Experiments on the Synthesis of the Pyrethrins. Part IX. The Addition of Ethyl Diazoacetate to Sorbic Esters.*

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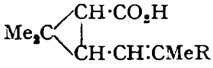
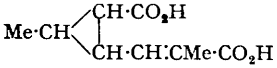
It is shown that ethyl diazoacetate adds predominantly to the γδ-ethylenic bond of methyl sorbate and α-methylsorbate to form the *cyclo*propane derivatives. From the adduct with methyl sorbate two crystalline isomeric 2-2′-carboxyvinyl-3-methyl*cyclo*propane-1-carboxylic acids are isolated, and their structures and configurations are established by degradation to isomeric 3-methyl*cyclo*propane-1 : 2-dicarboxylic acids.

This opens the way to a synthesis of chrysanthemumdicarboxylic acid, or a stereoisomer thereof, by the addition of ethyl diazoacetate to an ester of αδ-dimethylsorbic acid.

The successful synthesis of the chrysanthemic acids (I; R = Me) developed by Campbell and Harper (*J.*, 1945, 283; cf. Harper, Reed and Thompson, *J. Sci. Food Agric.*, 1951, 2, 94), through the addition of ethyl diazoacetate to 2 : 5-dimethylhexa-2 : 4-diene, has led us to examine a similar approach to the synthesis of the chrysanthemumdicarboxylic acids (I; R = CO_2H). A (+)-*trans*-chrysanthemumdicarboxylic acid arises from the hydrolysis of (+)-*trans*-pyrethric acid (I; R = CO_2Me), the acidic component of cinerin-II and pyrethrin-II.



(I)



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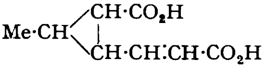

(III)

The olefinic component required would be an ester of the hitherto undescribed αδ-dimethylsorbic acid, and successful synthesis would necessitate addition at the γδ-ethylenic bond. To gain information on the latter point attention was directed, initially, to the addition of ethyl diazoacetate to esters of the readily accessible sorbic and α-methylsorbic acids.

As the mechanism of the " high-temperature " addition of aliphatic diazo-compounds to olefins remains uncertain, though with a bias in favour of the participation of free radicals, confident prediction of the influence of polar groups cannot be made. Existing evidence relating to dienes is scanty and conflicting. Heide (*Ber.*, 1904, **37**, 2101) showed that, with 1-phenylbutadiene, ethyl diazoacetate adds to the γδ-ethylenic bond. In contrast, Guha and Sankaran (*Ber.*, 1937, **70**, 2109) observed terminal addition of diazomethane to ethyl muconate. Of other additions probably proceeding by a free-radical mechanism, epoxidation of methyl sorbate by perbenzoic acid gives γδ-addition, as does peroxidation (Heinänen, *Suomen Kem.*, 1935, **8**, *B*, 5; 1938, **11**, *B*, 2). Hence it seemed

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* Part VIII, *J.*, **1952**, **869**.

likely that γδ-addition of ethyl diazoacetate to simpler sorbic esters would predominate but the formation of several geometrical isomers owing to lack of symmetry, and of structural isomers owing to the non-identity of the ethylenic bonds, would render the isolation of pure individuals more difficult than in the case of the chrysanthemic acids.

Ethyl diazoacetate was added to methyl sorbate and to methyl α-methylsorbate in refluxing light petroleum (b. p. 100—120°) in the presence of copper bronze. Vigorous evolution of nitrogen occurred and subsequent distillation gave the adduct in 25—30% yield. Great difficulty was encountered in obtaining any crystalline products either after hydrolysis or on ozonolysis. First success was achieved with the adduct from methyl α-methylsorbate. Ozonolysis of this adduct gave, after decomposition, in the steam-distillate pyruvic acid, identified as the 2 : 4-dinitrophenylhydrazone and presumably derived from the intermediate methyl pyruvate by ready hydrolysis. From the portion involatile in steam a crystalline dibasic acid, m. p. 138°, of the formula $C_6H_8O_4$ was isolated and characterised by crystalline di-*p*-nitrobenzyl, di-*p*-bromophenacyl, and di-*p*-phenylphenacyl esters. This acid could be only a 3-methyl*cyclo*propane-1 : 2-dicarboxylic acid and, therefore, derived from an adduct acid (II) formed by γδ-addition of ethyl diazoacetate. The isolation of pyruvic acid substantiated this conclusion. None of the products that would arise from the degradation of an adduct resulting from αβ- or αδ-addition was isolated.

Attention was redirected then to the adduct from ethyl diazoacetate and methyl sorbate. On a larger scale the adduct was fractionally distilled and the fractions were separately hydrolysed to gummy acids which partially and slowly crystallised. Fractional crystallisation of the solid gave a less soluble acid, m. p. 184°, and a more soluble acid, m. p. 195°. Each acid was characterised as its di-*p*-nitrobenzyl and di-*p*-phenylphenacyl ester. These acids were isomeric, dibasic, and of the expected formula $C_8H_{10}O_4$. Furthermore, both showed a high-intensity absorption band at 229 mμ, indicative of the presence of $\cdot CH{:}CH \cdot CO_2H$. Ozonolysis of the acid, m. p. 195°, gave the same 3-methyl*cyclo*propane-1 : 2-dicarboxylic acid, m. p. 138°, as was obtained from the methyl α-methylsorbate adduct; their identity was established by comparison of the di-*p*-nitrobenzyl, di-*p*-bromophenacyl, and di-*p*-phenylphenacyl esters. Ozonolysis of the acid, m. p. 184°, also gave a 3-methyl*cyclo*propane-1 : 2-dicarboxylic acid, m. p. 135°, but characterisation of this acid as its di-*p*-nitrobenzyl and di-*p*-phenylphenacyl esters showed it to be not identical with the acid of m. p. 138°. The adduct acids, m. p.s 184° and 195°, therefore, are stereoisomers of the desired structure (III), arising from γδ-addition to the sorbic ester. However, the low yield (*ca.* 15%) of these acids points to the presence of other stereoisomers or structural isomers; no further crystalline products were obtained.

It remained to elucidate the stereochemistry of these " bisnor "-chrysanthemumdicarboxylic acids by consideration of the identity of the two 3-methyl*cyclo*propane-1 : 2-dicarboxylic acids. Three optically inactive forms of the latter acids are possible, (IV)—(VI). Although the identification of these acids and the assignment of their configurations was a controversial issue of the 1920's, throughout the controversy no derivatives of these acids were prepared. The sole remaining criterion of identity is the melting points of the acids which, however, were shown to be markedly depressed by traces of moisture or solvent. If the configurations assigned by Goss, Ingold, and Thorpe (*J.*, 1923, **123**, 3342) are accepted, the *trans*-acid (IV) * has m. p. 195°, and is thus removed from further consideration. The *trans*-3 : *cis*-2-acid (V) was ascribed m. p. 132° by Goss, Ingold, and Thorpe (*loc. cit.*) but later (*idem, ibid.*, 1925, **127**, 460) was shown to be identical with the acid of m. p. 147° isolated by Feist (*Annalen*, 1924, **436**, 125; cf. Kon and Nanji, *J.*, 1932, 2557). The *cis-cis*-acid (VI), first obtained by Preisweck (*Ber.*, 1903, **36**, 1085), was ascribed the m. p. 108° (solvated form ?) and may be identical with a *cis*-acid, m. p. 94°, obtained by Feist (*loc. cit.*).

It was evident that mere inspection did not permit of identification. We repeated, therefore, Goss, Ingold, and Thorpe's synthesis which utilises the condensation of ethyl sodiomalonate with ethyl αβ-dibromobutyrate. In our hands, however, prolonged hydro-

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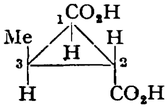
* In this designation the CO_2H at position 1 is the reference group for both *cis*-2 and *trans*-3.

chloric acid hydrolysis of the intermediary triethyl *cis*-3-methyl*cyclo*propane-1 : 1 : 2-tricarboxylate gave no 3-methyl*cyclo*propane-1 : 2-dicarboxylic acid but γ-methylparaconic acid, the product of fission of the *cyclo*propane ring. Brief acid hydrolysis gave *cis*-3-methyl*cyclo*propane-1 : 1 : 2-tricarboxylic acid, better obtained by alkaline hydrolysis. Decarboxylation of the tricarboxylic acid was accompanied by the evolution of water, pointing to the preferential formation of the anhydride of (VI). Hydrolysis gave *cis*-3-methyl*cyclo*propane-1 : *cis*-2-dicarboxylic acid (VI), which separated from benzene in a solvated form of indistinct melting point. Preparation of the di-*p*-nitrobenzyl and the di-*p*-phenylphenacyl ester and comparison showed then to be identical with the derivatives of our acid (m. p. 135°) derived from the adduct acid, m. p. 184°.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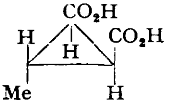
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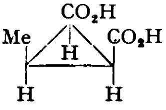
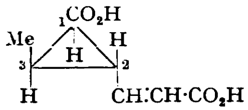

(VI)

Four isomeric 2-2′-carboxyvinyl-3-methyl*cyclo*propane-1-carboxylic acids could be formed from methyl *trans-trans*-sorbate, (VII) and (VIII) by addition without inversion and (IX) and (X) by addition with inversion (the carboxyvinyl group having the *trans*-configuration throughout). Of these, only (X) can give rise to (VI) on ozonolysis, which is therefore the configuration of the acid, m. p. 184°. By exclusion the 3-methyl*cyclo*propane-1 : 2-dicarboxylic acid of m. p. 138° is the *trans*-3 : *cis*-2-isomer (V). Now of the remaining adduct acids (VII)—(IX), only (VIII) can give rise to (V) on ozonolysis, which is therefore the configuration of the adduct acid, m. p. 195°, from methyl sorbate (also of the acid present but not isolated in the adduct from methyl α-methylsorbate).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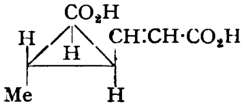
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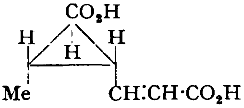
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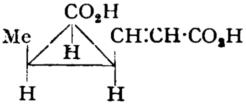
(X)

That ordinary sorbic acid has the *trans-trans*-configuration is well established; the evidence has been summarised recently by Eisner, Elvidge, and Linstead (*J.*, 1953, 1372). These authors showed that partial inversion to *cis-trans* markedly affects the ultra-violet light absorption, the single high-intensity band (*e.g.*, for methyl sorbate, $\lambda_{max.}$ 258 mμ, ε 31,500) giving way to less intense absorption showing multiple bands. The configuration of the only known form of α-methylsorbic acid, prepared by the Reformatski reaction, has remained uncertain. We find that methyl α-methylsorbate shows the single high-intensity band ($\lambda_{max.}$ 263 mμ, ε 27,400) that would be expected for a *trans-trans*-configuration, with the additional methyl substituent producing a bathochromic shift of 5 mμ.

Addition of ethyl diazoacetate to the $\gamma\delta$-ethylenic bond of methyl sorbate has occurred both with and without inversion at one of the γ or the δ carbon atoms. Hence reaction does not proceed by a broadside approach of an ethoxycarbonylmethylene radical and simultaneous addition at both ends of the ethylenic bond. Addition of ethyl diazoacetate must be (at least) a two-stage process in which either a pyrazoline ring is formed and then broken or the ethoxycarbonylmethylene radical adds in two stages. Both would lead to a diradical intermediate which could retain or lose configuration at the free-radical carbon atoms. The course of the reaction would then parallel the photochemically catalysed addition of chlorine to olefins.

It has been generally assumed in additions of aliphatic diazo-compounds that the olefin retains its configuration, and configurations have been assigned on this basis. However, few additions have been studied by earlier workers in which inversion could have been unequivocally established. Only two other cases have been found, that of the addition of diazomethane to dimethyl *trans*-but-2-ene-2 : 3-dicarboxylate (von Auwers and König, *Annalen*, 1932, **496**, 252) and of diazo*iso*propane to ethyl maleate (Guha and Sankaran, *Ber.*, 1937, **70**, 1688).

EXPERIMENTAL

Ultra-violet light absorptions were determined in EtOH in a Unicam SP. 500 spectrophotometer by Mr. K. C. Sleep.

Sorbic acid, m. p. 133—134°, was prepared by the Reformatski method in 18% yield and better by the Knoevenagel method in 28—32% yield (cf. Allan and VanAllan, *Org. Synth.*, 1944, **24**, 92). Methyl sorbate had b. p. 72°/12 mm., n_D^{25} 1·4950, d_4^{25} 0·9605. α-Methylsorbic acid, m. p. 100°, was prepared exclusively by the Reformatski method (cf. von Auwers and Heyna, *Annalen*, 1923, **434**, 157) in 25% yield. *Methyl α-methylsorbate*, prepared with methanolic sulphuric acid, had b. p. 86°/12 mm., n_D^{20} 1·5044 ; light absorption, see text (Found : C, 68·3; H, 8·7. $C_8H_{12}O_2$ requires C, 68·55; H, 8·65%).

Addition of Ethyl Diazoacetate to Methyl α-Methylsorbate.—Methyl α-methylsorbate (56 g., 0·4 mol.) in light petroleum (50 ml., b. p. 100—120°) containing copper bronze (0·5 g.) was heated to the b. p. under reflux, the source of heat removed, and ethyl diazoacetate (23 g., 0·2 mol.; prepared by the method of Harper, Reed, and Thompson, *J. Sci. Food Agric.*, 1951, **2**, 94) added slowly : a vigorous exothermic reaction with evolution of nitrogen ensued. Distillation gave the adduct ester, b. p. 122—128°/3 mm., in approx. 10% yield (on the ethyl diazoacetate). Hydrolysis with ethanolic potassium hydroxide yielded the adduct acid(s) as a gum which did not crystallise.

The adduct ester (5·0 g.) was treated with excess of ozone in chloroform at 0° and the ozonide treated with water and steam-distilled. Addition of 2 : 4-dinitrophenylhydrazine in dilute hydrochloric acid to the distillate gave a precipitate of pyruvic acid 2 : 4-dinitrophenylhydrazone (0·5 g.), m. p. and mixed m. p. 212°. Evaporation of the solution of the involatile product gave a gum that slowly and partially crystallised. Recrystallisation of the solid from ethyl acetate gave *trans*-3-methyl*cyclo*propane-1 : *cis*-2-dicarboxylic acid (0·33 g.), m. p. 138° [Found : C, 50·5; H, 5·2%; equiv., 71·8, 72·2. Calc. for $C_4H_6(CO_2H)_2$: C, 50·0; H, 5·6%; equiv., 72·1]. By standard procedures the *di*-p-*nitrobenzyl*, plates (from ethanol), m. p. 129° (Found : C, 58·1; H, 4·5. $C_{20}H_{18}O_8N_2$ requires C, 58·0; H, 4·4%), the *di*-p-*bromophenacyl*, needles (from ethanol), m. p. 171° (Found : C, 48·9; H, 3·7. $C_{22}H_{18}O_6Br_2$ requires C, 49·1; H, 3·4%), and the *di*-p-*phenylphenacyl ester*, laths (from ethanol), m. p. 193° (Found : C, 76·7; H, 5·3. $C_{34}H_{28}O_6$ requires C, 76·7; H, 5·3%), were prepared.

Addition of Ethyl Diazoacetate to Methyl Sorbate.—By proceeding as for methyl α-methylsorbate and recycling the recovered methyl sorbate, 234 g. of crude adduct ester were obtained from 300 g. of methyl sorbate. This adduct ester was separated by fractional distillation into six fractions (24·0, 29·5, 20·2, 36·4, 65·1, and 40·0 g.) within the range of b. p. 138—151°/12 mm., having n_D^{25} rising from 1·469 to 1·479, d_4^{25} within the range 1·095—1·100 and $[R_L]_D$ rising from 53·8 to 54·8 (Calc. : 53·54). These fractions were separately hydrolysed with ethanolic potassium hydroxide, and the isolated gummy acids kept during several months during which slow partial crystallisation occurred. Trituration with ethyl acetate enabled the solids (0, 0·5, 4·8, 4·0, 6·4, and 9·5 g.) to be separated from the remaining gums. No further crystallisation occurred.

Separate crystallisation from ethyl acetate gave the same less soluble product, cis-2-(trans-2-*carboxyvinyl*)-cis-3-*methyl*cyclo*propane*-1-*carboxylic acid* (5·8 g.), m. p. 184°, $\lambda_{max.}$ 229 mμ (ε 17,600) [Found : C, 56·4, 56·5; H, 5·5, 5·8%; equiv., 85·0, 85·1. $C_6H_8(CO_2H)_2$ requires C, 56·5; H, 5·9%; equiv., 85·1]. The *di*-p-*nitrobenzyl ester* crystallised in plates, m. p. 134°, from ethanol (Found : C, 59·9; H, 4·6. $C_{22}H_{20}O_8N_2$ requires C, 60·0; H, 4·6%), and the *di*-p-*phenylphenacyl ester* crystallised from acetone–ethanol in plates, m. p. 164° (Found : C, 77·5; H, 5·4. $C_{36}H_{30}O_6$ requires C, 77·4; H, 5·4%).

Evaporation of the filtrates from the above acid and extraction of the residue with hot water yielded a second acid. Recrystallisation of this from ethyl acetate gave cis-2-(trans-2-*carboxyvinyl*)-trans-3-*methyl*cyclo*propane*-1-*carboxylic acid* (0·74 g.), m. p. 195°, $\lambda_{max.}$ 229 mμ (ε 19,400) (Found : C, 56·8; H, 5·5%; equiv., 85·6, 85·7). The *di*-p-*nitrobenzyl ester* crystallised from ethanol in prisms, m. p. 112° (Found : C, 60·3; H, 4·9%), and the *di*-p-*phenylphenacyl* ester crystallised from acetone–ethanol in granules, m. p. 153° (Found : C, 77·8; H, 5·7%).

Ozonisations.—The acid (0·5 g.), m. p. 184°, was treated with excess of ozone in chloroform at 0°. The solution was evaporated under reduced pressure, the residue warmed with water, and the aqueous solution evaporated. The resulting gum slowly crystallised and on recrystallisation from benzene gave *cis*-3-methyl*cyclo*propane-1 : *cis*-2-dicarboxylic acid (0·21 g.), m. p. 135° [Found : C, 49·8; H, 5·6%; equiv., 73·0, 73·5. Calc. for $C_4H_6(CO_2H)_2$: C, 50·0; H, 5·6%; equiv., 72·1]. The *di*-p-*nitrobenzyl ester* crystallised from ethanol in plates, m. p. 135°

(Found: C, 58·1; H, 4·3. $C_{20}H_{18}O_8N_2$ requires C, 57·95; H, 4·4%), and the *di*-p-*phenylphenacyl ester* similarly, m. p. 175° (Found: C, 76·9; H, 5·3. $C_{34}H_{28}O_6$ requires C, 76·7; H, 5·3%).

The acid (0·25 g.), m. p. 195°, being insoluble in cold chloroform, was treated with excess of ozone at 0° in ethyl acetate–chloroform (2 : 3). Working up as above and crystallising from benzene gave *trans*-3-methyl*cyclo*propane-1 : *cis*-2-dicarboxylic acid (0·1 g.) in solvated form, m. p. 95—105° with evolution of vapour, which at 100° in a vacuum crumbled to a powder, m. p. 138° (Found: equiv., 71·7, 73·7). The di-*p*-nitrobenzyl ester had m. p. and mixed m. p. 129° (Found: C, 57·7; H, 4·5%), the di-*p*-bromophenacyl ester, m. p. and mixed m. p. 171° (Found: C, 48·9; H, 3·2. Calc. for $C_{22}H_{18}O_6Br_2$: C, 49·1; H, 3·4%), and the di-*p*-phenylphenacyl ester, crystallised from acetone–ethanol, had m. p. and mixed m. p. 193° (Found: C, 76·5; H, 5·1%).

Hydrolysis of Triethyl cis-3-*Methyl*cyclo*propane*-1 : 1 : 2-*tricarboxylate*.—Triethyl *cis*-3-methyl*cyclo*propane-1 : 1 : 2-tricarboxylate, b. p. 158—172°/18 mm., was prepared in up to 70% yield by Goss, Ingold, and Thorpe's method (*J.*, 1923, **123**, 3352) (although 96 g. of sodium was presumed to be a misprint for 9·6 g.). It has since been observed by Mr. R. J. D. Smith that continuous illumination with ultra-violet light reduces the time of reaction of bromine with ethyl crotonate from several days to 2—3 hr.

(i) [With Miss M. W. Lowe.] The triethyl ester (29 g.) was boiled during 30 hr. with 20% hydrochloric acid (200 ml.) under a short air-condenser that permitted loss of alcohol vapour, following Goss, Ingold, and Thorpe (*loc. cit.*). Additional hydrochloric acid was added to maintain the volume. Complete evaporation and keeping the residue in vacuum on a porous tile gave a crystalline solid (8·3 g.). Crystallised from a large volume of benzene this gave (what is considered to be) γ-methylparaconic acid as triangular plates, m. p. 78—79°. Fittig (*Annalen*, 1889, **255**, 18) gives m. p. 78—79°.

(ii) The triethyl ester (44·5 g.) was boiled with 1 : 1 aqueous hydrochloric acid (270 ml.) under a water-condenser (the ester appeared to be steam-volatile). As soon as homogeneity was attained (2·5 hr.) the solution was evaporated under reduced pressure. Prolonged keeping of the gummy acid in a vacuum gave a semi-solid mass, which resisted treatment with ether and benzene. Eventually ethyl acetate extracts were found to deposit a microcrystalline solid, *cis*-3-methyl*cyclo*propane-1 : 1 : 2-tricarboxylic acid (5·0 g.), m. p. 208° with evolution of vapour. Preisweck (*Ber.*, 1903, **36**, 1085) recorded m. p. 215° (decomp.). No further crystalline product was obtained.

(iii) The triethyl ester (48 g.) and potassium hydroxide (40 g., 4 equiv.) in ethanol (400 ml.) were heated to reflux during 2·5 hr. Some deposition of the monoethyl dipotassium salt occurred as observed by Preisweck (*loc. cit.*). However, working up at this stage disclosed that hydrolysis was incomplete. Hence ester plus acid (42 g.), recovered by continuous ether-extraction, and potassium hydroxide (40 g.) in water (400 ml.) were refluxed for a further 2 hr. After continuous ether-extraction of the hydrolysate and rejection of the small oily extract, the aqueous solution was acidified with concentrated hydrochloric acid and again continuously ether-extracted. Evaporation and evacuation of the extract gave semisolid acid (30·5 g.). Trituration of the solid with cold ethyl acetate gave slightly impure *cis*-3-methyl*cyclo*propane-1 : 1 : 2-tricarboxylic acid (15·0 g.). Crystallisation by percolation with boiling ethyl acetate raised the m. p. to a constant value of 207° (decomp.).

cis-3-*Methyl*cyclo*propane*-1 : cis-2-*dicarboxylic Acid*.—The above tricarboxylic acid (5·0 g.) was melted and kept at 225° until vapour evolution was complete (30 min.). The resultant gummy anhydride was warmed with water until it dissolved. The solution was treated with decolorising carbon and then evaporated under reduced pressure to a gum which was dissolved in boiling benzene, and the remaining water was removed by azeotropic distillation. Slow crystallisation of solvated acid took place as clusters of prisms which became opaque on drying (2·0 g.). Fractional crystallisation from benzene did not separate any less soluble *trans*-acid (cf. Goss, Ingold, and Thorpe, *loc. cit.*) but all the fractions had vague m. p.s in the range 90—120° with evolution of solvent. Storage at 100°/0·03 mm. during 1 hour gave liquids which after solidification still had m. p.s *ca.* 95—105° (Found: equiv., 71·5). Nevertheless, this product was substantially *cis-cis*-acid for the main fraction readily gave pure derivatives. The di-*p*-nitrobenzyl ester crystallised from ethanol in plates, m. p. and mixed m. p. 137° (corr.), and the di-*p*-phenylphenacyl ester crystallised from 1 : 1 acetone–ethanol as plates, m. p. and mixed m. p. 179° (corr.).

The *di*-p-*bromophenacyl ester* crystallised from ethanol in flattened needles, m. p. 166° (corr.) (depressed to 150° on admixture with the isomer of m. p. 171°) (Found: C, 49·2; H, 3·3; Br, 29·9. $C_{22}H_{18}O_6Br_2$ requires C, 49·1; H, 3·4; Br, 29·7%). From the concentrated filtrates from this ester a few crystals of different type separated and were picked out. Recrystallisation gave an isomeric *di*-p-*bromophenacyl ester*, m. p. 123·5° (corr.), as prisms from ethanol (Found: C, 49·1; H, 3·3; Br, 29·9%), presumably derived from 3-methyl*cyclo*propane-1 : *trans*-2-dicarboxylic acid.

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