Stereochemistry of Thermolytic Base-catalysed Decarboxylation to form Conjugated Diene–Acids: Synthesis using Ethylidenemalonic Ester Condensation

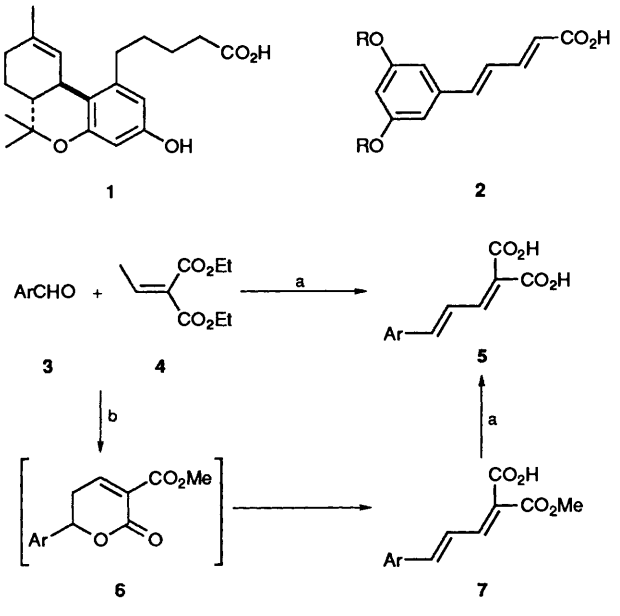
Leslie Crombie and W. Mary L. Crombie
Department of Chemistry, The University of Nottingham, Nottingham NG7 2RD, UK

The condensation of aromatic aldehydes with ethylidenemalonic ester in the presence of benzyltrimethylammonium hydroxide leads to 2(*E*),4(*E*)-half-esters, which are decarboxylated in refluxing pyridine to 2(*E*),4(*E*)-esters. When decarboxylated by thermolysis in quinoline at 130 °C cinnamylidenemalonic acid gives almost pure 5-phenylpenta-2(*Z*),4(*E*)-dienoic acid which slowly stereomutates, but on continued heating at 170 °C it passes over to give almost pure 2(*E*),4(*E*)-acid. In pyridine near its boiling point, however, the malonic acid is converted into a 64:36 mixture of 2(*Z*),4(*E*)-:2(*E*),4(*E*)-acids, the composition of which does not change on continued refluxing.

The use of carboxy-labelled dideuteriomalonic acid in the pyridine reaction leads to 5-phenylpenta-2(*Z*),4(*E*)-dienoic acid and its 2(*E*),4(*E*)-stereoisomer, each having similar ~2:1 α/γ deuterium labelling. The latter stereoisomer does not arise by stereomutation, and a dual pathway originating from a common deuteriated lactone is proposed. Decarboxylation of the deuteriomalonic acid in quinoline at 130 °C, giving almost pure 2(*Z*),4(*E*)-dienoic acid with ~2:1 α/γ labelling, involves only one of the pathways.

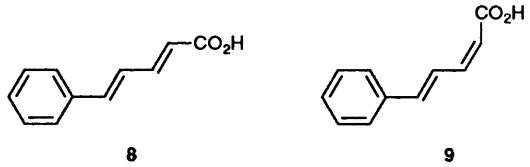
The ethylidenemalonic acid method is suitable for the preparation of 2(*E*),4(*E*)-half-esters and 5-phenylpenta-2(*Z*),4(*E*)-dienoic acids having both electron-withdrawing as well as electron-releasing aryl substituents. 2(*Z*),4(*E*)-Sorbic acid can also be made from the corresponding malonic acid by quinoline-catalysed decarboxylation, whereas the classical pyridine-catalysed Doebner reaction forms almost entirely 2(*E*),4(*E*)-sorbic acid.

In earlier work[1] we were concerned with the synthesis of the psychotomimetic Δ^1-tetrahydrocannabinol (Δ^1-THC), having the modification of a polar side-chain terminus (compound **1**), for examination of its possible decreased passage through the blood–brain barrier. The use of terpenylation methods led to a requirement for the acids **2** (R = Me, $PhCH_2$ and $MeOCH_2$) in which isotopic hydrogen labels could be readily inserted and deprotection then carried out. A suitable method appeared to be that of Gardner *et al.*[2] using the condensation of ethylidenemalonic ester **4** with an aromatic aldehyde **3**, *e.g.* 3,5-dimethoxybenzaldehyde (Scheme 1). The product obtained



Scheme 1 Ethylidenemalonic ester route to arylidenemalonic acids. *Reagents:* a, KOH–EtOH; b, Triton B–MeOH.

was found to be dependent on the base used. Whilst ethanolic potassium hydroxide led to the diacid **5** as reported, we found that methanolic benzyltrimethylammonium hydroxide (Triton B) in such cases led not to diesters, but to half-esters **7** with ester interchange.[3] Clearly, a Stobbe-type mechanism must be involved, with lactone ester **6** as intermediate,[3] and this is in agreement with other studies involving propylidenemalonic acid.[4,5] The decarboxylation of malonic acids of type **5** was first reported at the turn of the century when Liebermann[6] stated that heating of cinnamylidenemalonic acid (2-carboxy-5-phenylpenta-2,4-dienoic acid) **5** (Ar = Ph) in quinoline gave 5-phenylpenta-2(*Z*),4(*E*)-dienoic acid (*allo*-acid) **9**, an observation little exploited in the literature. On the other hand, Doebner[7] reported that heating of diacid **5** (Ar = Ph) in pyridine gave 5-phenylpenta-2(*E*),4(*E*)-dienoic acid **8**. These differing findings, coupled with reported isotopic studies,[8] led us to investigate the stereochemistry of such decarboxylations further, and the present paper records our findings.



First the question of product formation was examined. Table 1 shows that the thermolysis of cinnamylidenemalonic acid for 2 h in quinoline (bath 130 °C) does give almost pure 5-phenylpenta-2,4-dienoic acid as the 2(*Z*),4(*E*)-stereoisomer, but that, on continued heating at this temperature, isomerisation to the 2(*E*),4(*E*)-isomer then begins. When the bath temperature was raised to 170 °C this isomerisation became more rapid and after *ca.* 7 h the product was almost completely the 2(*E*),4(*E*)-form. As Table 2 shows, however, thermolysis in refluxing pyridine (b.p. 115–116 °C) gave a 2(*Z*),4(*E*):2(*E*),4(*E*) mixture

Table 1 Stereochemistry of the products from thermolysis of cinnamylidenemalonic acid in quinoline

Bath temperature (T/°C)	Time	Unchanged (%)	5-Phenylpenta-2,4-dienoic acid		
			2(Z),4(E) (%)	2(E),4(E) (%)	2(Z):2(E)
130	30 min	53.5	46	0.5	99:1
130	2 h	2	96	2	98:2
130	5 h	0	85.5	14.5	86:15
170	12 min	0	81	19	81:19
170	1 h	0	50	50	50:50
170	3 h	0	22	78	22:78
170	7 h	0	4	96	4:96
170	9 h	0	4	96	4:96

Table 2 Stereochemistry of the products from thermolysis of cinnamylidenemalonic acid in pyridine

Bath temperature (T/°C)	Time	Unchanged (%)	5-Phenylpenta-2,4-dienoic acid		
			2(Z),4(E) (%)	2(E),4(E) (%)	2(Z):2(E)
130	30 min	96	3	1	
130	1 h	76.5	15	8.5	64:36
130	2 h	31	43.5	25.5	63:37
130	3.5 h	0	64	36	64:36
130	7.75 h	0	66	34	66:34

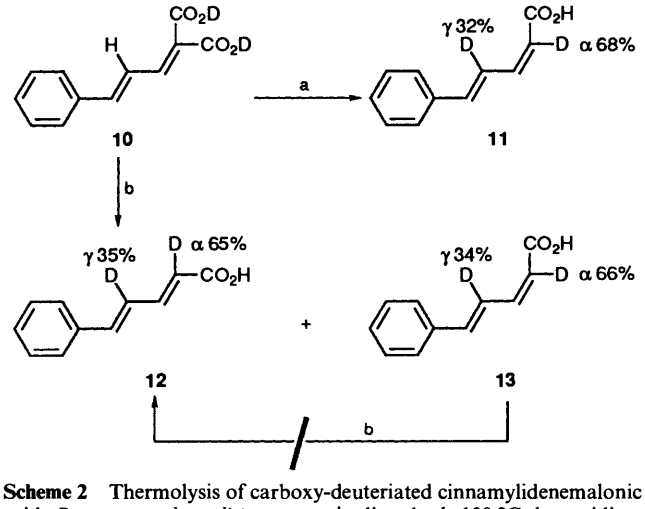
Table 3 Stereochemistry of the products from thermolysis of cinnamylidenemalonic acid in various bases

Bath temperature (T/°C)	Time	Unchanged (%)	5-Phenylpenta-2,4-dienoic acid		
			2(Z),4(E) (%)	2(E),4(E) (%)	2(Z):2(E)
Piperidine					
110	2 min	100	0	0	
110	30 min	0	6	94	6:94
130	30 min	0	2	98	2:98
130	80 min	0	2	98	2:98
DBU					
140	10 min	99	0.6	0.4	
140	90 min	13	50.5	36.5	58:42
140	105 min	0	56	44	56:44
140	3 h 40 min	0	55	45	55:45
140	6 h	0	52	48	52:48
DABCO					
170	20 min	0	99	1	99:1
170	60 min	0	50	50	50:50

in the ratio 64:36, and that this does not change appreciably over a heating period of nearly 8 h. This differs from an apparent assumption that the product is solely the 2(E),4(E)-acid.[8] The reason for the earlier misconception is possibly that the 2(E),4(E)-stereoisomer is much less soluble than the 2(Z),4(E)-acid, and only the former was isolated by crystallisation.

The effects of three other bases are examined briefly in Table 3. Piperidine at reflux (b.p. 106 °C) gave almost pure 2(E),4(E)-acid whilst 1,4-diazabicyclo[2.2.2]octane (DABCO) after brief heating at 170 °C brought about decarboxylation to form almost pure 2(Z),4(E)-material: continued heating soon caused isomerisation to the 2(E),4(E)-form. Like pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 140 °C produced a mixture, fairly stable to heating over a period of 6 h, though somewhat different in quantitative composition.

Attention was now turned to the question of deuterium label originating from the carboxylic acid deuterons during thermolysis. Cinnamylidenemalonic acid was deuteriated at the labile carboxylic acid positions by being stirred in D_2O–MeOD and then dried. When decarboxylated in quinoline (bath 130 °C), this carboxy-deuteriated cinnamylidenemalonic acid **10** gave almost entirely the 2(Z),4(E)-stereoisomer of 5-phenylpentadienoic acid with a mean ratio of deuterium labelling at the α- and γ-position of 68:32 as shown in structure **11** (Scheme 2). The isotopic ratios were evaluated both by ^1H and by ^2H NMR spectroscopy and were averaged (see Experimental section). This transference of labelling to the γ-position is a clear indicator of formation of a lactone in the decarboxylation process.[8]

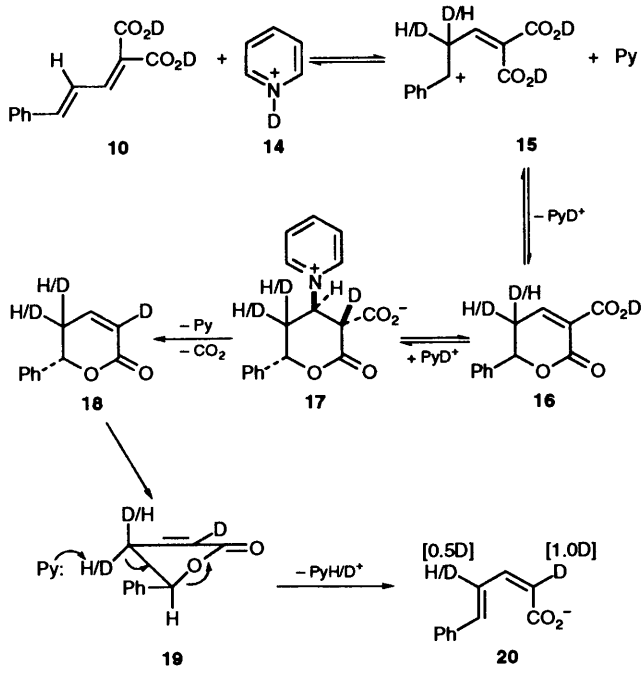


Scheme 2 Thermolysis of carboxy-deuteriated cinnamylidenemalonic acid. *Reagents and conditions:* a, quinoline, bath 130 °C; b, pyridine, near b.p.

Carboxydeuteriated cinnamylidenemalonic acid was now decarboxylated by heating it in pyridine near its boiling point (Scheme 2). The product was separated by HPLC into 2(*Z*),4(*E*)- and 2(*E*),4(*E*)-5-phenylpentadienoic acids and the ratios of deuterium incorporation at the α- and γ-positions were determined as before (see structures **12** and **13**). The mean ratio for α- and γ-position was 66:34 for the 2(*Z*),4(*E*)-stereoisomer isolated and 65:35 for the 2(*E*),4(*E*)-isomer, *i.e.* an approximate 2:1 α/γ ratio for the relative labelling. A second experiment was carried out and the α- and γ-incorporation ratios were very similar to those above, *i.e.* for the 2(*Z*),4(*E*)- 68:32 and for the 2(*E*),4(*E*)- 67:33. Elvidge *et al.*,[8] who isolated only the 2(*E*),4(*E*)-isomer in a similar tritiation experiment, give a ratio of 74:26 for relative labelling at the α- and γ-position.

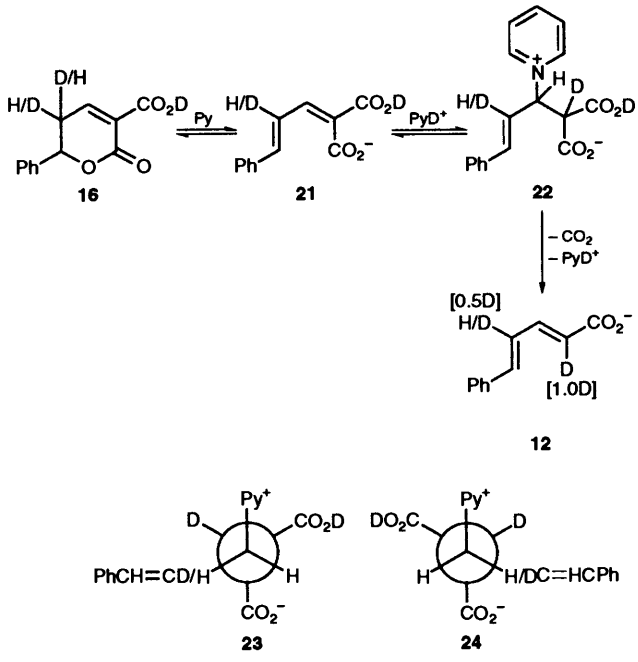
Since the labelling patterns are similar, at first sight our results might indicate that the origin of the 2(*E*),4(*E*)-product is through stereoisomerisation of the 2(*Z*),4(*E*)-compound, but Table 2 shows that this is not so as there is insufficient progressive isomerisation. This was confirmed by heating of the pure 2(*Z*),4(*E*)-isomer in pyridine near its boiling point for 9 h, when any conversion into 2(*E*),4(*E*) material was < 1%.

Our interpretation of the results obtained from thermolysis in pyridine is that the two geometric isomers probably have a common deuteriated precursor, which we suggest is lactone **16**. The essential difference between mechanisms leading to the 2(*Z*),4(*E*)- and to the 2(*E*),4(*E*)-stereoisomer then lies in whether decarboxylation precedes lactone opening (Scheme 3) or lactone opening precedes decarboxylation (Scheme 4).



Scheme 3 Proposed mechanism for the thermolysis of cinnamylidenemalonic acid in pyridine: formation of 5-phenylpenta-2(*Z*),4(*E*)-dienoic acid having 2- and 4-deuterium labelling

Deuteriation at the γ-position of carboxydeuteriated cinnamylidenemalonic acid (to give compound **15**) is envisaged as being catalysed by a deuteriopyridinium ion **14**, its deuteron being delivered to both the *re* and *si* faces of the olefin, leading to the pyridine-solvated benzylic carbonium ion **15** with, statistically, half-deuteriation in each prochiral position (Scheme 3). There are alternative possibilities. For example, compound **15** could arise by α-attack followed by allylic rearrangement, and stage **15** ⟶ **16** could be achieved *via*



Scheme 4 Proposed mechanism for the thermolysis of cinnamylidenemalonic acid in pyridine: formation of 5-phenylpenta-2(*E*),4(*E*)-dienoic acid having 2- and 4-deuterium labelling

displacement of a pyridinium group attached to C-5 of diacid **15**. Lactonisation (structure **16**) regenerates the catalytic species **14**. Stages between diacid **10** and lactone **17** are viewed as being reversible. In the final step, **19** ⟶ **20**, 0.5D is released along with 0.5H which will equilibrate with the deuterium of stages **10**–**17** so that the 'D' labelling will be somewhat diluted. The important point is that the deuterium marking the carboxy group and position 5 in lactones **16** and **17** is of the same 'strength', so that ratios remain undisturbed.

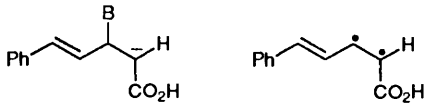
Reversible addition of PyD^+ to lactone **16**,* together with carboxylate dedeuteronation, leads to compound **17**, which undergoes irreversible decarboxylative elimination by a *trans*-diaxial process to give lactone **18**. At this stage the molecule carries overall the original complement of deuterium found in diacid **10**, but opening of the lactone in the stable conformation[14] by *trans*-elimination (structure **19**), effected by pyridine as the base, leads to the 2(*Z*),4(*E*)-ion **20** carrying a relative α/γ labelling of 2:1. An analogous mechanism is envisaged for the quinoline reaction which also forms the 2(*Z*),4(*E*)-acid carrying a relative α/γ labelling of 2:1.

We suggest that the 2(*E*),4(*E*)-acid formed in the pyridine reaction also arises from the δ-lactone **16**, but *via* the opened form **21** (Scheme 4). 1,2-Addition of PyD^+ gives a species **22** which now undergoes stereospecific decarboxylative elimination of pyridine, using the favoured conformations **23**/**24**, leading to the 2(*E*),4(*E*)-acid **12** having a similar α/γ distribution of deuterium to that of the 2(*Z*),4(*E*)-form **20**.

When pyridine is replaced by quinoline at a bath temperature of 130 °C, this latter mechanism is in little evidence. On the other hand the product stereochemistry (Table 1) suggests that a mechanism similar to that of Scheme 4 is dominant in the case of basic piperidine at reflux (b.p. 106 °C). Although in the cases of pyridine and DBU the ratios of 2(*Z*)- to 2(*E*)-acid shift only a little with time under the conditions used, in the cases of

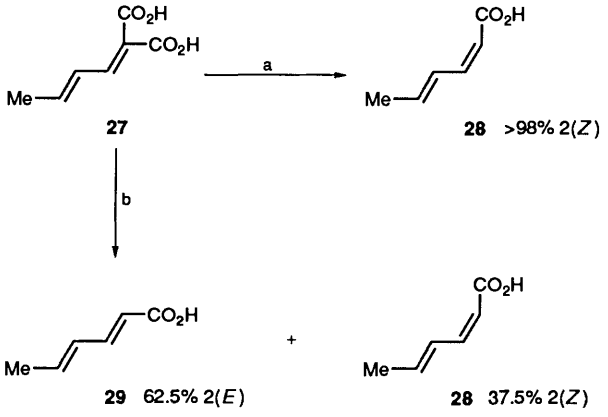
* See the important mechanistic studies of Corey[9–11] and Klein and Meyer.[12] In the case of secondary amines, intermediates from reversible addition have been isolated:[13] they decarboxylate readily.

quinoline continued heating or raising of the temperature moves the composition of the very-2(*Z*)-rich product towards the thermodynamically preferred very-2(*E*)-rich product. Table 1 shows that quinoline can, under the correct conditions, be used in a preparative method for the latter as well as for its 2(*Z*),4(*E*)-geometric isomer. Presumably an addition/elimination mechanism (see structure **25**) is involved in the stereomutation. However, some of the 2(*Z*),4(*E*)-acids mentioned in the Experimental section stereomutate to 2(*E*),4(*E*)-forms on melting without the presence of a solvent, so involvement of a biradical process (such as species **26**) cannot be ruled out.



25 **26**

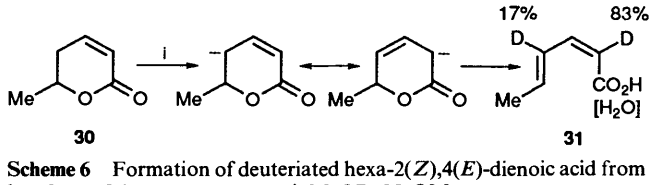
Up to the present, discussion has centred on the 5-aryl series, but thermolysis of but-2-enylidenemalonic acid **27** in quinoline at 130 °C for 2.5 h (Scheme 5) also provides an excellent



27 **28** >98% 2(*Z*) **29** 62.5% 2(*E*) **28** 37.5% 2(*Z*)

Scheme 5 Thermolysis of (but-2-enylidene)malonic acid. *Reagents and conditions:* a, quinoline, bath 130 °C; b, pyridine, reflux.

preparation of (2*Z*,4*E*)-hexa-2,4-dienoic acid [2(*Z*),4(*E*)-sorbic acid] **28** with only a trace of the 2(*E*),4(*E*)-stereoisomer **29** (ratio 99.6 : 0.4 as determined by GLC after silylation). It was identical with material formed by the established method[15] involving opening of the δ-lactone **30** (Scheme 6) by sodium methoxide

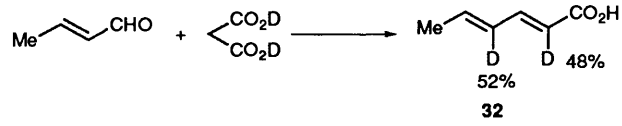


30 **31**

Scheme 6 Formation of deuteriated hexa-2(*Z*),4(*E*)-dienoic acid from hex-2-eno-δ-lactone. *Reagents:* i, MeOD, NaOMe.

in methanol. With deuteriated methanol the latter method gave an α/γ deuterium distribution of 85 : 15. When pyridine near its boiling point was used in the thermolysis of but-2-enylidenemalonic acid for 1.5 h, analysis by GLC indicated that a 37.5 2(*Z*),4(*E*)- : 62.5 2(*E*),4(*E*)-ratio was obtained. Further experiments showed that this ratio was distinctly condition dependent, but the conclusion that, qualitatively, substantial amounts of 2(*E*),4(*E*)-material were formed was maintained. The situation thus resembles, in this respect, that found for cinnamylidenemalonic acid.

On the other hand, the direct condensation of crotonaldehyde with malonic acid in pyridine at 98 °C for 1 h (the classic Doebner reaction)[16] gave sorbic acid of >98% 2(*E*),4(*E*)-quality (GLC after silylation). When a specimen of deuteriated malonic acid was used in a similar experiment, the ratio of deuterium in the α- : γ-position of monoacid **32** was 48.1 : 51.9 as estimated by ^{2}H NMR spectroscopy (Scheme 7). This agrees

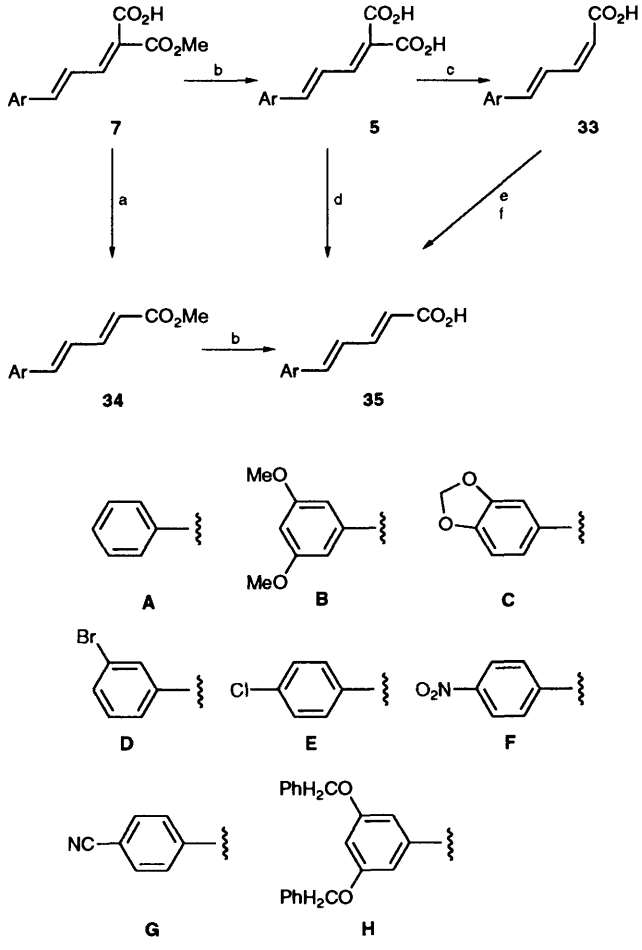


32

Scheme 7 Doebner reaction using carboxy-deuteriated malonic acid. *Reagent and conditions:* pyridine, reflux.

well with the deuteriation figure given by Elvidge and his colleagues: 46.9% for α, 53.1% for γ in a similar experiment,[8] but further work beyond such isotopic ratios is needed to suggest a plausible, detailed mechanistic path. The Doebner reaction to give sorbic acid is more complicated than the thermolysis of but-2-enylidenemalonic acid as it consists of three processes: condensation, dehydration and decarboxylation: water is eliminated and can equilibrate with the deuteriated carboxy groups.

The ethylidenemalonic ester method is preparatively valuable for making 2(*E*)-half-esters **7** (or mixed diesters of known geometry), ylidene malonic acids **5**, 2(*Z*),4(*E*)-**33** or 2(*E*),4(*E*)-**35** diene acids, or 2(*E*),4(*E*)-esters **34** as outlined in Scheme 8.



7 **5** **33** **34** **35** **A** **B** **C** **D** **E** **F** **G** **H**

Scheme 8 Ethylidenemalonic routes for the preparation of 5-arylpenta-2(*Z*),4(*E*)- and -2(*E*),4(*E*)-dienoic acids having various aryl substitutions. *Reagents and conditions:* a, pyridine, reflux; b, KOH or H^+, hydrolysis; c, heat with quinoline; d, piperidine or pyridine, reflux (then crystallisation); e, I_2, *hν*; f, melt.

Hitherto the ethylidenemalonic acid condensation has been confined to the phenyl or oxygenated phenyl examples[1,2,17]

but a range of examples **A–H** carrying electron-releasing or -withdrawing aryl substitutents are described in the Experimental section. Under the thermolytic quinoline reaction conditions the products were converted into the series of 2(*Z*),4(*E*)-diene acids **33A–H**. A point of interest is the morphological change some of the crystalline products undergo during determination of the m.p.

Experimental

^{1}H NMR spectra were run in $CDCl_3$ unless specified otherwise, on a Perkin-Elmer R 32 (90 MHz), or a Bruker WM 250 or AM 400 spectrometer. Acidic protons were identified by exchange with D_2O. Coupling constants *J* are in Hz. In ^{13}C NMR spectra the DEPT sequence was employed. Mass spectra were recorded on either an AEI MS902 or a VG 7070 upgraded instrument, normally using electron impact (EI) methods. IR spectra were recorded on a Pye-Unicam SP3-100 IR spectrometer. M.p.s were measured on a calibrated hot-stage microscope.

*5-Phenylpenta-*2(Z),4(E)*-dienoic Acid* **9** (*Ar = Ph*).—Cinnamylidenemalonic acid **5** (Ar = Ph) (500 mg) was heated in stirred quinoline (10 cm^3) at 170 °C for 10 min under nitrogen. The product was diluted with diethyl ether and extracted with aq. potassium hydroxide (5%). The extracts were acidified (HCl) and the product was filtered off, dried, and crystallised from benzene to give the 2(*Z*),4(*E*)-acid **9** (75%), m.p. 140–140.5 °C (lit.,[6] 138 °C); $\delta_H(CDCl_3)$ 5.8 (1 H, d, *J* 11.4, 2-H), 6.8–6.9 (2 H, m, 3- and 5-H), 7.3–7.4 (3 H, m, ArH), 7.55 (2 H, d, *J* 7.9, ArH) and 8.11 (1 H, dd, *J* 11.6 and 15.7, 4-H).

*5-Phenylpenta-*2(E),4(E)*-dienoic Acid* **8**.—A reference specimen was made by the refluxing of cinnamaldehyde (16.5 g, 0.125 mol) with malonic acid (13 g, 0.125 mol) in pyridine (26 cm^3) overnight. When crystallised from chloroform to free it from the 2(*Z*)-isomer, the title compound had m.p. 166.5–167.5 °C (lit.,[8] 164–165 °C); $\delta_H(CDCl_3)$ 6.01 (1 H, d, *J* 15.2, 2-H), 6.88–6.99 (2 H, m, 4- and 5-H), 7.31–7.4 (3 H, m, ArH), 7.49 (2 H, d, *J* 8.0, ArH) and 7.55 (1 H, dd, *J* 9 and 15.3, 3-H). The ^{1}H spectrum of the 2(*E*),4(*E*)-isomer has been reported by Saljoughian and Williams[18] and the full calculated spectrum has δ 6.00 ($J_{2,3}$ 15.00, $J_{2,4}$ −0.18), 6.90 ($J_{4,5}$ 14.25, $J_{4,3}$ 9.92, $J_{4,2}$ −0.18), 6.96 ($J_{5,4}$ 14.25, $J_{5,3}$ 0.58) and 7.56 ($J_{3,2}$ 15.00, $J_{3,4}$ 9.92, $J_{3,5}$ 0.58).

Analytical Systems for the Separation and Estimation of 5-*Phenylpenta-*2(Z),4(E)- *and* -2(E),4(E)*-dienoic Acids and Cinnamylidenemalonic Acid.*—(i) A suitable TLC system was silica gel, developed with hexane–diethyl ether (1:1). The R_f-value for the 2(*Z*),4(*E*)-acid **9** was 0.65, and for the 2(*E*)4,(*E*)-acid **8** 0.50: cinnamylidenemalonic acid tails only a short distance from the starting line.

(ii) For normal-phase high performance liquid chromatography (HPLC) a μ-Porasil filled column was employed, and the product was eluted with hexane–diethyl ether (1.5:1) containing 0.1% formic acid, at a flow rate of 2 cm^3 min^{-1}. Cinnamylidenemalonic acid is insoluble in the chloroform used to dissolve the initial mixture for application to the column. The t_R-value for the 2(*Z*),4(*E*)-acid was 8.0 min, and for the 2(*E*),4(*E*)-acid 10.2 min.

(iii) For estimation of the content of cinnamylidenemalonic acid in reaction mixtures reversed-phase HPLC was employed using a Waters C_{18}-Z module, and elution with methanol–water (7:1) at a flow rate of 1 cm^3 min^{-1}. Its t_R was 3.6 min. The 2(*Z*),4(*E*)- and 2(*E*),4(*E*)- acids were not separable under these conditions, but elute together at t_R 7.2 min.

Thermolysis of Cinnamylidenemalonic Acid **5** (*Ar = Ph*) *in Quinoline at* 170 °C *and* 130 °C.—Typically, cinnamylidenemalonic acid (100 mg) was heated under nitrogen in quinoline (3.5 cm^3) at the appropriate temperature, with monitoring by TLC and removal of samples at intervals for analysis. These were worked up by dilution with diethyl ether and extraction with 5% aq. potassium hydroxide followed by acidification (HCl). Analysis was by a combination of normal and reversed-phase HPLC (see above). The results are shown in Table 1.

Thermolysis of Cinnamylidenemalonic Acid in Pyridine (*Bath* 130 °C).—Experiments were carried out as above using cinnamylidenemalonic acid (200 mg) in pyridine (5 cm^3). Results are shown in Table 2.

Heating of 5-phenylpenta-2(*Z*),4(*E*)-dienoic acid (50 mg) in pyridine (3 cm^3) at reflux, and monitoring of the reaction by both TLC and HPLC, caused no conversion into the 2(*E*),4(*E*)-stereoisomer even after 9 h of heating.

Thermolysis of Cinnamylidenemalonic Acid **5** (*Ar = Ph*) *in Other Bases.*—(i) The acid (100 mg) and DABCO (2.0 g, m.p. 154–157 °C) were heated at 170 °C under a reflux condenser and the mixture was sampled at 20 min, and at 1 h, with work-up and analysing in the usual way. Results are in Table 3. The yield of mixed stereoisomers was 53 mg.

(ii) The acid (100 mg) and DBU (1.5 cm^3) were heated at 140 °C, worked up, and sampled at intervals, with the results given in Table 3. The reaction mixture became very brown.

(iii) The acid (100 mg) and piperidine (2 cm^3) were heated in a bath at 130 °C. There was effervescence which ceased after a short while: yields of 2(*E*),4(*E*)-acid appeared to be poor.

Preparation and Thermolysis of Carboxy-deuteriated Cinnamylidenemalonic Acid **10** *in Quinoline at* 130 °C.—Cinnamylidenemalonic acid (0.86 g) was stirred (2 h) in D_2O (5 cm^3) with MeOD added to assist solubility. The mixture was evaporated, and was again treated with the deuteriation mixture for 5 h, evaporated, and dried *in vacuo*. Thermolysis of cinnamylidenemalonic [$^2H_2$]acid **10** (90 mg) in dry quinoline (2 cm^3) for 2 h in a bath at 130 °C gave, after work-up, almost pure 2(*Z*),4(*E*)-acid **11** (60 mg), which was finally purified by normal-phase HPLC as above to give the pure crystalline acid (44 mg). The deuterium ratios, and their positional locations, were obtained from ^{1}H and ^{2}H NMR spectra. Integration of the ^{1}H spectrum ($CDCl_3$) using the α-doublet at δ 5.8 and the γ-double-doublet at δ 8.1 gave a ratio for α/γ deuteriation of 66.4:33.6. Integration of the ^{2}H spectrum ($CHCl_3$) using the broad α-signal near δ 5.8 and the broad γ-signal near δ 8.1 gave a ratio for α/γ deuteriation of 69.8:30.2. Mean α/γ deuteriation ratio, 68.1:31.9.

Preparation and Thermolysis of Carboxy-deuteriated Cinnamylidenemalonic Acid **10** *in Pyridine* (*Bath* 130 °C).—Thermolysis of cinnamylidenemalonic [$^2H_2$]acid (100 mg, prepared as above) in dry pyridine (2 cm^3) for 3.5 h in a bath at 130 °C gave a product after work-up (64 mg) containing both 5-phenylpenta-2(*Z*),4(*E*)- and -2(*E*),4(*E*)-dienoic acids, which were separated by HPLC to give pure 2(*Z*),4(*E*)- (26.4 mg) and 2(*E*),4(*E*)- (16.2 mg) dienoic acids. The deuterium ratios, and their positional locations, were obtained from ^{1}H and ^{2}H NMR spectra.

For the 2(*Z*),4(*E*)-acid **13**: integration of the ^{1}H spectrum ($CDCl_3$) using the α-doublet at δ 5.8 and the γ-double-doublet at δ 8.1 gave a ratio for α/γ deuteriation of 65.9:34.1. Integration of the ^{2}H spectrum ($CHCl_3$) using the broad α-signal near δ 6 and the broad γ-signal near δ 8 gave a ratio for α/γ deuteriation of 65.8:34.2. Mean α/γ deuteriation ratio, 65.9:34.1%.

For the 2(*E*),4(*E*)-acid **12**: integration of the ^{1}H spectrum ($CDCl_3$) using the α-doublet at δ 6.01 and the γ- + δ-multiplet signals at δ 6.88–6.99 gave a ratio for α/γ

deuteriation of 62.5:37.5. Integration of the ^2H spectrum ($CHCl_3$) using the broad α-signal near δ 6 and the broad γ-signal near δ 7 gave a ratio for α/γ deuteriation of 66.8:33.2. Mean α/γ deuteriation ratio, 64.7:35.3%.

A second set of experiments on similar lines was carried out and the results were as follows. For the 2(*Z*),4(*E*)-product, mean α/γ deuteriation ratio 68.2:31.8. For the 2(*E*),4-(*E*)-product, mean α/γ deuteriation ratio 67.0:33.0. In these last experiments concerning the 2(*E*),4(*E*)-isomer, acetone and [$^2H_6$]acetone were used as solvents where appropriate.

General Procedure for Preparation of 5-Aryl-2-carboxypenta-2,4-(E)-dienoic Acids (Cinnamylidenemalonic Acids) **5**.—Potassium hydroxide (0.03 mol) was added to a mixture of the aromatic aldehyde **3** (0.01 mol) and diethyl ethylidenemalonate **4** (0.01 mol) in dry methanol (20 cm^3) and the mixture was stirred at 20 °C for 48 h. Ice was added and the solution was neutralised (pH paper) with 10% HCl. Filtration and crystallisation gave the diene **5**, usually as yellow crystals.

3',5'-Dimethoxycinnamylidenemalonic acid **5B**. Obtained in 66% yield, m.p. 223–224 °C (decomp.) (from EtOH) (lit.,[2] 212.5–213.5 °C) (Found: C, 60.2; H, 5.25%; M^+, 278.080. Calc. for $C_{14}H_{14}O_6$: C, 60.4; H, 5.05%; M, 278.079); ν_{max}(KBr)/cm^{-1} 1702 (CO_2H), 1640 (C=C) and 1588 (aryl); λ_{max}(EtOH)/nm 209 (ε 22 000), 248 (6600) and 337 (23 200); δ_H[$(CD_3)_2SO$] 3.70 (6 H, s, 2 × OMe), 6.34 (1 H, t, *J* 3, 4'-H), 6.49 (2 H, d, *J* 3, 2'- and 6'-H), 6.96–7.3 (3 H, m, olefinic protons) and 10.2–12.0 (2 H, br, exchangeable OHs).

3'-Bromocinnamylidenemalonic acid **5D**. Obtained in 80% yield from 3-bromobenzaldehyde; formed clusters of yellow needles, m.p. 191–192 °C (effervescence) (from aq. EtOH) (Found: C, 48.6; H, 3.0. $C_{12}H_9BrO_4$ requires C, 48.5; H, 3.05%).

4'-Chlorocinnamylidenemalonic acid **5E**. Obtained in 66% yield from 4-chlorobenzaldehyde; m.p. 204–205 °C (effervescence) yellow needles from aq. MeOH (Found: C, 57.25; H, 3.45. $C_{12}H_9ClO_4$ requires C, 57.05; H, 3.6%); δ_H([$^2H_6$]acetone) 7.4–7.51 (3 H, m, includes 2 × Ar-H, d, *J* 8.5 and 5-H), 7.70 (2 H, d, *J* 8.5, 2 × ArH) and 7.95–8.1 (2 H, m, 3- and 4-H).

4'-Nitrocinnamylidenemalonic acid **5F**. Obtained by hydrolysis of the half-ester (below); orange-yellow needles, m.p. 201–202 °C (gas evolution) from aq. MeOH (Found: C, 51.85; H, 3.95; N, 4.9. $C_{12}H_9NO_6 \cdot H_2O$ requires C, 51.25; H, 3.95; N, 5.0%); δ_H([$^2H_6$]acetone) 7.49 (1 H, d, *J* 15.0, 5-H), 7.83–7.87 (4 H, m, ArH), 7.91 (1 H, d, *J* 11.6, 3-H) and 8.05 (1 H, dd, *J* 11.6 and 15.1, 4-H).

4'-Cyanocinnamylidenemalonic acid **5G**. Obtained from 4-cyanobenzaldehyde and was crystallised from methanol (yellow needles). During m.p. determination (Kofler microscope) new crystals formed from ~ 205 °C and these melted at 245–247 °C with the original material, decarboxylating at the same time (Found: C, 64.05; H, 3.8; N, 5.5. $C_{13}H_9NO_4$ requires C, 64.2; H, 3.75; N, 5.75%); δ_H([$^2H_6$]acetone) 7.49 (1 H, d, *J* 15.1, 5-H), 7.8–7.86 (4 H, m, ArH), 7.92 (1 H, d, *J* 11.6, 3-H) and 8.05 (1 H, dd, *J* 15.1 and 11.6, 4-H).

3',4'-Methylenedioxycinnamylidenemalonic acid **5C**. Obtained in 53% yield from piperonal by condensation with diethyl ethylidenemalonate in the presence of Triton B, followed by hydrolysis at 0 °C for 5 h with 4 mol dm^{-3} HCl. When crystallised from aq. ethanol it had m.p. 224–225 °C (effervescence) (lit.,[17] 225–226 °C; lit.,[2] 206–209 °C).

General Procedure for Preparation of 5-Aryl-2-methoxycarbonylpenta-2(E),4(E)-dienoic Acids **7**.—A solution of the aromatic aldehyde (0.01 mol) in dry methanol (15 cm^3) was stirred whilst diethyl ethylidenemalonate (0.01 mol) and Triton B (40% solution in methanol, 15 cm^3) were added. The mixture was stirred at 20 °C for 48 h, ice was added, and the solution was neutralised (pH paper) with 10% HCl. Filtration and crystallisation gave the monomethyl half-ester, usually as yellow crystals.

5-(3',5'-Dimethoxyphenyl)-2-(methoxycarbonyl)penta-2(Z),-4(E)-dienoic acid **7B**. Prepared in 66% yield; m.p. 155–157 °C (from EtOH) (Found: C, 61.5; H, 5.4%; M^+, 292.096. $C_{15}H_{16}O_6$ requires C, 61.65; H, 5.5%; M, 292.095); ν_{max}(KBr)/cm^{-1} 1703 (carbonyls), 1639 (C=C) and 1592 (aromatic); λ_{max}(EtOH)/nm 209 (21 700), 249 (6800) and 338 (26 400); δ_H[$(CD_3)_2SO$] 3.82 (3 H, s, CO_2Me), 3.85 (6 H, s, 2 × OMe), 6.58 (1 H, t, *J* 3, 4'-H), 6.77 (2 H, t, *J* 3, 2'- and 4'-H), 7.15–7.32 (2 H, m, olefinic protons) and 7.35–7.6 (1 H, m, olefinic proton).

2-Methoxycarbonyl-5-(4'-nitrophenyl)penta-2(Z),4(E)-dienoic acid **7F**. Prepared in 72% yield; m.p. 175–176 °C (from aq. MeOH) (Found: C, 56.25; H, 3.9; N, 5.15%; M^+, 277. $C_{13}H_{11}NO_6$ requires C, 56.3; H, 4.0; N, 5.05%; M, 277); δ_H($CDCl_3$) 3.98 (3 H, s, CO_2Me), 7.27 (1 H, d, *J* 15.6, 5-H), 7.77 (2 H, complex d, *J* 8.7, ArH), 8.02 (1 H, dd, *J* 11.6 and 0.8, 3-H), 8.27 (2 H, complex d, *J* 8.7, ArH) and 8.61 (1 H, dd, *J* 11.5 and 15.6, 4-H).

2-Methoxycarbonyl-5-(3',4'-methylenedioxyphenyl)penta-2(Z),4(E)-dienoic acid **7C** was crystallised from ethanol, m.p. 168–170 °C, in 55% yield (Found: M^+, 276.065. $C_{14}H_{12}O_6$ requires M, 276.063); ν_{max}($CHCl_3$)/cm^{-1} 1730 (ester), 1650 (acid), 1610 (C=C), 1580 and 1571 (Ar); λ_{max}(EtOH)/nm 313 (17 000) and 344 (31 000).

5-(3',5'-Dibenzyloxyphenyl)-2-(methoxycarbonyl)penta-2(Z),4(E)-dienoic acid **7H**. This was reported in our earlier work.[1]

Methyl 5-(3',5'-Dimethoxyphenyl)penta-2(E),4(E)-dienoate **34B**.—The half-ester **7B** (2 g) was refluxed in pyridine (20 cm^3) for 48 h, and the mixture was poured into dil. hydrochloric acid and extracted with diethyl ether. Work-up gave the title ester (890 mg, 52%), m.p. 115–116 °C (lit.,[19] 114–115 °C) (Found: M^+, 248.106. Calc. for $C_{14}H_{16}O_4$: M, 248.105); ν_{max}(mull)/cm^{-1} 1707 (ester), 1610 (C=C), 1590 (aromatic) and 1000 [(*E*)-HC=CH def.]; λ_{max}(EtOH)/nm 209 (19 500), 239 (10 100) and 315 (27 400); δ_H($CDCl_3$) 3.80 (3 H, s, CO_2Me), 3.85 (6 H, s, 2 × OMe), 5.96 (1 H, d, *J* 16, 2-H), 6.41 (1 H, t, *J* 3, 4'-H), 6.58 (2 H, d, *J* 3, 2'- and 6'-H), 6.80 (2 H, m, 4- and 5-H) and 7.41 (1 H, m, 3-H).

5-(3',5'-Dimethoxyphenyl)penta-2(Z),4(E)-dienoic Acid **33B**.—A solution of dicarboxylic acid **5B** (0.5 g, 0.0018 mol) was stirred in quinoline at 170 °C for 12 h and was then cooled, diluted with diethyl ether, and washed with aq. sodium hydroxide (10%). Acidification of the alkaline phase and extraction with diethyl ether gave, after evaporation and crystallisation from benzene, the 2(*Z*),4(*E*)-*dienoic acid* **33B** (310 mg, 74%), m.p. 143–144 °C (Found: C, 66.45; H, 6.0%; M^+, 234.090. $C_{13}H_{14}O_4$ requires C, 66.65; H, 6.0%; M, 234.089); ν_{max}(Nujol)/cm^{-1} 1680 (CO_2H), 1612 (C=C), 1589, 1571 (aryl) and 993 and 968 [(*E*)-HC=CH def.]; λ_{max}(EtOH)/nm 210 (20 400), 240 (9000) and 314 (21 300); δ_H($CDCl_3$) 3.84 (6 H, s, 2 × OMe), 5.72 (1 H, d, *J* 12, 2-H), 6.42 (1 H, t, *J* 3, 4'-H), 6.63 (2 H, 2'- and 6'-H), 6.83 (2 H, m, 3- and 5-H), 7.98 (1 H, dd, *J* 12 and 16, 4-H) and 9.3–10.3 (1 H, br, OH).

The 2(*Z*),4(*E*)-*methyl ester* (189 mg), prepared from the acid (200 mg) by reaction with diazomethane, had m.p. 124–125 °C (from Et_2O) (Found: M^+, 248.106. $C_{14}H_{16}O_4$ requires M, 248.105); ν_{max}(film)/cm^{-1} 1722 (ester); λ_{max}(EtOH)/nm 210 (20 300), 242 (8500) and 318 (24 800); δ_H($CDCl_3$) 3.75 (3 H, CO_2Me), 3.81 (6 H, s, 2 × OMe), 5.68 (1 H, d, *J* 11, 2-H), 6.37 (1 H, t, *J* 3, 4'-H), 6.62 (2 H, d, *J* 3, 2'- and 4'-H), 6.66 (2 H, 3- and 5-H) and 8.03 (1 H, dd, *J* 16 and 11, 4-H).

5-(3'-Bromophenyl)penta-2(Z),4(E)-dienoic Acid **33D**.—The bromo dicarboxylic acid **5D** (300 mg) was heated in quinoline

(5 cm^3) at 134 °C for 1.5 h. Work-up as above gave the 2(*Z*),4(*E*)-acid containing ~5% 2(*E*),4(*E*)-stereoisomer (0.19 g, 66%). The mixture was separated by HPLC using a silica Radpak (Waters) column, and elution (2 cm^3 min^{-1}) with diethyl ether–hexane (1:1.5) containing 0.1% formic acid, to give the pure 2(Z),4(E)-*acid* **33D** as needles, m.p. 177–178 °C (Found: C, 52.2; H, 3.6. $C_{11}H_9BrO_2$ requires C, 52.2; H, 3.6%); $\delta_H(CDCl_3)$ 5.80 (1 H, d, *J* 11.2, 2-H), 6.7–6.9 (2 H, m, 3- and 5-H), 7.21–7.67 (4 H, m, ArH) and 8.08 (1 H, ddd, *J* 15.7, 11.4 and 0.8, 4-H).

Continued elution gave the 2(E),4(E)-stereoisomer **35D** as needles, m.p. 179–180 °C (Found: C, 52.45; H, 3.7%); $\delta_H(CDCl_3)$ 6.03 (1 H, d, *J* 15.7, 2-H), 6.94–6.88 (2 H, m, 4- and 5-H), 7.23–7.8 (4 H, m, ArH) and 7.51 (1 H, ddd, *J* 15.1, 8.7 and 1.7, 3-H).

A mixture of the 2(*Z*),4(*E*)-acid with the 2(*E*),4(*E*)-stereoisomer began to melt at 135 °C and was completely melted at 150 °C. During the m.p. determination of the 2(*Z*),4(*E*)-isomer (Kofler hot-stage) spicules grew on the side of the slide from ~150 °C until they were the main product: no melting occurred until these melted at 177–178 °C. The melted material was examined by TLC, when it was found to be identical with the 2(*E*),4(*E*)-acid [R_f 0.40: (2*E*) 0.40, (2*Z*) 0.55].

5-(4′-*Chlorophenyl*)*penta*-2(Z),4(E)-*dienoic Acid* **33E**.—The dicarboxylic acid **5E** (0.25 g) was stirred with quinoline for 2 h at 135 °C. Work-up gave a *product* (96%) which was almost entirely the 2(*Z*),4(*E*)-acid containing <5% 2(*E*),4(*E*)-acid when examined by TLC and HPLC. Crystallisation from aq. methanol gave the 2(*Z*),4(*E*)-*acid* **33E**, m.p. 157–158 °C (Found: C, 63.5; H, 4.35. $C_{11}H_9ClO_2$ requires C, 63.3; H, 4.35%); $\delta_H(CDCl_3)$ 5.78 (1 H, d, *J* 11.2, 2-H), 6.83 (1 H, d, *J* ~15, 5-H), 6.87 (1 H, d, *J* ~11.2, 3-H), 7.34 (2 H, d, *J* 8.6, ArH), 7.47 (2 H, d, *J* 8.6, ArH) and 8.07 (1 H, ddd, *J* 15.7, 11.6 and 1.0, 4-H).

5-(4′-*Nitrophenyl*)*penta*-2(Z),4(E)-*dienoic Acid* **33F**.—The dicarboxylic acid **5F** was stirred with quinoline (1 cm^3) at 135 °C for 75 min. The solution darkened and was worked up to give a brown solid (0.08 g), the composition of which, as shown by HPLC, was 82% 2(*Z*),4(*E*)-title acid:18% 2(*E*),4(*E*)-stereoisomer. The mixture was separated by HPLC [silica; elution with hexane–diethyl ether (1.5:1) containing 0.1% formic acid; at 2 cm^3 min^{-1}] to give the title acid as fine orange needles from aq. methanol, m.p. 216–217 °C (at ~155 °C new spicules started to appear, and these melted with the main sample) (Found: M^+, 219. $C_{11}H_9NO_4$ requires M, 219); $\delta_H(CDCl_3)$ 5.91 (1 H, d, *J* 11.4, 2-H), 6.8–6.93 (2 H, m, 3- and 5-H), 7.66 (2 H, d, *J* 8.7, ArH), 8.22 (2 H, d, *J* 8.7, ArH) and 8.19–8.3 obscured (1 H, 4-H). Even after HPLC purification the compound showed ~5% 2(*E*),4(*E*)-stereoisomer as evidenced by the signal at δ 6.13 (d, *J* 15.2) in the NMR spectrum.

The 2(*Z*),4(*E*)-acid was heated at 190–195 °C for 10 min. The sample did not melt but typical spicules appeared, and on NMR analysis the product was found to have a 2(*Z*),4(*E*):2(*E*),4(*E*) ratio of ~1:1.

5-(4′-*Cyanophenyl*)*penta*-2(Z),4(E)-*dienoic Acid* **33G**.—The cyano diacid **5G** (90 mg) was stirred with quinoline at 133 °C for 105 min and the dark solution was worked up to give 5-(4′-cyanophenyl)penta-2(*Z*),4(*E*)-dienoic acid containing <5% 2(*E*),4(*E*)-material (HPLC) (50 mg, 68%). The product was purified by HPLC [silica; elution with hexane–diethyl ether (1.5:1) containing 0.1% formic acid] to give the pure *title acid* as very pale yellow needles, m.p. 160–161 °C (from MeOH containing a trace of water). There was a phase change at ~130 °C when spicules appeared without melting: these had the same m.p. as the original crystals (Found: C, 72.1; H, 4.65; N, 6.75. $C_{12}H_9NO_2$ requires C, 72.35; H, 4.55; N, 7.05%); $\delta_H(CDCl_3)$ 5.88 (1 H, d, *J* 11.3, 2-H), 6.85 (1 H, d, *J* 16.4, 5-H), 6.89 (1 H, d, *J* 11.3, 3-H), 7.61 (2 H, d, *J* 8.5, ArH), 7.67 (2 H, d, *J* 8.5, ArH) and 8.19 (1 H, dd, *J* 15.8 and 11.3, 4-H).

5-(3′,4′-*Methylenedioxyphenyl*)*penta*-2(Z),4(E)-*dienoic Acid* **33C** (*Experiment by Dr. J. C. Williams*).—Diacid **5C** (85 mg) was heated in quinoline (1 cm^3) for 12 min. Work-up gave the title acid (53 mg, 71%), which was crystallised from benzene or toluene, m.p. 149–150 °C (lit.,[17] 155 °C after sintering from 145 °C); ν_{max}(mull)/cm^{-1} 1681 (CO_2H), 1621 (C=C), 1597, 1582 (aromatics) and 990 [(*E*)-HC=CH def.]; λ_{max}(EtOH)/nm 239 (10 700), 260 (9550), 308 (15 200) and 343 (24 200). It was identical with a specimen made by partial hydrogenation (Lindlar catalyst/H_2) of 5-(3′,4′-methylenedioxyphenyl)pent-4(*E*)-en-2-ynoic acid. Esterification with diazomethane gave the *methyl ester* (80%), m.p. 70–70.5 °C (from hexane) (Found: C, 67.15; H, 5.5%; M^+, 232.073. $C_{13}H_{12}O_4$ requires C, 67.25; H, 5.2%; M, 232.074). Irradiation (by sunlight) of a benzene solution containing a trace of iodine caused stereomutation of the 2(*Z*),4(*E*)-acid to the 2(*E*),4(*E*)-acid, m.p. and mixed m.p. 214–215 °C, identical with an authentic specimen of (*E*),(*E*)-piperic acid. Treatment of the 2(*Z*),4(*E*)-acid with thionyl dichloride and conversion into the piperidide caused stereomutation, giving only (*E*),(*E*)-piperine.

Hexa-2(Z),4(E)-*dienoic Acid* **28**.—(±)-Hex-2-eno-δ-lactone **30**, b.p. 105–106 °C/11 mmHg; n_D^{16} 1.4720 (lit.,[15] b.p. 102.5–103 °C/12 mmHg; n_D^{18} 1.4710) originated from our earlier work.[20] Sodium (0.12 g) was dissolved in dry methanol (13 cm^3), hexenolactone (0.5 g) was added, and the mixture was kept for 30 min, when it was concentrated and water was added. Extraction with diethyl ether gave an oil, which crystallised from pentane at 0 °C under nitrogen to give hexa-2(*Z*),4(*E*)-dienoic acid **28** (0.18 g) as needles, m.p. 32.5–36 °C (lit.,[15] 32–35 °C); $\delta_H(CDCl_3)$ 1.92 (3 H, dd, *J* 7.1 and 1.5, Me), 5.58 (1 H, dd, *J* 11.4 and 0.7, 2-H), 6.1–6.3 (1 H, m, *J* 13.5 and 7, 5-H), 6.66 (1 H, t, *J* 11.4, 3-H) and 7.34 (1 H, complex t, *J* 13.5, 4-H).

Hexa-2(*E*),4(*E*)-dienoic acid **29** had $\delta_H(CDCl_3)$ 1.88 (3 H, d, *J* 5, Me), 5.77 (1 H, d, *J* 15, 2-H), 6.15–6.3 (2 H, m, 4- and 5-H) and 7.3–7.4 (complex dd, *J* 15 and 10.1, 3-H).

Deuteriated Hexa-2(Z),4(E)-*dienoic Acid* **31**.—Hexenolactone **30** (0.26 g) was added to a cooled solution of sodium methoxide {sodium (0.06 g) dissolved in methan[^{2}H]ol (5 cm^3)} and the solution was kept for 3.5 h. Work-up as above gave the title deuteriated acid. By using the 2-H and the 4-H signals in the ^{1}H NMR spectrum a deuterium-labelling ratio of 84.6:15.4 was found for the α- and γ-position: there was no incorporation elsewhere. From the ^{2}H spectrum a ratio of 80.5:19.5 was found from the broad signals near δ 5.5 and 7.3. Mean of the two determinations: α-82.6%, β-17.4%.

Analytical Systems for the Separation and Estimation of Hexa-2(Z),4(E)- *and* -2(E),4(E)-*dienoic Acids*.—(i) TLC was carried out on silica plates with hexane–diethyl ether (1:1) containing 0.1% formic acid for development. The R_f-value for the 2(*Z*),4(*E*)-compound was 0.68 and that for the 2(*E*),4(*E*)-stereoisomer was 0.59. With hexane–diethyl ether (2:1) containing 0.1% formic acid, the corresponding R_f-values were 0.53 and 0.43.

(ii) After silylation, the stereoisomers were separated by GLC using a SCOT OV 225 column at 80 °C. The elution times t_R were 5.1 min for the 2(*Z*),4(*E*)-compound and 6.5 min for the 2(*E*),4(*E*)-stereoisomer.

(iii) HPLC was carried out on a silica RCM Radpak column, eluted with hexane–diethyl ether (1.5:1) containing 0.1% formic

acid at 2 cm^3 min^{-1}. The elution times t_R were 5.8 min for the 2(*Z*),4(*E*)-compound and 8.0 min for the 2(*E*),4(*E*)-stereoisomer.

Condensation of Crotonaldehyde (But 2-enal) with Carboxy-deuteriated and -undeuteriated Malonic Acid in Pyridine at 98 °C.—Malonic acid (0.60 g) and crotonaldehyde (0.50 g) were heated together at 98 °C in dry, stirred pyridine (0.5 cm^3) for 1 h. After the mixture had cooled, water and HCl were added and the precipitate was extracted into diethyl ether; the extract was dried ($MgSO_4$) and evaporated. Examination of the sorbic acid product (0.32 g) by TLC and, after silylation, by GLC, showed it to be the 2(*E*),4(*E*)-isomer (>98%) containing <2% of the 2(*Z*),4(*E*)-isomer.

Carboxy-deuteriated malonic acid was made by stirring malonic acid (2.68 g) with D_2O (5 cm^3) for 3 h. The solution was evaporated, and dried by gentle heating. Deuteriated malonic acid (0.30 g) and crotonaldehyde (0.25 g) were heated together in dry pyridine (0.25 cm^3) at 100 °C for 1 h. Work-up as above gave the 2(*E*),4(*E*)-isomer **32** (40 mg) containing no detectable amount of 2(*Z*),4(*E*)-isomer as evaluated by TLC or GLC. From the ^1H NMR signals for 2-H (δ 5.77) and 4-H + 5-H (δ 6.15–6.3), and assuming labelling in the latter pair is only at 4-H, an estimate of 2-H labelling to 4-H labelling was 50:50. From the broad ^2H NMR signals near δ 5.8 and near δ 6.2, an estimate of 2-H : 4-H labelling of 46.2 : 53.8 was obtained. The mean of the two estimates (2-H: 48.1%, 4-H: 51.9%) is in good agreement with the value of 46.9 and 53.1%, respectively, given by Elvidge and his colleagues [8] for a similar experiment.

*Heating of Hexa-*2(Z),4(E)*-dienoic Acid with Malonic Acid in Pyridine at* 100 °C.—The pure 2(*Z*)-acid (10 mg) was heated with malonic acid (14 mg) in pyridine (60 mm^3) at 100 °C for 1 h. Work-up and examination of the product by GLC showed that a 73% 2(*Z*),4(*E*)/27% 2(*E*),4(*E*) mixture had been formed. Whilst some 2(*Z*)-to-2(*E*) interconversion occurs under these conditions, the experiment does not support the origin of almost pure 2(*E*)-acid in the crotonaldehyde–malonic acid condensation (above) as being from the 2(*Z*)-isomer by stereomutation.

(But-2-enylidene)malonic Acid **27**.—Malonic acid (5.0 g) and crotonaldehyde (3.6 g) were kept in pyridine (15 cm^3) at room temperature for 5 days. Excess of saturated aq. potassium carbonate was added (evolution of CO_2) and the alkaline solution was extracted with diethyl ether to remove any remaining crotonaldehyde. The aqueous solution was acidified (HCl) and the precipitate was filtered off to give sorbic acid (0.79 g). The aqueous solution was extracted with diethyl ether (3×) and the extracts were dried ($MgSO_4$), and evaporated under reduced pressure to give a solid (1.28 g). The latter was taken up onto dry silica and packed on a dry silica column (2.3 × 15 cm). Elution first with hexane, and then hexane–diethyl ether (2:1) containing 0.1% formic acid, followed by hexane–diethyl ether (3:3.5) containing 0.1% formic acid, gave (but-2-enylidene)malonic acid **27**,[21] m.p. 108–111 °C (decomp.), (lit.,[22] ~75 °C) (Found: M^+, 156. Calc. for $C_7H_8O_4$: M, 156); λ_{max}(EtOH)/nm 274 (20 800); $\delta_H(CD_3OD)$ 7.60 (1 H, d, *J* 11.6, 3-H), 6.99 (1 H, ddd, *J* 15.0, 11.6 and 1.6, 4-H), 6.54 (1 H, dq, *J* 15.0 and 6.9, 5-H) and 1.95 (3 H, dd, *J* 6.9 and 1.6, Me); δ_C 169.6 (s) and 169.1 (s) (2 × CO_2H), 150.8 (d), 149.0 (d) and 129.4 (d) (3 × CH), 121.1 [s, $C(CO_2H)_2$] and 19.5 (t, Me).

A sample was also prepared by hydrolysis of diethyl (but-2-enylidene)malonate but in this case the diacid was isolated in a less pure state, m.p. 93–95 °C.

Thermolysis of (But-2-enylidene)malonic Acid in Quinoline.—(But-2-enylidene)malonic acid **27** (60 mg) was heated in quinoline (2 cm^3) at 130 °C for 3 h under nitrogen. Work-up in the usual way gave hexa-2(*Z*),4(*E*)-dienoic acid **28** (31 mg), purity 99.6% as estimated by GLC after silylation, and >98% as estimated by HPLC. The 2(*E*),4(*E*)-acid **29** could not be detected by TLC.

Thermolysis of (But-2-enylidene)malonic Acid in Pyridine.—(But-2-enylidene)malonic acid **27** (60 mg) was refluxed in pyridine (2 cm^3) for 90 min under nitrogen. Work-up in the usual way gave a mixture of hexa-2(*E*),4(*E*)-dienoic acid **29** (62.5%) and hexa-2(*Z*),4(*E*)-dienoic acid **28** (37.5%) by GLC after silylation. On the other hand a sample of the dicarboxylic acid heated (bath 100 °C) in pyridine (0.5 cm^3) for 3 h gave a 2(*E*):2(*Z*) ratio of 86.6:13.4 (analysis by HPLC), whilst a sample heated (bath 90–95 °C) in pyridine for 2 h gave a 2(*E*):2(*Z*) ratio of 27.6:72.4 (analysis by HPLC).

Acknowledgements

We thank Professor J. A. Elvidge for helpful comments on the manuscript. Some experiments on the 3,5-dimethoxy series were carried out by G. Kilbee and P. Tuchinda, whom we also thank.

References

1 L. Crombie, W. M. L. Crombie and P. Tuchinda, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1255.
2 P. D. Gardner, W. J. Horton, G. Thompson and R. R. Twelves, *J. Am. Chem. Soc.*, 1952, **74**, 5527.
3 L. Crombie, W. M. L. Crombie, G. Kilbee and P. Tuchinda, *Tetrahedron Lett.*, 1979, 4773.
4 M. Giraud and D. Molho, *Bull. Soc. Chim. Fr.*, 1970, 2651.
5 S. Rebuffat, M. Giraud and D. Molho, *Bull. Soc. Chim. Fr.*, 1978, II-457.
6 C. Liebermann, *Ber. Dtsch. Chem. Ges.*, 1895, **28**, 1438.
7 O. Doebner, *Ber. Dtsch. Chem. Ges.*, 1902, **35**, 2129.
8 J. A. Elvidge, J. R. Jones, R. B. Mane and M. Saljoughian, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1191.
9 E. J. Corey, *J. Am. Chem. Soc.*, 1952, **74**, 5897.
10 E. J. Corey, *J. Am. Chem. Soc.*, 1953, **75**, 1163.
11 E. J. Corey and G. Fraenkel, *J. Am. Chem. Soc.*, 1953, **75**, 1168.
12 J. Klein and A. Y. Meyer, *J. Org. Chem.*, 1964, **29**, 1038.
13 R. Tanikaga, N. Konya and A. Kaji, *Chem. Lett.*, 1985, 1583.
14 J. A. Elvidge and P. D. Ralph, *J. Chem. Soc. B*, 1966, 243.
15 U. Eisner, J. A. Elvidge and R. P. Linstead, *J. Chem. Soc.*, 1953, 1372.
16 J. R. Johnson, *Org. React.*, 1942, **1**, 210; H. O. House, *Modern Synthetic Reactions*, W. A. Benjamin, Menlo Park, CA, 2nd edn., 1972, p. 650.
17 H. Lohaus, *J. Prakt. Chem.*, 1928, **119**, 235.
18 M. Saljoughian and P. G. Williams, *J. Org. Chem.*, 1987, **52**, 3481.
19 C. G. Pitt, D. T. Hobbs, H. Schran, C. E. Twine, Jr. and D. L. Williams, *J. Labelled Compd. Radiopharm.*, 1976, **11**, 551.
20 L. Crombie and P. A. Firth, *J. Chem. Soc. C*, 1968, 2852.
21 H. Meerwein, *Justus Liebigs Ann. Chem.*, 1907, **358**, 82.
22 A. Riedel, *Justus Liebigs Ann. Chem.*, 1908, **361**, 94.

Paper 4/00493K
Received 26th *January* 1994
Accepted 8th *February* 1994