulated to decompose with migration of a hydrogen and expulsion of nitrogen.

Scheme B



The scheme of decomposition of the pyrazoline intermediate in each reaction depends upon the reaction conditions employed, yielding a mixture of acyclic and cyclopropane adducts in any proportion.

EXPERIMENTAL

Addition of Ethyl Diazoacetate to Ethyl $\alpha\delta$-Dimethylsorbate. a) Ethyl diazoacetate (10 g.) was added slowly to a large excess of ethyl $\alpha\delta$-dimethylsorbate (60 g.) at 80-90° and this temperature was maintained for several hours, and then the reaction mass was carefully distilled under an effective vacuum to remove the unreacted $\alpha\delta$-dimethylsorbate.

Attempted acetylation with acetyl chloride in the usual way gave no acetyl compound, but the residue was characteristic of pyrazoline in every respect when qualitatively tested.

The residue was gently heated with copper powder until evolution of nitrogen ceased, and then hydrolyzed with ethanolic potassium hydroxide to give a crystalline mass (*ca.* 3 g.). Fractional crystallization of the solid gave the acid, mp. 185-6° (0.5 g.), the acid mp. 206-8° (0.4 g.) and the acid, mp. 208-9° (0.15 g.), fractions of intermediate melting point amounting *ca.* 2 g.

b) A mixture of ethyl diazoacetate (14 g., 0.12 mole) and ethyl $\alpha\delta$-dimethylsorbate (20 g., 0.12 mole) was slowly added to a suspension of copper powder (0.5 g.) in a small quantity of $\alpha\delta$-dimethylsorbate preheated at 110°. A violent reaction occurred with a vigorous evolution of nitrogen and the rate of addition was adjusted so that the reaction temperature was maintained at 110-130°, but under this condition the temperature rose to *ca.* 150-180° immediately after the addition. The distillation of the adduct gave a fraction, bp. 91-2°/0.05 mm., n_D^{15} 1.4725, (9.5 g.) and hydrolysis with ethanolic potassium hydroxide gave exclusively the acid, mp. 185-6°, (3 g.) which was identical with that obtained from th addition of diazoacetate to the Reformatski ester (see Part IV). Small proportion of the cyclopropane adduct, which was characterized by the ultra-violet absorption and melting point in the course of crystallization, was obtained (0.7 g.).

c) About 1 ml. of ethyl diazoacetate was added to a solution of ethyl $\alpha\delta$-dimethylsorbate (42 g.) in equal volume of ligroin containing 1 g. of copper powder, and the mixture heated until reaction set in with the evolution of nitrogen (temperature being kept at 125-130°). The remaining diazoacetate (15 g.) was then added at such a rate that the steady reflux and a smooth evolution of

nitrogen maintained, without external heating. After the the removal of the solvent and unchanged sorbate by distillation under reduced pressure, the oily residue was fractionated to give a fraction, bp. 113-4°/1.5 mm., n_D^{13} 1.4776. This procedure was repeated by recycling the recovered *aδ*-dimethylsorbate and 29 g. of crude adduct ester were obtained (*ca.* 46 %). The ester fractions were hydrolyzed with ethanolic potassium hydroxide and the resluting acid mixture was kept in a refrigerator. Crystallization occurred and fractional recrystallization from ethyl acetate and methanol-water gave the acid, (4.8 g.) mp. 185-6° and (±)-trans-3-(trans-2'-*carboxypropenyl*)-2,2-*dimethylcyclopropane*-1-*carboxylic acid* (7 g.) mp. 206-8°, *equivalent weight* by titration 99.5 (Calcd. for $C_8H_{12}(CO_2H)_2$ 99.1) (*Anal.* Found: C, 60.63; H, 7.11. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12). By standard method, *di*-p-*phenylphenacyl ester*, mp. 133-5° (*Anal.* Found: C, 77.68; H, 5.98. Calcd. for $C_{38}H_{34}O_6$: C, 77.79; H, 5.84) and *dimethyl ester*, mp. 78-9° (*Anal.* Found: C, 63.70; H, 8.02. Calcd. for $C_{12}H_{18}O_4$: C, 63.97; H, 7.93). Ultra-violet light absorption of this acid showed $\lambda_{max.}$ 237 mμ, ε 15,400. For infra-red spectrum, see Figs. 6 and 7 in the text.

Fractional crystallization gave the second acid, (±)-*cis*-3-(*trans*-2'-*carboxypropenyl*)-2,2-*dimethylcyclopropane*-1-*carboxylic acid* (4.5 g.) mp. 208-9°, *equivalent weight* by titration 99.7 (Calcd. 99.1) (*Anal.* Found: C, 60.60; H, 7.07. Calcd: for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12). The melting point was depressed by the mixed melting point comparison with the former acid, mp. 206-8°. In contrast to those of the former acid, *dimethyl ester* and *di*-p-*phenylphenacyl ester*, prepared by standard methods, were liquid. The *dimethyl ester* boiled at 100.5-101.5°/0.5 mm. and had n_D^{20} 1.4882. The *phenacylester* was resinous and uncrystallizable. Ultra-violet light absorption showed $\lambda_{max.}$ 234 mμ, ε 14,700. For infra-red absorption spectrum, see Figs. 6 and 7 in the text.

Ozonisation :- The acid, mp. 206-8° (0.8 g.) in chloroform (40 ml.) was treated with excess of ozone for several hours at 0°. The solvent was removed at 25° under reduced pressure, and the oily ozonide was decomposed with addition of a small amount of water on a water bath for ten minutes. The resulting aqueous solution was then distilled under reduced pressure. From the distillate caught in a chilled receiver, pyruvic acid was isolated as a 2,4-*dinitrophenylhydrazone*, mp. 218° (mixed) (*Anal.* Found: C, 40.39; H, 3.10. Calcd. for $C_9H_8O_6N_4$: C, 40.30; H, 3.01). (±)-*trans*-Caronic acid (310 mg.) separated out from the residue and melted at 212° after crystallizations from methanol-water. (*Anal.* Found: C, 53.36; H, 6.21. Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.37). Mixed melting point comparison with the authentic specimen resulted no depression of the melting point.

Ozonisation of the second acid, mp. 208-9°, (0.6 g.) was performed exactly in the same way as described above and (±)-*cis*-caronic acid was obtained (200 mg.), mp. 173-4° (*Anal.* Found: C. 53.40; H, 6.44. Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.37), together with pyruvic acid, which was identified as a 2,4-*dinitrophenylhydrazone*, mp. 218° (*Anal.* Found: C, 40.21; H, 3.08. Calcd. for $C_9H_8O_6N_4$: C, 40.30; H, 3.10). These resulted no depression of melting points by the admixture of authentic specimens repectively.

VI. OPTICAL RESOLUTION OF (±)-*trans*-3-(*trans*-2'-CARBOXYPROPENYL)-2,2-DIMETHYLCYCLOPROPANE-1-CARBOXYLIC ACID[46)47)]

As was described in the preceding chapters, (±)-*trans*-3-(*trans*-2'-carboxypropenyl)-2,2-dimethylcyclopropane-1-carboxylic acid was shown to be the racemic form of the naturally derived chrysanthemum-dicarboxylic acid.

Complete resolution of this racemic acid into diastereoisomers was achieved by means of the synthetic base, optically active α-phenylethylamine, with results which are summarized below (rotation in ethanol).

	M.p.	$[\alpha]_D^{11}$
(+)-acid	163-4°	+70.9°
(±)-acid	206-8°	0
(−)-acid	163-4°	−70.5°

The dextrorotatory acid was identical with the naturally derived acid in every respect, thereby accomplishing the total synthesis of the chrysanthemum-dicarboxylic acid.

EXPERIMENTAL

(+)-*trans*-3-(*trans*-2'-Carboxypropenyl)-2,2-dimethylcyclopropane-1-carboxylic Acid. To a boiling solution of the racemate (4.1 g.) in 120 ml. of methanol were added 2.5 g. of (−)-α-phenylethylamine, having $[\alpha]_D^{11}$ −38.9°, in 10 ml. of methanol. The solution was kept overnight and the first crop of salt (2.6 g.) was separated and the mother liquor evaporated, this procedure being repeated so that five crops were obtained by successive reduction of the volume. After fractional recrystallizations of these crops and combining crops with approximately the same rotation to the first crop and recrystallizing the combined salt many times from methanol, there was finally obtained the pure (−)-α-phenylethylamine salt of the (+)-acid (0.7 g.), mp. 224-5°, $[\alpha]_D^{11}$ +28.3° (*c*, 1.1, methanol). (*Anal.* Found: C, 67.91; H, 8.06; N, 4.25. Calcd. for $C_{10}H_{14}O_4 \cdot C_8H_{11}N$: C, 67.79; H, 7.89; N, 4.39). Further recrystalization did not alter these values. Subsequent decomposition of this salt (0.5 g.) by dilute sulphuric acid gave a pure crystalline (+)-trans-3-(trans-2'-*carboxypropenyl*)-2,2-*dimethylcyclopropane*-1-*carboxylic acid* (0.23 g.) mp. 163-4°, $[\alpha]_D^{11}$ +70.9° (*c*, 3.3, ethanol), (*Anal.* Found: C, 60.54; H, 7.19. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12). The melting point was not depressed when mixed with the naturally derived chrysanthemum-dicarboxylic acid, mp. 164°, $[\alpha]_D^{11}$ +71.2° (*c*, 1.5, ethanol) (*cf.* Staudinger, Ruzicka[1)], $[\alpha]_D^{17}$ +72.8°). *Di*-p-*phenylphenacylester*, mp. 151-2° (mixed), $[\alpha]_D^{11}$ +123.3° (*c*, 0.9, chloroform), (*Anal*, Found: C, 77.51; H, 5.91. Calcd. for $C_{38}H_{34}O_6$: C, 77.79; H, 5.84), was prepared by standard method.

(−)-*trans*-3-(*trans*-2'-Carboxypropenyl)-2, 2-dimethylcyclopropane-1-carboxylic Acid. The combined filtrate from (−)-base(+)-acid salt was evaporated, decomposed with dilute sulphuric acid and recovered by extraction. To a boiling solution of the recovered acid (3.4 g.) in 80 ml. of methanol were added 2.1 g. of (+)-α-phenylethylamine, having $[\alpha]_D^{11}$ +39.4°, in 15 ml. of methanol.

The solution was kept overnight and the first crop (1.4 g.) was obtained

and the mother liquor concentrated, this procedure being repeated so that four crops were obtained, the specific rotations of which varied $-15°$ to $+3°$. On fractional crystallization as before, was obtaind the pure (+)-α-phenylethylamine salt of the (−)-acid (0.6 g.), mp. 223-4°, $[\alpha]_D^{11}$ $-28.0°$ (*c*, 1.1, methanol) (*Anal.* Found: C, 67.93; H, 8.08; N, 4.28. Calcd. for $C_{10}H_{14}O_4 \cdot C_8H_{11}N$: C, 67.69; H, 7.89; N, 4.39). Further crystallization did not alter these values. The salt (0.5 g.) was decomposed by pouring an aqueous solution into a dilute sulphuric acid and extraction and recrystallization gave the pure (−)-acid (0.26 g.) mp. 163-4°, $[\alpha]_D^{11}$ $-70.5°$ (*c*, 1.0, ethanol) (*Anal.* Found: C, 60.87; H, 7.28. Calcd. for $C_{10}H_{14}O_4$; C, 60.59; H, 7.12). *Di*-p-*phenylphenacylester*, mp. 151-2°, $[\alpha]_D^{11}$ $-123.0°$ (*c*, 0.91, chloroform) (*Anal.* Found: C, 77.97; H, 6.05. Calcd. for $C_{33}H_{34}O_6$: C, 77.79; H, 5.84) was prepared by standard method.

Melting and boiling points were uncorrected in this study. Microanalyses were carried out by Microanalytical Laboratory of Prof. Mitsui, to whom the author's thanks are due. Samples were completely dried over phosphorus pentoxide *in vacuo* at appropriate temperature for each.

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