462. *The Third Isomeric* (cis-trans-)*Muconic Acid.*

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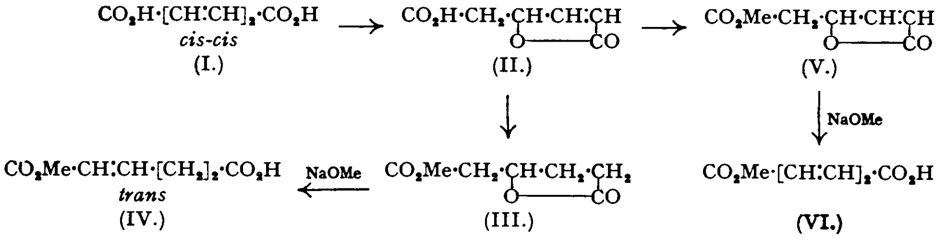
Isomerisation of γ-carbomethoxymethyl-Δ^{α}-butenolide (V) with sodium methoxide in methanol affords a methyl hydrogen muconate (VI) which has a *trans-cis*-configuration. Hydrolysis with alkali gives the corresponding *trans-cis*-muconic acid (VII), and reaction with diazomethane yields the methyl *cis-trans*-muconate (VIII). The *cis-cis*- and *cis-trans*-forms of muconic acid show a remarkable similarity which has hitherto concealed the existence of the new isomeride. The m. p.s of the free acids are nearly the same and their dimethyl esters likewise have almost identical melting points, although those of the benzhydryl esters differ from one another. The three pairs of compounds show distinct depressions of melting point although this is not large for the free acids. The ultra-violet and infra-red light absorption characteristics of the three muconic acids and their esters are recorded. The stereochemical stabilities of the *cis-cis*- and *cis-trans*-muconic acids have been studied. *cis-cis*-Muconic acid is quantitatively inverted to *cis-trans*-muconic acid merely on boiling with water. The significance of this observation in relation to results obtained by earlier workers in the field is pointed out.

We have recently described the lactonisation of *cis-cis*-muconic acid (I) (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *J.*, 1950, 2228). The product (II) on hydrogenation and esterification gave the saturated lactonic ester, γ-carbomethoxymethylbutanolide (δ-carbomethoxyvalerolactone) (III). This could readily be isomerised by means of sodium methoxide to methyl hydrogen *trans*-Δ^{α}-dihydromuconate (but-1-ene-1 : 4-dicarboxylate) (IV).

This isomerisation, together with those observed by Pauly and his co-workers on the higher homologue (*Annalen*, 1914, **403**, 119; 1918, **416**, 1), made it appear probable that the ***unsaturated*** lactonic ester (V) would rearrange similarly to an acid ester of muconic acid (VI). Moreover, an interesting stereochemical point arose. In the ring-opening of (III) to (IV) a *trans*-Δ^{α}-double bond is formed. This falls into line with recent work on the alkaline fission of β-acyloxy-



$$\underset{\textit{cis-cis}}{CO_2H\cdot[CH{:}CH]_2\cdot CO_2H}\ \text{(I.)} \longrightarrow \begin{array}{l} CO_2H\cdot CH_2\cdot CH\cdot CH{:}CH \\ \qquad\qquad\quad O\text{———}CO \end{array}\ \text{(II.)} \longrightarrow \begin{array}{l} CO_2Me\cdot CH_2\cdot CH\cdot CH{:}CH \\ \qquad\qquad\quad O\text{———}CO \end{array}\ \text{(V.)}$$

$$\text{(II.)} \longrightarrow \begin{array}{l} CO_2Me\cdot CH_2\cdot CH\cdot CH_2\cdot CH_2 \\ \qquad\qquad\quad O\text{———}CO \end{array}\ \text{(III.)} \xrightarrow{NaOMe} \underset{\textit{trans}}{CO_2Me\cdot CH{:}CH\cdot[CH_2]_2\cdot CO_2H}\ \text{(IV.)}$$

$$\text{(V.)} \xrightarrow{NaOMe} CO_2Me\cdot[CH{:}CH]_2\cdot CO_2H\ \text{(VI.)}$$

acids and esters. It has been found, for example, that acyl derivatives of β-hydroxybutyric acid yield *trans*-crotonic acid with alkaline reagents (Linstead, Owen, and Webb, unpublished observations). It thus appeared probable that the substituents about the *new* double bond, formed in the ring opening (V) ⟶ (VI), would have the *trans*-configuration, whereas the double bond pre-existing in the ring would be *cis*. This would mean that the product would be a derivative of a new *cis-trans*-muconic acid and differing from the known isomerides melting at about 187° (*cis-cis*) and 300° (*trans-trans*).

Treatment of the unsaturated lactonic ester with sodium methoxide in methanol gave the expected methyl hydrogen muconate (VI) in about 30% yield. From the mother-liquors lævulic acid [presumably derived from (V) *via* hydrolysis to β-ketoadipic acid] was isolated as the 2 : 4-dinitrophenylhydrazone. Over a platinum catalyst (VI) took up 2 mols. of hydrogen and gave a product which yielded adipic acid on acid hydrolysis. Hydrolysis of (VI) gave a muconic acid (VII), m. p. 184°, which in admixture with *cis-cis*-muconic acid (m. p. 184°; made by oxidation of phenol with peracetic acid) melted at 180—184°. The melting points and mixed melting point of these acids vary with the rate of heating in a manner described later. Esterification either of the muconic acid or of the half-ester (VI) with diazomethane yielded a dimethyl ester with a melting point (75°) almost identical with that (73·5°) of the *cis-cis*-dimethyl ester. However, a mixture of the two esters gave an unmistakable depression of some 15—20°, so that clearly the ester of m. p. 75°, derived from the lactone, was not identical with dimethyl *cis-cis*-muconate; nor was it identical with dimethyl *trans-trans*-muconate which melts at 157°. On the other hand, the analytical values, including methoxyl determination, gave good agreement with those required for a dimethyl muconate, and the ultra-violet absorption spectrum also agreed.

It thus appeared that, in spite of the similarities, the compounds prepared from the lactonic ester (V) did in fact belong to a new geometrically isomeric series. This was confirmed by an examination of the benzhydryl esters. The two known muconic acids and the new isomeride, on treatment with diphenyldiazomethane, gave three distinct esters, with m. p.s 157° (*cis-cis*), 191° (*trans-trans*), and 143·5° (from the new acid). These gave correct analytical figures and each depressed the m. p. of the other two.

Although the existence of a third muconic acid was by now certain, we were perplexed by a lack of reproducibility in the results. Thus the following series of conversions was carried out several times by three separate workers :

Phenol ⟶ *cis-cis*-acid (I) ⟶ (II) ⟶ (V) ⟶ (VI)

and the dimethyl esters were prepared from (I) and (VI). Generally, two distinct esters were formed, giving a m. p. depression of about 20° as described above, but on two or three occasions the esters obtained were identical, which made it appear at first sight that sometimes the inversion failed to occur during the changes (I) ⟶ (VI). Subsequently the following reactions were carried out, which, although apparently puzzling, actually provided the clue to the problem. A sample of muconic acid, " A," freshly made from phenol, was converted by diphenyldiazomethane into the new benzhydryl ester of m. p. 143·5° instead of into the expected *cis-cis*-isomeride of m. p. 157°. The ester was hydrolysed and the acid so obtained, " B," together with the starting material " A " were converted into dimethyl esters which were compared with the authentic esters, m. p. 73·5° and m. p. 75° respectively, of the *cis-cis*- and of the " new " acid. It was found that A and B were identical with one another and with the new acid : their esters and the new ester had the same m. p.s and mixed m. p.s, but gave a large depression with the *cis-cis* ester. *Thus the explanation of the anomaly was not that the inversion*

(I) ⟶ (VI) *was unreliable but that the starting material had sometimes become inverted in the course of its preparation.*

We accordingly prepared some *cis-cis*-muconic acid under carefully controlled conditions. All use of heat was avoided and access to light was kept to the minimum. The acid was then subjected to various purification procedures, and the various samples of the acid were identified by conversion into methyl or benzhydryl esters and comparison with authentic material. It was found that the *cis-cis*-acid could be crystallised unchanged from boiling methanol or ethanol and was unaffected by dissolution in alkali and liberation with mineral acid. The solid *cis-cis*-acid could be kept at 100° for 4 hours without change, and was unchanged by exposure to daylight (4—5 weeks). Moreover, solutions of the acid in ethanol or alkali were unchanged by exposure to ultra-violet light for 30 minutes and 3 minutes, respectively. The sodium salt was stable to boiling water, at least for short periods. However, crystallisation of the free acid from boiling water was sufficient to bring about rapid and complete inversion. A full explanation was thus provided for the earlier lack of reproducibility : some samples of acid had been crystallised from boiling water and had thus been inverted; others had not. Incidentally, crystallisation from boiling water had been used by previous workers for the purification of the *cis-cis*-acid : we return to this point later.

It is thus established that the muconic acid formed by the oxidation of phenol can be converted into an isomeride by boiling water or, indirectly, through the lactonic acid (II). The new compound must be a muconic acid because it is hydrogenated to adipic acid and converted into *trans-trans*-muconic acid when an aqueous solution containing a trace of iodine is irradiated by ultra-violet light. The muconic acid structure is also supported by the ultra-violet and infra-red spectra. It seems very probable that the oxidation product of phenol has the *cis-cis*-configuration. The assignment of the *trans-trans*-configuration to the long-known acid of m. p. 300° appears established (see summary by Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *loc. cit.*). This leaves the *cis-trans*-configuration for the new acid and this is supported (i) by the argument advanced earlier, and (ii) by the fact that the new acid is intermediate in stability between the other two isomerides, being readily formed from one in boiling water and converted into the other by ultra-violet light. The muconic acids and their esters provide a further interesting example of the isolation in all three possible stereochemical forms of a 1 : 3-butadiene system. Farmer (*J.*, 1923, **123**, 2531) has described the three forms of ethyl αα′-dibromomuconate, and the three stereoisomers of diphenylbutadiene have been prepared and investigated by Strauss and Müller (*Annalen*, 1905, **342**, 190) and by Pinckard, Wille, and Zechmeister (*J. Amer. Chem. Soc.*, 1948, **70**, 1938).

Because of the general similarity between the *cis-cis*- and *cis-trans*-muconic acids a number of their properties have been carefully determined. Analytically pure *cis-cis*-acid is best obtained by crystallisation from ethanol, from which it separates as stout prisms or rhombs. The *cis-trans*-acid, prepared by either of the methods already described, separates from ethanol or water in long prismatic needles. The melting point and mixed melting point, determined in the usual way, have already been described. If the specimens are placed in a bath at 165° and the temperature raised rapidly (10° per minute), then differences between the two acids are more apparent, the *cis-cis* melting at 194—195°, the *cis-trans* at 190—191°, and a mixture at 180—185° or even lower.

The properties of the three muconic acids are described in detail in the experimental section : light absorption data are recorded in the table (p. 2238).

It is to be noted that the positions of the ultra-violet absorption maxima are the same for each stereoisomer. In the carotenoids it has been observed (Zechmeister, *Chem. Rev.*, 1944, **34**, 267) that a single *trans*- to *cis*-inversion shifts the position of the main absorption band by ~75 A. toward shorter wave-lengths. In the diphenylbutadienes the corresponding shift is 140—150 A. (Pinckard, Wille, and Zechmeister, *loc. cit.*) which is close to that observed for the change *trans*- to *cis*-stilbene. Methyl fumarate and maleate show absorption maxima at 2087 A. ($\varepsilon = 32{,}180$) and 1927 A. ($\varepsilon = 28{,}290$), respectively (Sörensen, *Annalen*, 1941, **546**, 57), the shift in this case being 160 A. In all these examples, however, the *trans*-forms absorb the more intensely.

Further points of interest arise from an examination of scale models (constructed on covalent atomic radii). The occurrence of resonance in conjugated systems and the concomitant requisite of a planar configuration are current conceptions which imply that there are in general only two allowable steric arrangements about each formal single bond within a conjugated system : these possible orientations are designated as *s-cis* and *s-trans*. Models show that with an *s-cis*-orientation (about the central single bond) steric interference with a planar configuration occurs in both the *cis-cis*- and the *cis-trans*-muconic acid and particularly their

Light absorption data for the muconic acids and esters.

Infra-red absorption : characteristic frequencies (cm.$^{-1}$). (Measurements by Mr. J. L. Hales, Chemical Research Laboratory, Teddington.)

	Acids (paste in " Nujol ").	Methyl esters (in CCl_4).
cis-cis	1250	1370
	830	900
		830
cis-trans	890	1310
	750	1095
		880
trans-trans	1020	—
	870	—

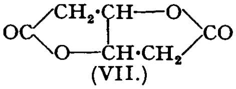
Ultra-violet absorption (the isomers are stable under the conditions of the determinations, see Experimental).

	Acids (in 0·1N-NaOH).		Methyl esters (in EtOH).		Benzhydryl esters (in EtOH).	
	$\lambda_{max.}$, A.	ε.	$\lambda_{max.}$, A.	ε.	$\lambda_{max.}$, A.	ε.
cis-cis	2510	15,600	2590	26,400	2650	30,400
	2580	17,000	2650	23,800		
	2640	15,300				
cis-trans	2510	23,400	2600	29,800	2660	33,200
	2590	25,600	2660	28,900		
	2650	23,400				
trans-trans	2510	25,600	2590	36,700	2660	35,600
	2590	29,100	2650	34,000		
	2640	25,600				

esters. Intramolecular interference effects are absent from the *s-trans*-forms, so that an *s-trans*-configuration for the *cis-cis-* and the *cis-trans*-isomer is strongly indicated. (Indeed, it is now generally conceded that the most elongated form of a conjugated system is the most stable.) The ultra-violet light absorption data are not inconsistent with such a view. The three muconic acids have been titrated electrometrically. All are strong acids and give closely similar titration curves. This therefore does not provide a method for the identification of the isomerides but it gives evidence which falls into line with the idea developed above that the *cis-cis-* and *cis-trans*-acids have extended configurations. On this basis the spacing between the carboxyl groups and hence the acid strengths would be roughly the same. It is noteworthy that the scale models indicate that there should be no difference in the ease of lactonisation of the *cis-cis-* and *cis-trans*-muconic acids, provided that they both exist in the *s-trans*-form. No difference has been detected experimentally.

Grundmann (*Ber.*, 1936, **69**, 1755) observed the iodine-catalysed photochemical inversion of *cis-cis-* to *trans-trans*-muconic acid and we have shown the change *cis-trans* ⟶ *trans-trans* occurs under the same conditions. It seemed possible that in comparative experiments involving the irradiation of aqueous solutions of the *cis-cis-* and *cis-trans*-acids there might be some difference in the rate of precipitation of the *trans-trans*-acid. None could, however, be detected. The simplest explanation is that the photochemical change *cis-cis* ⟶ *cis-trans* is faster than the second stage, *cis-trans* ⟶ *trans-trans*, although this is in truth very rapid.

The rapid and complete inversion of *cis-cis*-muconic acid to the *cis-trans*-isomer in boiling water is remarkable, the more so in view of the stability of the *cis-cis*-form under other conditions where a slow isomerisation might have been expected. It is unlikely that the inversion proceeds *via* the lactonic acid (II) : evidence that a lactone can scarcely be an *intermediate* in the inversion was provided by the production of the dilactone (VII) on prolonged boiling of *cis-cis*-muconic acid with water. The dilactone was more readily formed from *cis-cis*-muconic acid by the action of boiling dilute hydrochloric acid and in this reaction the lactonic acid (II) may well be an intermediate. Under these conditions the formation of (VII) occurred even more easily from (II) than from *cis-cis*-muconic acid.


(VII.)

In view of the similarity between the m. p.s of *cis-cis-* and *cis-trans*-muconic acids, and also in the m. p.s of their methyl esters, it is not surprising that previous workers in the field failed to observe the inversion which accompanies the crystallisation of *cis-cis*-muconic acid from boiling water. The specimens of muconic acid, m. p. 187°, which Farmer (*J.*, 1923, **123**, 2531) (see also Farmer and Duffin, *J.*, 1927, 402), Böeseken (*Proc. Acad. Sci. Amsterdam*, 1929, **32**, 1043), and Böeseken and Kerkhoven (*Rec. Trav. chim.*, 1932, **51**, 964) described and regarded as the *cis-cis*-isomer were in each case crystallised from water. As a consequence, it is highly probable that the purified material obtained by these workers was in fact the *cis-*

trans-isomer, although there is little doubt that the crude product of the oxidation of phenol which Böeseken and Kerkhoven obtained was *cis-cis*-muconic acid. It is also possible that the conclusions which the last authors drew from their experiments on the oxidation of their muconic acid are not valid since it seems very likely that recrystallised material was employed. The true stereochemical identity of the methyl muconate of m. p. 75° prepared by Farmer (*loc. cit.*) and reinvestigated by Böeseken and Kerkhoven also remains uncertain. Repetition of the work of Farmer and of Böeseken will be necessary to clear up these points.

EXPERIMENTAL.

(M. p.s marked * were taken from a bath at 165°, with the temperature rising at 10°/minute. Other m. p.s were determined normally.)

† *The Action of Sodium Methoxide on γ-Carbomethoxymethyl-Δ^{α}-butenolide* (3-*Hydroxy*-4-*carbomethoxy-but*-1-*ene*-1-*carboxylic Acid Lactone*) (V) : *Formation of a Methyl Hydrogen* trans-cis-*Muconate*.—The lactonic ester (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *loc. cit.*) (4·5 g.) in dry methanol (10 c.c.) was kept for 30 minutes with sodium methoxide in methanol (12 c.c.; 2·5N.). The solvent was then evaporated under reduced pressure, the residue taken up in water, and the solution acidified to Congo-red with concentrated hydrochloric acid. An oil separated which rapidly solidified. From benzene, the *methyl hydrogen* trans-cis-*muconate* (VI) formed needles (1·5 g.; 32%), m. p. 101° (Found: C, 54·25; H, 5·4; OMe, 19·7%; equiv., 155·3. $C_7H_8O_4$ requires C, 53·9; H, 5·2; OMe, 19·9%; equiv., 156).

In another experiment the lactonic ester (1·4 g.) and sodium methoxide gave methyl hydrogen *trans-cis*-muconate (0·4 g.) in 29% yield. The filtrate was kept for 10 days, then extracted with ether, and the ethereal solution evaporated. Treatment of the residue in ethanol with 2 : 4-dinitrophenylhydrazine in dilute hydrochloric acid gave an orange precipitate (0·9 g., 35%) which crystallised from chloroform to give orange needles of lævulic acid 2 : 4-dinitrophenylhydrazone, m. p. 205° and mixed m. p. 205—206°. Treatment of the derivative (0·1 g.) with ethereal diazomethane afforded orange needles (from ethanol) of methyl lævulate 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 141°.

† cis-trans-*Muconic Acid*.—The foregoing half-ester (250 mg.) was heated with 10% aqueous sodium hydroxide (2 c.c.) on the steam-bath for 10 minutes. The solution was cooled and acidified with hydrochloric acid, and the precipitate crystallised from hot water to give prismatic needles (200 mg., 90%), m. p. 190—191°,* of cis-trans-*muconic acid* (Found: C, 51·0; H, 4·45%; equiv., 70·8. $C_6H_6O_4$ requires C, 50·7; H, 4·25%; equiv., 71). For mixed m. p. of this and the *cis-cis*-acid, see p. 2237.

Hydrogenation of *cis-trans*-muconic acid (100 mg.) in ethanol in the presence of Adams's catalyst (hydrogen uptake: 35·5 c.c. at 21°/765 mm. Calc. for 2 double bonds: 33·9 c.c.) gave adipic acid, m. p. and mixed m. p. 150°.

† *Methyl* cis-trans-*Muconate*.—(*a*) Methyl hydrogen *trans-cis*-muconate (150 mg.) was treated with a small excess of diazomethane in ether, the solution evaporated under reduced pressure, and the residue crystallised from aqueous methanol. *Methyl* cis-trans-*muconate* (yield almost quantitative) formed needles, m. p. 75° (Found: C, 56·8, 56·5; H, 6·3, 6·0; OMe, 37·1%; hydrolysis-equiv., 86·8. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9; OMe, 36·5%; equiv., 85). A mixture with methyl *cis-cis*-muconate (m. p. 73·5°) had m. p. 50—55°.

(*b*) Reaction of *cis-trans*-muconic acid (100 mg.) with ethereal diazomethane similarly afforded methyl *cis-trans*-muconate (needles from aqueous methanol), m. p. and mixed m. p. 75°, but depressed by methyl *cis-cis*-muconate.

Lactonisation of cis-trans-*Muconic Acid*.—A suspension of the acid (1 g.) in 75% sulphuric acid (5 c.c.) was kept for 24 hours and poured on crushed ice (20 g.), and the bulk of the acid neutralised with concentrated ammonia solution. The solution (just acid to Congo-red) was extracted with ether for 40 hours, the extract evaporated, and the crystalline residue recrystallised from benzene–ethanol. γ-Carboxymethyl-Δ^{α}-butenolide separated as prisms, m. p. 110° alone or on admixture with material prepared from the *cis-cis*-acid.

cis-cis-Muconic acid was prepared as described by Elvidge, Linstead, Orkin, Sims, Baer, and Pattison (*loc. cit.*) except that particular care was taken to avoid the application of heat at any stage, and access of light was kept to an absolute minimum. The crude acid had m. p. 179—183°: treatment of a portion (0·5 g.) with diazomethane in ether gave a quantitative yield of methyl *cis-cis*-muconate, m. p. 73° (from aqueous methanol) depressed to 50—55° by methyl *cis-trans*-muconate. The crude acid (0·5-g. portions) did not undergo inversion on crystallisation from methanol or ethanol; from ethanol, cis-cis-*muconic acid* separated as prisms or rhombs (0·2 g.), m. p. 194—195° * (Found: C, 51·05; H, 4·4%; equiv., 70·9. $C_6H_6O_4$ requires C, 50·7; H, 4·25%; equiv., 71).

Methyl cis-cis-*muconate* was obtained from both the crude and the preceding purified *cis-cis*-acid with diazomethane in ether, and crystallised from aqueous methanol and from hexane as needles, m. p. 73·5° (Found: C, 56·15; H, 5·9; OMe, 36·2. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9; OMe, 36·5%).

Dependence of M. P. upon Stereochemical Purity.—The m. p.s of known mixtures of methyl *cis-cis*- and *cis-trans*-muconates were: 50 : 50, m. p. 50—55°; 85 : 15, 60—63°; 95 : 5, 67—69°.

trans-trans-Muconic acid (Ingold, *J.*, 1921, **119**, 951) was recrystallised from a large volume of boiling water and thus obtained as minute prisms, m. p. 301° (Found: equiv., 70·3. Calc. for $C_6H_6O_4$: equiv., 71). Its dimethyl ester, prepared from the acid and diazomethane, crystallised from ethanol as needles, m. p. 157°.

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† With B. A. Orkin, Harvard University.

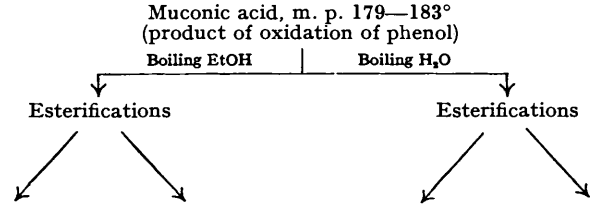
Benzhydryl Muconates.—Diphenyldiazomethane, prepared by shaking benzophenone hydrazone (2·2 g.) with yellow mercuric oxide (2·28 g.) in light petroleum (b. p. 40—60°) (20 c.c.) for 8 hours (Staudinger, Anthes, and Pfenniger, *Ber.*, 1916, **49**, 1932), was dissolved in ether (30 c.c.). To a portion (10 c.c.) *trans-trans*-muconic acid (0·2 g.) and methanol (2 c.c.) were added, and the mixture was kept in the dark for several hours. Evaporation of the ether under reduced pressure and crystallisation of the residue from methanol gave needles, m. p. 191°, of *benzhydryl* trans-trans-*muconate* (Found : C, 80·95; H, 5·7. $C_{32}H_{26}O_4$ requires C, 81·0; H, 5·5%). Similarly prepared and crystallised were *benzhydryl* cis-trans-*muconate*, needles, m. p. 143·5° (Found : C, 80·9; H, 5·7%), and *benzhydryl* cis-cis-*muconate*, needles, m. p. 157° (Found : C, 80·9; H, 5·8%). Mixtures of the three pairs of esters showed m. p. depressions of 20—30°.

Hydrolysis of Esters.—(i) After being kept overnight with concentrated hydrochloric acid (1 c.c.), benzhydryl *cis-trans*-muconate (50 mg.) was recovered unchanged (40 mg.; m. p. and mixed m. p. 143·5°). (ii) Benzhydryl *cis-trans*-muconate (0·5 g.) was refluxed with 10% aqueous sodium hydroxide (5 c.c.) for 8 hours, and the mixture cooled and extracted with ether (2 × 20 c.c.). The aqueous layer was acidified to Congo-red with concentrated hydrochloric acid, and the white precipitate collected and treated with diazomethane in ether. From aqueous methanol the product crystallised as needles, m. p. 73°; mixtures with methyl *cis-trans*- and *cis-cis*-muconate had m. p.s 73—74° and 50—55°, respectively. (iii) Methyl *cis-trans*-muconate (0·5 g.) was heated on the steam-bath with 10% sodium hydroxide solution (1 c.c.) for 30 minutes. The solution was acidified and the white precipitate, m. p. 184°, was treated with diphenyldiazomethane in ether. The product separated from methanol as needles, m. p. 143° undepressed by benzhydryl *cis-trans*-muconate.

Stereochemical Stability of cis-cis-*Muconic Acid and its Esters.*—(i) The acid was stable to boiling methanol and ethanol, as described above. (ii) The finely powdered acid (0·5 g.) was heated at 100° for 4 hours, without protection from light and air, and then treated with diazomethane in ether. A quantitative yield of methyl *cis-cis*-muconate was obtained, m. p. and mixed m. p. 73·5°, depressed to 50—55° by methyl *cis-trans*-muconate. (iii) A solution of the acid (0·5 g.) in aqueous sodium hydroxide (25 c.c.; 0·1N.) was kept at room temperature for 4 days, without protection from light. The solution was then acidified to Congo-red with concentrated hydrochloric acid and cooled to 0° for 4 hours (in the dark), and the precipitate treated with ethereal diazomethane. The product (500 mg., 83%) had m. p. 71—72° undepressed by methyl *cis-cis*-muconate but depressed to 50—55° by the *cis-trans* ester. (iv) A solution of the acid (0·5 g.) in aqueous sodium hydroxide (25 c.c.; 0·1N.) was heated to boiling for 1 minute, cooled, acidified, and kept at 0° as above. Reaction of the precipitate with ethereal diazomethane gave a crystalline solid (0·5 g.), m. p. 70—72° undepressed by methyl *cis-cis*-muconate but depressed to 50—55° by the *cis-trans* ester. (v) The acid (95 mg.) was dissolved in aqueous sodium hydroxide (2 c.c.; 0·4N.) contained in a 1-cm. quartz cell and exposed for 3 minutes to the radiation from a condensed spark between tungsten-steel electrodes (this was thrice the irradiation received during determination of the ultra-violet absorption spectrum). The solution was acidified to Congo-red with concentrated hydrochloric acid and kept at 0° for 4 hours in the dark. The *cis-cis*-muconic acid (80 mg., 85%) thus recovered was converted by diazomethane into the ester (85 mg.), m. p. 70—72°, which did not depress the m. p. of authentic methyl *cis-cis*-muconate but depressed that of the *cis-trans* ester. (vi) A solution of the acid (0·5 g.) in ethanol (10 c.c.) was irradiated for 30 minutes with ultra-violet light from a Hanovia lamp. Evaporation of the solution under reduced pressure and reaction of the residue with diazomethane gave only methyl *cis-cis*-muconate (needles from aqueous methanol), m. p. and mixed m. p. 73·5°. (vii) 50-Mg. samples of the methyl and the benzhydryl ester of *cis-cis*-muconic acid in ethanol were similarly irradiated with ultra-violet light for 15 minutes. The recovered esters had m. p.s 73° and 157°, respectively, undepressed by the corresponding esters of authentic *cis-cis*-muconic acid.

Inversion Experiments.—(a) *Conversion of* cis-cis- *into* cis-trans-*muconic acid.* (i) *cis-cis*-Muconic acid (2 g.) was heated to boiling with just sufficient water to effect solution. When the filtrate was cooled, small prismatic needles of *cis-trans*-muconic acid separated (yield, 95%), m. p. 190—191° * depressed on admixture with the starting material. The acid was treated with ethereal diazomethane and the product crystallised from methanol–water to give needles of methyl *cis-trans*-muconate, m. p. and mixed m. p. 75°, depressed to 50—55° by the *cis-cis*-ester.

(ii) Crude *cis-cis*-muconic acid (1 g.), direct from the oxidation of phenol (above), was divided into two equal portions, one of which was crystallised from boiling ethanol and the other from boiling water. The recovered acids were each divided into two portions, one of which was treated with diazomethane and the other with diphenyldiazomethane. The four esters thus obtained were recrystallised in the usual way, and mixed m. p. determinations with the appropriate authentic *cis-cis* and *cis-trans* esters made as indicated :



	Methyl ester, m. p. 73°	Benzhydryl ester, m. p. 157°	Methyl ester, m. p. 75°	Benzhydryl ester, m. p. 143·5°
Mixed with *cis-cis*...	73°	157°	51—55°	121—126°
Mixed with *cis-trans*	50—54°	125—129°	75°	143·5°

(b) *Conversion of* cis-cis- *and* cis-trans- *into* trans-trans-*muconic acid.* (i) 100-Mg. samples of *cis-cis*- and *cis-trans*-muconic acids were separately dissolved in 5-c.c. portions of methanol containing a trace of iodine and simultaneously irradiated with ultra-violet light from a Hanovia lamp. In each case a precipitate began to form after 2 minutes. After 15 minutes' irradiation, the precipitates were collected : each weighed 95 mg. (95%) and had m. p. 301° undepressed by authentic *trans-trans*-muconic acid. (ii) In a second experiment the two solutions were simultaneously irradiated with light from a 100-watt electric lamp. In each case precipitates began to form after 8 minutes. After a total of 15 minutes, the precipitates were collected and each again was found to weigh 95 mg. and have m. p. 301°. (iii) A solution of *cis-cis*-muconic acid (0·1 g.) in ethanol (10 c.c.) containing a trace of iodine was kept in diffuse daylight for 20 days. *trans-trans*-Muconic acid (0·08 g.) separated as beautiful small laths, m. p. 300—301° undepressed by an authentic specimen.

(c) *Conversion of methyl and benzhydryl* cis-cis-*muconates into the* trans-trans-*muconates.* 50-Mg. samples of the two *cis-cis*-esters were separately dissolved in ethanol containing a trace of iodine and irradiated for 60 minutes with ultra-violet light from a Hanovia lamp. Evaporation of the solutions gave respectively methyl *trans-trans*-muconate, m. p. 154° and mixed m. p. 154—157°, and benzhydryl *trans-trans*-muconate, m. p. 188° and mixed m. p. 188—190°.

(d) *Attempted conversion of* cis-cis- *into* trans-trans-*muconic acid* : *formation of the butanolidobutanolide* (VII), 3 : 7-*diketo*-2 : 6-*dioxa*bicyclo[3 : 3 : 0]*octane.* (i) *cis-cis*-Muconic acid (0·5 g.) was heated under reflux with water (5 c.c.) for 3 hours. On cooling, crystals of *cis-trans*-muconic acid separated (50 mg.), m. p. 184—188° (moderately rapid rate of heating), identified by reaction with diazomethane to yield methyl *cis-trans*-muconate (needles from methanol–water), m. p. and mixed m. p. 75°. Evaporation of the aqueous filtrate to dryness on the steam-bath afforded a solid which dissolved almost completely in ethanol (5 c.c.). After treatment with charcoal, and filtration, the solution was concentrated to small bulk, and benzene (2 c.c.) added. At 0° colourless plates separated : recrystallised from ethanol–benzene the butanolidobutanolide (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *loc. cit.*) formed platelets (0·2 g.), m. p. 131° (Found : C, 50·7; H, 4·3. Calc. for $C_6H_6O_4$: C, 50·7; H, 4·25%). The compound depressed the m. p. of γ-carboxymethyl-Δ^{α}-butenolide and was insoluble in aqueous sodium hydrogen carbonate. When kept for several days with water, the solution became acidic. (ii) *cis-cis*-Muconic acid (0·5 g.) was heated under reflux with water (5 c.c.) containing a few drops of concentrated hydrochloric acid, and after 30 minutes the mixture was evaporated to dryness on the water-bath. The residual oil crystallised on cooling ; from ethanol–benzene the product separated as plates (0·3 g., 60%), m. p. 129—130° undepressed by the previously obtained dilactone.

Conversion of γ-Carboxymethyl-Δ^{α}-butenolide (II) *into the Butanolidobutanolide* (VII).—A solution of the lactonic acid (0·5 g.) in water (5 c.c.) containing a few drops of concentrated hydrochloric acid was refluxed for 10 minutes, then evaporated to dryness on the water-bath to give an oil which set to a solid on cooling. From ethanol–benzene the butanolidobutanolide (0·3 g.) formed small plates, m. p. and mixed m. p. 128—129°. A mixture with the lactonic acid had m. p. 91—98°.

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